**Table 4** Change in scores on the Japanese version of the Zarit Caregiver Burden Interview depending on the presence of behavioral and psychological symptoms of dementia

| BPSD | No. patients | Change from baseline | *P* (paired *t*-test) |
|---|---|---|---|
| Overall | 169 | −1.9 ± 9.5 | 0.009 |
| Abulia/apathy | | | |
| Overall | 71 | −0.4 ± 10.3 | 0.732 |
| Improved | 22 | −4.1 ± 12.4 | 0.135 |
| Unchanged | 46 | 0.4 ± 8.3 | 0.738 |
| Worsened | 3 | 13.7 ± 8.3 | 0.738 |
| Depression | | | |
| Overall | 27 | −2.0 ± 10.0 | 0.302 |
| Improved | 17 | −4.8 ± 9.5 | 0.053 |
| Unchanged | 7 | 0.3 ± 6.2 | 0.907 |
| Worsened | 3 | 8.3 ± 15.0 | 0.437 |
| Delusion | | | |
| Overall | 30 | −2.4 ± 12.4 | 0.306 |
| Improved | 18 | −5.6 ± 9.4 | 0.022 |
| Unchanged | 11 | 2.8 ± 15.8 | 0.567 |
| Worsened | 1 | −1.0 | – |
| Hallucination | | | |
| Overall | 12 | −1.8 ± 14.2 | 0.678 |
| Improved | 10 | −5.5 ± 9.8 | 0.110 |
| Unchanged | 2 | 17.0 ± 22.6 | 0.481 |
| Worsened | 0 | – | – |
| Anxiety | | | |
| Overall | 50 | −2.4 ± 9.1 | 0.074 |
| Improved | 25 | −4.8 ± 8.5 | 0.009 |
| Unchanged | 21 | −1.7 ± 7.5 | 0.321 |
| Worsened | 4 | 9.3 ± 13.3 | 0.258 |
| Dependency | | | |
| Overall | 68 | −1.1 ± 10.0 | 0.349 |
| Improved | 22 | −4.7 ± 8.1 | 0.014 |
| Unchanged | 42 | −0.8 ± 9.7 | 0.581 |
| Worsened | 4 | 15.0 ± 6.9 | 0.022 |
| Wandering | | | |
| Overall | 12 | −0.9 ± 16.1 | 0.848 |
| Improved | 5 | −7.8 ± 8.4 | 0.108 |
| Unchanged | 4 | 14.8 ± 14.3 | 0.132 |
| Worsened | 3 | −10.3 ± 15.5 | 0.368 |
| Aggression | | | |
| Overall | 43 | −1.3 ± 9.3 | 0.361 |
| Improved | 16 | −2.1 ± 8.4 | 0.328 |
| Unchanged | 23 | 0.0 ± 10.4 | 0.984 |
| Worsened | 4 | −5.8 ± 1.7 | 0.007 |
| Resistance | | | |
| Overall | 31 | −0.3 ± 10.9 | 0.896 |
| Improved | 3 | −8.3 ± 12.3 | 0.363 |
| Unchanged | 25 | 0.3 ± 10.8 | 0.884 |
| Worsened | 3 | 3.0 ± 10.1 | 0.660 |
| Irritation | | | |
| Overall | 46 | −2.3 ± 8.7 | 0.073 |
| Improved | 20 | −2.9 ± 9.0 | 0.175 |
| Unchanged | 22 | −2.2 ± 8.5 | 0.240 |
| Worsened | 4 | −0.8 ± 10.0 | 0.890 |

BPSD, behavioral and psychological symptoms of dementia.

**Table 5** Number of patients reported adverse reactions

| Adverse reaction | No. patients | % |
|---|---|---|
| Safety analysis population (398 subjects) | 36 | 9.0 |
| Metabolic and nutritional disorder | 4 | 1.0 |
| Anorexia | 2 | 0.5 |
| Loss of appetite | 2 | 0.5 |
| Psychological disorder | 12 | 3.0 |
| Aggression | 2 | 0.5 |
| Agitation | 10 | 2.5 |
| Anger | 1 | 0.3 |
| Corporalia | 1 | 0.3 |
| Depression | 1 | 0.3 |
| Insomnia | 1 | 0.3 |
| Anxiety | 1 | 0.3 |
| Neurological disorder | 3 | 0.8 |
| Dizziness | 1 | 0.3 |
| Headache | 2 | 0.5 |
| Parkinsonism | 1 | 0.3 |
| Cardiac disorder | 1 | 0.3 |
| Atrial fibrillation | 1 | 0.3 |
| Gastric and intestinal disorder | 15 | 3.8 |
| Diarrhea | 5 | 1.3 |
| Erosive gastritis | 1 | 0.3 |
| Nausea | 8 | 2.0 |
| Vomiting | 2 | 0.5 |
| Skin and subcutaneous disorder | 1 | 0.3 |
| Pruritus | 1 | 0.3 |
| Musculoskeletal and connective tissue disorder | 1 | 0.3 |
| Back pain | 1 | 0.3 |
| Systemic and local disorder | 1 | 0.3 |
| Irritability | 1 | 0.3 |

company in 2009. In the present study, the frequently observed adverse reactions included agitation ($n = 10$ patients; 2.5%), nausea ($n = 8$ patients; 2.0%), diarrhea ($n = 5$ patients; 1.3%) and two patients each (0.5%) reporting poor appetite, loss of appetite, aggression, headache and vomiting. Other adverse reactions also observed were anger, coprolalia, depression, insomnia, uneasiness, dizziness, parkinsonism, atrial fibrillation, erosive gastritis, pruritus, back pain and irritation ($n = 1$ patient each; Table 3). Severe adverse reactions included agitation and atrial fibrillation ($n = 1$ patient each; 0.3%).

## DISCUSSION

In the present study, J-ZBI scores were reduced after donepezil treatment for 12 weeks. This reduction can be attributed to the effects of donepezil because patients who changed nursing services, which may have had potential effects on care burden, were excluded from analysis. Thus, the present results suggest that donepezil is effective in reducing caregiver burden in AD.

The present study addressed changes in care burden from baseline to Week 12 using J-ZBI and showed a significant difference in the mean J-ZBI score (–1.9 ± 9.5). This result is in line with that of a study conducted in mild to moderate AD patients with a similar drug, rivastigmine,[23] which showed that the mean ZBI score decreased by 1.7 ± 8.6 after 6 months treatment. Although the reduction in J-ZBI score by 2 points seems to be an relatively unimportant improvement, Arai *et al.* defined any reduction in J-ZBI in subjects classified as having mild AD as a successful.[24] Accordingly, because the average care burden was classified as mild in the present study, the change in J-ZBI score observed is considered meaningful for caregivers.

There was no significant correlation between changes in ZBI and MMSE scores. This suggests that a decreased burden is not the direct result of improvements in cognitive function. Conversely, in patients with BPSD, J-ZBI scores were significantly decreased, whereas in patients without BPSD the decrease in J-ZBI scores was not significant. Gort *et al.* reported that BPSD was associated with care burden after assessing care burden and care collapse in relation to various risk factors using the ZBI.[25] In addition, there are many other reports that indicate a correlation between improvements in BPSD and care burden.[11,26–28] Although the correlation between improvements in BPSD and decreased ZBI scores was not analyzed directly in the present study, improvements in BPSD may consequently lead to a reduction in a caregiver's burden.

In the subscales of J-ZBI, there was a significant decrease in personal strain ($P < 0.01$), although a similar decrease was not observed in role strain. Role strain is considered to represent burden that occurs when the caring task restricts established daily activities. This finding shows that donepezil could not reduce everyday life restrictions felt by caregivers. Conversely, it is considered that personal strain was improved along with improvements in BPSD because personal strain reflects subjective difficulty.

It is important to acknowledge that there are some limitations to the present post-marketing observational study. First, there were many drop outs compared with randomized control trials (RCT) and there were only 169 patients for whom valid data were available for analysis. Similarly, in a 6 month post-marketing observational study of rivastigmine conducted in Belgium with an original 434 patients,[23] valid data for analysis was only available for 175 patients, indicated a comparable drop out rate to that seen in the present study. Therefore, it seems inevitable that there will be considerable drop outs in post-marketing observational studies. Second, many patients and caregivers may have dropped out because the care burden worsened. In other words, the patients may have required hospitalization, institutionalization, or the addition of care services because their condition worsened. In any case, these patients were removed from the final analysis. However, this should not have had a major impact on the results because the number of patients who required hospitalization or institusionalization in the present study was small (five patients). Third, because the J-ZBI is a subjective evaluation, the impact of placebo effects cannot be denied. This issue can only be resolved by performing an RCT. However, unlike the RCT, which is conducted under unusual condition with selected patients and families, the present study was performed to elucidate the impact of donepezil under normal clinical settings. For these reasons, the present results must be interpreted with caution.

In conclusion, the results of the present post-marketing survey suggest that donepezil may improve cognitive function, BPSD, and hence care burden and, thus, can be expected to contribute to a better and lasting QOL of family caregivers.

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ORIGINAL ARTICLE

# Neuropsychiatric symptoms of progressive supranuclear palsy in a dementia clinic

Yusuke YATABE,[1] Mamoru HASHIMOTO,[2] Keiichirou KANEDA,[1] Kazuki HONDA,[1] Yusuke OGAWA,[1] Seiji YUUKI,[1] Shiho MATSUZAKI,[1] Atsuko TUYUGUCHI,[1] Hiroko KASHIWAGI[1] and Manabu IKEDA[2]

[1]Department of Psychiatry and Neuropathobiology, Kumamoto University Graduate School of Medical Science, and [2]Department of Psychiatry and Neuropathobiology, Faculty of Medical and Pharmaceutical Sciences, Kumamoto University, Kumamoto, Japan

*Correspondence:* Dr Yusuke Yatabe, MD, Department of Psychiatry and Neuropathobiology, Kumamoto University Graduate School of Medical Science, 1-1-1 Honjo, Kumamoto-city, Kumamoto 860-8556, Japan. Email: yatababychan@yahoo.co.jp

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## Abstract

**Background:** Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by supranuclear gaze palsy, postural instability, akinesia and other parkinsonism. Recently, the relationship between PSP and frontotemporal dementia (FTD) has been recognized, which includes clinical, pathological, biochemical and genetic features. However, there have been few studies that directly compared neuropsychiatric symptoms between PSP and FTD. The aim of the present study was to investigate comprehensive psychiatric and behavioural symptoms in PSP and compared them with those in FTD.

**Methods:** Patients with PSP ($n$ = 10) and FTD ($n$ = 13) were selected on the basis of inclusion/exclusion criteria from a consecutive series in the dementia clinic of Kumamoto University Hospital. We assessed their comprehensive neuropsychiatric features by using the Neuropsychiatric Inventory (NPI), the Stereotypy Rating Inventory (SRI) and a specific antisocial behaviour checklist.

**Results:** There were no significant differences in the total NPI and NPI subscale scores between the two groups. Both groups showed quite a similar pattern in the features of neuropsychiatric symptoms: apathy showed the highest score, followed by aberrant motor behaviour and disinhibition. The PSP group was significantly lower in the total SRI and eating and cooking behaviour scores than those in the FTD group. The prevalence of antisocial behaviours in PSP (50%) was equal to those in the FTD group (46%).

**Conclusions:** In a dementia clinic, the neuropsychiatric profile in patients with PSP closely resembled those in the FTD group. The present results suggest that PSP should be considered as not only a movement disorder, but also a disorder with a wide range of neuropsychiatric symptoms.

***Key words:*** *frontotemporal dementia, frontotemporal lobar degeneration, hypersexuality, neuropsychiatric symptoms, progressive supranuclear palsy, stereotypical behaviour.*

## INTRODUCTION

Progressive supranuclear palsy (PSP) is a neurodegenerative disease characterized by supranuclear gaze palsy, postural instability, akinesia and other parkinsonism.[1,2] Although PSP is categorized as a movement disorder, patients with PSP often present dementia with psychiatric symptoms and behavioural disturbances. Approximately 60–70% of patients with PSP are estimated to be suffering from dementia.[3,4] The features of dementia symptoms in PSP are known as 'subcortical dementia' characterized by bradyphrenia and executive dysfunction based on involvement of the frontal-subcortical circuit.[1,4–6] In addition, several studies documented that patients with PSP showed apathy and disinhibition.[7–9]

Executive dysfunction and apathetic/disinhibited behavioural change have also been seen in frontotemporal dementia (FTD), which presents with

predominantly frontal involvement.[10–12] FTD is one of the clinical subtypes of frontotemporal lobar degeneration (FTLD).[10] A wide range of behavioural changes have been reported in FTD, including loss of insight, impulsivity, emotional blunting, antisocial behaviour and stereotypical behaviour, in addition to apathy and disinhibition.[10–16]

Recently, the relationship between PSP and FTD has been recognized, which includes clinical, pathological, biochemical and genetic features.[17] Despite these similarities, there have been few studies that directly compared neuropsychiatric symptoms between PSP and FTD. Furthermore, there has been no systematic study to investigate stereotypical and antisocial behaviours in PSP. Elucidating their distinctive neuropsychiatric features can be useful for differentiating these diseases and choosing appropriate neuropsychiatric management. In the present study, we investigated comprehensive psychiatric and behavioural symptoms in PSP and compared them with those in FTD.

## METHODS

### Patients

All procedures of the present study strictly followed the 2010 Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and were approved by the Internal Review Board. After a complete description of all procedures of the present study, written informed consent was obtained from patients or their caregivers.

The subjects were 10 consecutive patients with PSP and 13 patients with FTD. They were selected on the basis of inclusion/exclusion criteria from a consecutive series of 975 patients who had been given a medical examination at the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, from April 2007 to September 2010. All of these patients were examined by senior neuropsychiatrists (M.I. and M.H.) with enough experience in seeing dementia, and were given routine laboratory tests and standard neuropsychological examinations, including the Mini-Mental State Examination (MMSE)[18] and Clinical Dementia Rating (CDR).[19] Psychiatric symptoms were assessed by the structured caregiver interviews using the Neuropsychiatric Inventory (NPI)[20,21] and the Stereotypy Rating Inventory (SRI).[15] In addition, brain magnetic resonance imaging (MRI) or computed tomography (CT), and I-123 iodoamphetamine (IMP) and single photon emission computed tomography (SPECT) of the brain were carried out. The clinical, neuropsychological and neuroimaging data collected prospectively in a standardized manner were entered into the Kumamoto University Dementia Follow-up Registry.

The diagnosis of PSP was based on the criteria for probable PSP of the National Institutes of Neurological Disorders and Stroke-Society for PSP (NINDS-SPSP).[2] All patients, except one, with PSP showed frontal hypoperfusion in visual assessment of SPECT. All patients presented onset of progressive vertical supranuclear gaze palsy and severe postural instability during the first year of symptom onset after 40 years-of-age. The diagnosis of FTD was based on the recent consensus criteria for FTLD.[10] All of the patients with FTD fulfilled five core symptoms: (i) insidious onset and gradual progression; (ii) early decline in social interpersonal conduct; (iii) early impairment in regulation of personal conduct; (iv) early emotional blunting; and (v) early loss of insight. In addition, all of the patients with FTD showed frontal hypoperfusion in visual assessment of SPECT. Patients with semantic dementia or progressive non-fluent aphasia were not included in the present study. The exclusion criteria were: (i) complication of other neurological diseases or unstable medical illnesses, such as diabetes mellitus, thyroid disease, vitamin deficiencies or malignant diseases; (ii) history of previous psychotic illness or substance abuse before onset of dementia; (iii) evidence of focal brain lesions on brain MRI or CT; (iv) absence of reliable informants; and (v) inability to obtain informed consent.

The demographic variables of the included patients are summarized in Table 1. There were no significant differences between the two groups in

**Table 1** Demographic variables of the progressive supranuclear palsy and frontotemporal dementia groups

| | PSP | FTD | *P*-value |
|---|---|---|---|
| Number | 10 | 13 | — |
| Sex (male/female) | 7/3 | 7/6 | 0.402 |
| Age (years) | 69.0 ± 5.6 | 66.5 ± 11.7 | 0.501 |
| Education (years) | 12.5 ± 2.5 | 11.3 ± 2.1 | 0.228 |
| Duration of illness (years) | 1.6 ± 0.7 | 1.9 ± 1.3 | 0.483 |
| MMSE score | 21.4 ± 5.5 | 18.3 ± 8.4 | 0.325 |
| CDR grade (0.5/1/2/3) | 5/2/3/0 | 4/5/1/2 | 0.433 |

Values are mean ± SD or *n*. CDR, Clinical Dementia Rating; FTD, frontotemporal dementia; MMSE, Mini-Mental State Examination; PSP, progressive supranuclear palsy.

age, sex, education, duration of illness and disease severity represented by MMSE or CDR grade.

### Assessments of psychiatric and behavioural symptoms

We assessed the patients' comprehensive neuropsychiatric symptoms semiquantitatively by an interview with their caregivers, using a Japanese version of the NPI[20,21] and the SRI.[15] In the NPI, the following 10 behavioural and psychological symptoms in dementia (BPSD) were rated on the basis of the patients' condition in the previous month before the interview: delusions, hallucinations, agitation, depression, anxiety, euphoria, apathy, disinhibition, irritability and aberrant motor behaviour. The SRI assesses five distinctive stereotypical behavioural disturbances often seen in patients with FTLD: eating and cooking behaviour (e.g. repetitively eating the same kind of food, repetitively cooking the same kind of dishes), roaming (e.g. stereotyped walking and driving), speaking (e.g. echolalia, sing the same song), movements (e.g. hand rubbing, foot tapping, and daily rhythm (e.g. clock watching, rigid adherence to routines). In these measurements, according to the criteria-based rating scheme, severity of each manifestation was classified into grades (from 1 to 3; 0 if absent), and frequency of each manifestation was also classified into grades (from 1 to 4; 0 if absent). The NPI score (severity × frequency) was calculated for each manifestation (range of possible scores, 0–12). The maximum total score for 10 manifestations is 120 in the NPI and the maximum total score for five manifestations is 60 in the SRI. Because these standardized measurements were not able to detect specific behavioural changes, so called antisocial behaviour, we carried out the semi-structured caregiver interview based on the previous studies[14,22] to investigate the presence or absence in the following five items: stealing, neglect of the traffic rules, physical assault, hypersexuality and public urination.

### Statistical analysis

Statistical differences between the two groups were assessed by the Student's *t*-test for age, education, duration of illness and MMSE. The Mann–Whitney U-test was carried out for the comparison of CDR grade, total NPI score, NPI subscale scores, total SRI score and SRI subscale scores. The Fisher's exact probability test was carried out for comparison of sex and frequency of each antisocial behaviour. A significance level of 0.05 (two tailed) was set for all analyses, which were carried out using SPSS for Windows, version 17.0.

## RESULTS

The total NPI scores of the both groups (mean ± SD) were 20.7 ± 17.7 for PSP and 17.8 ± 9.2 for FTD, and the differences were not significant ($P = 0.779$). Figure 1 shows the mean NPI subscale scores of both patient groups. There were no significant differences in the mean NPI subscale scores between the two groups. Furthermore, both groups showed quite a similar pattern in the 10 BPSD manifestations in which apathy showed the highest score, followed by aberrant motor behaviour and disinhibition, whereas delusions, hallucinations and depression showed low scores.

The total SRI scores of the two groups (mean ± SD) were 5.0 ± 5.4 for PSP and 10.0 ± 6.2 for FTD, and the difference was significant ($P = 0.027$). Figure 2 shows the mean SRI subscale scores of both patient groups. All stereotypical behaviour domains were lower in the PSP group than those in the FTD group, except for the roaming domain. In particular, the score of the eating and cooking behaviour domain in the PSP group was lower than in the FTD group ($P = 0.041$). The speaking domain in the PSP group was also lower than in the FTD group, although these differences did not reach statistical significance ($P = 0.052$).

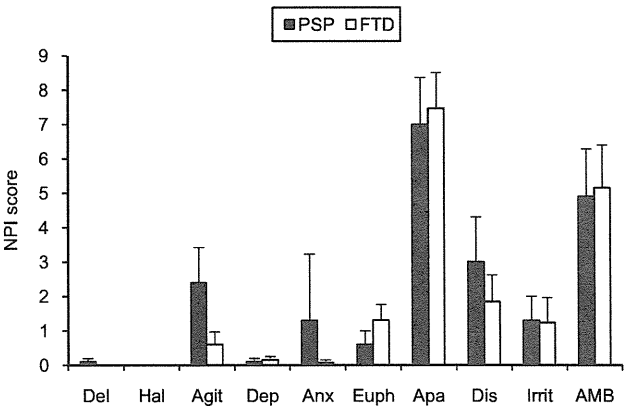


**Figure 1** The scores of the Neuropsychiatric Inventory (NPI) subscale in the progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) groups. Bars indicate the standard errors. Agit, agitation; AMB, aberrant motor behavior; Anx, anxiety; Apa, apathy; Del, delusions; Dep, depression; Dis, disinhibition; Euph, euphoria; Hal, hallucinations; Irrit, irritability.

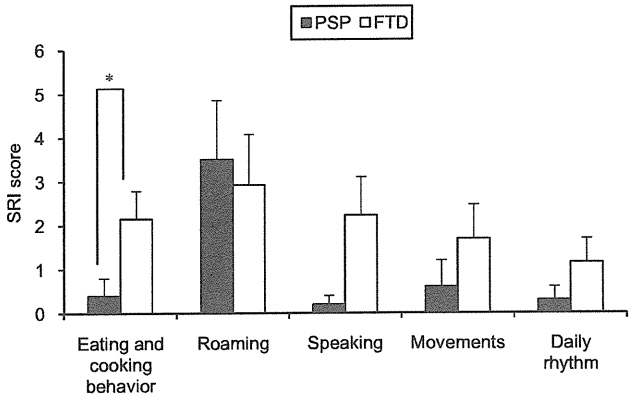


**Figure 2** The scores of the Stereotypy Rating Inventory (SRI) subscale in the progressive supranuclear palsy (PSP) and frontotemporal dementia (FTD) groups. *$P < 0.05$.

**Table 2** Frequency of specific antisocial behavior in progressive supranuclear palsy and frontotemporal dementia groups

| | PSP *n* (%) | FTD *n* (%) | *P*-value |
|---|---|---|---|
| Stealing | 0/10 (0) | 0/13 (0) | — |
| Neglect of the traffic rules | 3/10 (30) | 3/13 (23) | 1.000 |
| Physical assault | 3/10 (30) | 2/13 (15) | 0.618 |
| Hypersexuality | 3/10 (30) | 0/13 (0) | 0.068 |
| Public urination | 1/10 (10) | 2/13 (23) | 1.000 |
| Any of antisocial behaviors | 5/10 (50) | 6/13 (47) | 1.000 |

FTD, frontotemporal dementia; PSP, progressive supranuclear palsy.

Table 2 shows the frequency (on a present/absent basis) of specific antisocial behaviours between the two groups. A total of 50% of patients with PSP and 46% of patients with FTD showed at least one of the antisocial behaviours. The PSP group had a history of physical assault (30%), hypersexuality (30%), neglect of the traffic rules (30%) and public urination (10%). The FTD group had a history of neglect of traffic rules (23%), public urination (15%) and physical assault (15%). In our cohort, no patients in either group presented stealing. Hypersexuality was more common in the PSP group than in the FTD group, although the differences did not reach statistical significance ($P = 0.068$).

## DISCUSSION

This is the first study to systematically investigate neuropsychiatric symptoms based on the data from consecutive patients with PSP in a dementia clinic and directly compare them with those in the FTD group. The feature of neuropsychiatric symptoms showed quite a similar pattern in both diseases, except for the profile of stereotypical behaviour represented by the SRI. Namely, apathy was one of the most predominant neuropsychiatric symptoms following aberrant motor behaviour and disinhibition. Delusions, hallucinations and depression were unusual in both diseases. It was surprising that the prevalence of antisocial behaviours in PSP (50%) was equal to those in the FTD (46%) in a dementia clinic.

Thus, we found a close resemblance in psychiatric symptoms and behavioural disturbances between PSP and FTD. Previous reports have shown that not only FTD,[22,23] but also PSP,[24,25] show hypoperfusion of frontal regions, although there is no study to directly compare the brain functional imaging between PSP and FTD. In the present study, the background of cerebral blood perfusion in both diseases was consistent with these previous studies.[22–25] The similarity of the neuropsychiatric symptoms in both diseases might be explained by frontal hypoperfusion. Furthermore, PSP and corticobasal degeneration (CBD) are considered to be the same spectrum as FTLD and are known as a single term, 'Pick complex', by some researchers because there are clinical, pathological, genetic and biochemical overlaps.[26] In recent years, PSP and CBD, together with tau-positive FTD, were included in FTLD-tau as neuropathological subtypes of FTLD.[27] The results in the present study support the validity of regarding PSP as FTLD from a clinical viewpoint to some extent, although there is an objection to including PSP, which has been recognized as a movement disorder in FTLD, which is recognized as a cortical dementia syndrome in clinical practice.

In the present study, patients with PSP showed apathy, aberrant motor behaviour and disinhibition, but rarely psychosis and depression. The feature of the neuropsychiatric symptoms in our PSP cohort was almost consistent with several previous studies.[7–9] Litvan *et al.*[7] investigated neuropsychiatric features in the patients with PSP using the NPI, and found that apathy and disinhibition were common, whereas delusions, hallucinations and depression were uncommon. Aarsland *et al.*[8] and Kulisevsly *et al.*[9] also reported the same pattern of BPSD in their PSP cohorts. The present study and these previous reports[7–9] were based on data from a dementia clinic. In contrast, Borroni *et al.*[28] showed that by using the NPI, that the patients with PSP in a movement disorder clinic had

more depression and less apathy. The difference among these studies,[7–9,28] including ours, could be explained by the location of the studies. The patients with PSP are mainly diagnosed and treated for movement disorders by neurology services. However, the first medical contact is sometimes with psychiatry services or dementia clinics, because cognitive impairment and behavioural change is quite often seen in patients with PSP and might appear before the neurological signs.[29]

In contrast to the similar results of the NPI, there were several differences in stereotypical behaviour between the patients with PSP and FTD. As shown by the SRI, the patients with PSP were less marked than those in the FTD group in stereotypical behaviour, especially stereotypical eating and cooking behaviour. Bozeat *et al.*[12] suggested that only stereotypical behaviour, changes in eating preference, disinhibition and features of poor social awareness reliably distinguished between FTD and AD. Our results also suggest that the lack of stereotypical eating behaviour might help to differentiate PSP from FTD. Furthermore, it is noteworthy that 30% of patients with PSP presented hypersexuality, whereas no patients with FTD presented hypersexuality in our cohort. Bathgate *et al.* showed that 58% of patients with FTD showed hyposexuality, whereas 19% of FTD showed hypersexuality.[30] To our knowledge, there is no study to investigate sexual behaviour in PSP. There is a possibility that the existence of frontal syndrome with sexually disinhibited behaviour suggests the diagnosis of PSP, but not FTD, although this suggestion requires further examination.

There are a few methodological issues that should be taken into consideration to appreciate our results fully. First, although we diagnosed all patients according to clinical consensus criteria[2,10] with brain MRI or CT and SPECT, diagnosis was not confirmed by autopsy. Second, the statistical evaluation was limited by the small number of patients. Third, as we described earlier, the present study was based on the data from a dementia clinic rather than population-based. It can be claimed that selection bias affected our results. Fourth, we assessed specific antisocial behaviour using a checklist that has not yet been standardized, because there is no standardized measurement for antisocial behaviours in dementia. As a result of these limitations, the findings in the present study might not be applied to all patients with PSP.

Despite these limitations, we believe that our findings are quite meaningful, because the present study based on the data from consecutive patients in a dementia clinic highlighted the variety of clinical manifestations in PSP. In a dementia clinic, the BPSD profile in patients with PSP closely resembled those in the FTD. Furthermore, the absence of stereotypical eating behaviour and the presence of hypersexuality might be useful for differential diagnosis between PSP and FTD, although further investigation with a larger sample is warranted. Clarifying the underlying mechanism of these symptoms should be also carried out using a method of neuroimaging analysis. We emphasize that PSP should be considered as not only a movement disorder, but also a disorder with a wide range of neuropsychiatric symptoms.

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RESEARCH ARTICLE

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# Association of cerebral small vessel disease with delusions in patients with Alzheimer's disease

Yusuke Ogawa[1], Mamoru Hashimoto[2], Yusuke Yatabe[2], Keiichiro Kaneda[2], Kazuki Honda[1], Seiji Yuuki[1], Toshinori Hirai[3] and Manabu Ikeda[2]

[1]Department of Psychiatry and Neuropathobiology, Graduate School of Medical Science, Kumamoto University, Kumamoto, Japan
[2]Department of Psychiatry and Neuropathobiology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan
[3]Department of Diagnostic Radiology, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan
*Correspondence to:* Manabu Ikeda, E-mail: mikeda@kumamoto-u.ac.jp

**Background:** Cerebral small vessel disease (SVD) is frequently observed in patients with Alzheimer's disease (AD). However, the association between SVD and clinical symptoms exhibited by patients with AD remains unclear. This study examined the association of SVD as observed on magnetic resonance imaging (MRI) with behavioural and psychological symptoms of dementia and cognitive function of patients with probable AD.

**Methods:** A total of 163 consecutive patients (55 men, 108 women) with probable AD were included in this cross-sectional study of a prospective cohort. Patients were divided into two groups based on the presence or absence of cerebral SVD [white matter hyperintensities (WMH) grade 0/1 (Fazekas scale) and no lacunes: SVD absent, WMH grade 2/3 (Fazekas scale) or the number of lacunes ≥1: SVD present]. Cognitive functions were assessed using the Mini mental state examination, word recall and recognition subtests in the Alzheimer's Disease Assessment Scale—Cognitive Subscale, as well as the letter fluency task and the category fluency task. Psychiatric symptoms were rated according to Neuropsychiatric Inventory.

**Results:** Patients with probable AD with cerebral SVD had significantly more delusions and depression than those without SVD. No significant differences were observed in other neuropsychiatric symptoms, MMSE or word recall and recognition tests between both groups.

**Conclusions:** Our results suggest that cerebral SVD observed on MRI of patients with AD is associated with delusions and depression. 

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## Introduction

Cerebral small vessel disease (SVD), including subcortical lacunar infarcts (lacunes) and white matter hyperintensities (WMH), is commonly observed on brain magnetic resonance imaging (MRI) of older people with and without dementia. Numerous post-mortem studies have shown that WMH correspond to several heterogeneous pathological substrates with a varying extent of demyelination, arteriolosclerosis and gliosis representing not only incomplete infarctions but also tissue degeneration (Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study, 2001; Fernando and Ince, 2004). Lacunes are small cavities located in the white matter or subcoritical gray matter. They have been considered small ischemic infarcts; however, several pathogenetic mechanisms have been proposed (Wardlaw *et al.*, 2003). Incidence of SVD increases with age and vascular risk factors (Pantoni and Garcia, 1995).

In older people, Alzheimer's disease (AD) is considered the most common cause of dementia, characterised by gradual progressive cognitive impairment (McKhann *et al.*, 1984). In addition to cognitive

impairment, behavioural and psychological symptoms of dementia (BPSD) are important manifestations of AD. These symptoms have been shown to be associated with a reduced quality of life (Shin *et al.*, 2005), a higher cost of care (Beeri *et al.*, 2002), institutionalisation (Steele *et al.*, 1990) and increased caregiver burden (Robert *et al.*, 2005). Vascular risk factors including hypertension (Skoog *et al.*, 1996; Kivipelto *et al.*, 2001), diabetes (Luchsinger *et al.*, 2001), hypercholesterolemia (Kivipelto *et al.*, 2001) and tobacco smoking (Ott *et al.*, 1998) are also associated with increased AD risk and their treatment reduces AD risk (Li *et al.*, 2011). Furthermore, examination of several patients with AD at autopsy has shown a high prevalence of undiagnosed vascular lesions (Lim *et al.*, 1999; Fernando and Ince, 2004).

MRI has revealed that SVD is more prevalent in patients with AD than in older people without dementia (Scheltens *et al.*, 1992; Jellinger and Mitter-Ferstl, 2003). SVD may play a role, at least to some extent, in the clinical symptoms of AD. WMH are known to affect frontal lobe function, resulting in executive dysfunction in patients with AD (Pantel *et al.*, 2004; Tullberg *et al.*, 2004). However, it is still unclear whether SVD is associated with other symptoms such as BPSD in AD. Reports about the roles of SVD and BPSD in AD have been conflicting. Associations among the following conditions have been reported: WMH and depression (O'Brien *et al.*, 2000); apathy (Scheltens *et al.*, 1992); suicidal ideation (Lopez *et al.*, 1997); delusional misidentification (Lee *et al.*, 2006); aberrant motor behaviour (Hirono *et al.*, 2000); and anxiety, aberrant motor behaviour and night-time disturbance (Berlow *et al.*, 2010). However, these studies had relatively small sample sizes, and only few of them could confirm the results of previous studies. Moreover, some studies failed to find any association between WMH and BPSD (Harrell *et al.*, 1991; Lopez *et al.*, 1992; Staekenborg *et al.*, 2008).

In this study, we assessed the relationship of SVD observed on MRI with BPSD and cognitive functions in a relatively large sample of patients with AD attending a memory clinic.

## Methods

### Subjects

All procedures followed the Clinical Study Guidelines of the Ethics Committee of Kumamoto University Hospital and were approved by the internal review board. A complete description of all procedures was provided to the patients, and written informed consent was obtained from them or their caregivers.

In this cross-sectional study of a prospective cohort, a total of 163 patients with probable AD were selected from a consecutive series of 1253 patients who underwent a medical examination at the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, from April 2007 to May 2011. All patients were examined comprehensively by two senior neuropsychiatrists (M. I. and M. H.), having sufficient experience in examining patients with dementia. Routine laboratory and standardised neuropsychological tests, such as the Mini mental state examination (MMSE) (Folstein *et al.*, 1975) and Alzheimer's Disease Assessment Scale—Cognitive Subscale Japanese version (ADAS-J cog; Honma *et al.*, 1992) were also conducted. Brain MRI, brain MR angiography and single photon emission computed tomography for cerebral perfusion were also performed. Information on patient demographics including prescribed medications collected from caregivers and investigative data were entered prospectively into the Kumamoto University Dementia Follow-up Registry in a standardised manner. Patients had to meet the criteria of the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (McKhann *et al.*, 1984) for probable AD to be included in this study. Patients under 60 years of age; those who had any evidence suggestive of vascular dementia (VaD), such as focal neurological signs, abrupt deterioration or stepwise progression of cognitive deficits; those with focal vascular lesions except SVD, such as hematomas; significant neurologic antecedents, such as brain trauma, brain tumour, epilepsy or inflammatory disease; those with serious psychiatric diseases, substance abuse or developmental abnormalities; those who had severe behavioural or communication problems that would make clinical or MRI examination difficult or those without a reliable informant were excluded from the study.

The subjects consisted of 108 women and 55 men with a mean age of $76.3 \pm 7.2$ years and a mean educational attainment of $10.5 \pm 2.7$ years. The mean duration of symptoms determined through interviews with caregivers was $2.5 \pm 1.8$ years. Forty-one patients (25.2%) were prescribed cholinesterase inhibitors at examination. The Clinical Dementia Rating scale (CDR; Hughes *et al.*, 1982) revealed a functional severity of very mild in 75 patients, mild in 71, moderate in 16 and severe in 1.

Subjects were divided into two groups based on the presence or absence of SVD, and cognitive functions and BPSD were compared between the two groups.

### Assessment of cognitive functions

All patients underwent neuropsychological tests to assess their general cognitive functioning as well as memory and executive functions. General cognitive functioning was assessed using MMSE. Memory function was assessed using ADAS-J cog word recall and recognition subtests. ADAS-J cog word recall subtest is equivalent to a verbal learning test in which the retention of a list of 10 written words was measured using free immediate recall after each of the three learning trials. The score is the mean number of correct responses in three repeated trials. In the ADAS word recognition subtest, the subject was asked to read aloud 12 written high-imagery words and then to select the target words among 24 words randomly mixed with 12 irrelevant words. The score is the mean number of correct responses in three repeated trials. Executive function was assessed using the letter fluency task and the category fluency task. In the letter fluency task, subjects were instructed to say as many words as possible that begin with the letter 'Ka' for 1 min. The score was the number of different words listed. In the category fluency task, the subjects were asked to list as many animals as possible within 1 min. The score was the number of different animals listed.

### Assessment of behavioural and psychological symptoms of dementia

We evaluated the comprehensive BPSD semiquantitatively through interviews with their caregivers using the Japanese version of the Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994; Hirono *et al.*, 1997). In NPI, the following 10 BPSD were rated on the basis of the patients' condition in the month before interviews: delusions, hallucinations, agitation, depression (dysphoria), anxiety, euphoria, apathy, disinhibition, irritability and lability and aberrant motor behaviour. According to the criteria-based rating scheme, severity of each manifestation was classified into four grades (from 1 to 3; 0 if absent), whereas frequency was classified into five (from 1 to 4; 0 if absent). The NPI score (severity × frequency) was calculated for each manifestation (range of possible scores, 0–12). Thus, the maximum total score for the 10 manifestations is 120.

### Assessment of small vessel disease

Scans were made on a 3.0-T MR scanner. Fluid-attenuated inversion recovery (FLAIR), T2-weighted, diffusion-weighted, magnetization-prepared rapid acquisition of gradient echo imaging and susceptibility-weighted imaging were performed. The presence of lacunes and the extent of WMH were determined by a neuroradiologist who was blinded to the clinical data, including cognitive test results and NPI scores. The extent of WMH severity was rated visually on axial FLAIR images using the Fazekas scale as grade 1 (punctate), grade 2 (early confluent) or grade 3 (confluent) (Fazekas *et al.*, 1987). In this study, WMH were considered present if the Fazekas grade was 2 or 3 (Pompili *et al.*, 2008; Staekenborg *et al.*, 2008). Changes in the basal ganglia were rated in the same way and considered as white matter lesions even if they were located in the gray matter nuclei. Lacunes were defined as lesions with diameters of more than 2 mm with hyperintensity on T2-weighted images with central hypointensity on FLAIR images. Seventy-nine patients (48.0%) showed WMH, whereas 54 patients (33.1%) showed with lacunes. Both WMH and lacunes were observed in 40 patients (24.5%). Patients were divided into two groups based on the presence or absence of SVD (WMH grade 0/1 and no lacunes: SVD absent, WMH grade 2/3 or the number of lacunes ≥ 1: SVD present).

### Statistical analysis

Group differences were analysed using two-tailed Student $t$ test, two-tailed Mann–Whitney $U$ test or $\chi^2$ test. $p < 0.05$ was considered to be statistically significant. No correction for multiple comparisons was performed because of the exploratory nature of the study. In the present study, patients with SVD were significantly older than those without SVD. Therefore, we also analysed group differences in the neuropsychological tests and NPI scores using analysis of covariance (ANCOVA) with age as the covariate. Furthermore, we performed ANCOVA, with age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR as covariates, as these variables might affect cognition and BPSD. Statistical analysis was performed with SPSS for Windows, version 17.0 (IBM Corporation, Armonk, NY, USA).

## Results

Demographic variables of the two groups (patients with SVD and patients without SVD) are shown in Table 1. Patients with SVD were significantly older than those without SVD ($p = 0.005$); however, no significant differences were observed for the male to female ratio, mean level of education, duration of

Table 1 Patient demographics

| | Total ($n = 163$) | SVD present ($n = 93$) | SVD absent ($n = 70$) | $p$ |
|---|---|---|---|---|
| Age (years) | 76.3 ± 7.2 | 77.8 ± 6.1 | 74.4 ± 8.1 | 0.005[a,**] |
| Sex (male/female) | 55/108 | 33/60 | 22/48 | 0.588[b] |
| Education (years) | 10.5 ± 2.7 | 10.3 ± 2.8 | 10.8 ± 2.5 | 0.208[a] |
| Duration of history (years) | 2.5 ± 1.8 | 2.4 ± 1.9 | 2.6 ± 1.7 | 0.596[a] |
| Cholinesterase inhibitor use | 41 (25.2) | 20 (21.5) | 21 (30) | 0.216[b] |
| CDR | 0.88 ± 0.47 | 0.94 ± 0.53 | 0.80 ± 0.38 | 0.116[c] |
| WMH present (Fazekas score ≥2) | 79 (48.5) | 79 | 0 | |
| Lacunes present | 55 (33.7) | 55 | 0 | |

Values are presented as mean ± SD, $n$ (%) or n.
SVD, small vessel disease; CDR, Clinical Dementia Rating; WMH, White Matter Hyperintensities
[a]$t$ test; [b]$\chi^2$ test; [c]Mann–Whitney $U$ test; $^{**}p < 0.01$.

symptoms and percentage of patients who were prescribed cholinesterase inhibitors between both groups.

Results of neuropsychological tests are shown in Table 2. No significant differences were observed for MMSE and ADAS-J cog word recall and recognition subtests between both groups. In contrast, patients with SVD were significantly more impaired than those without SVD on the letter fluency task ($p = 0.013$). This difference remained significant after adjustment for age ($p = 0.021$, ANCOVA), but the significance disappeared after adjustment for age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.065$, ANCOVA).

Results of NPI are given in Table 3. In the total cohort of 163 patients, prevalence of any BPSD was 90.8%, with a median NPI score of 7 (range, 0–63). Furthermore, apathy was found to be the most common symptom, whereas euphoria was the rarest (affecting 67% and 1% of the patients, respectively). Delusions were present in 39 patients (23.9%). The total NPI score was significantly higher in patients with SVD than in those without SVD after adjustment for age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.042$, ANCOVA). Patients with SVD had significantly higher scores than those without SVD in the delusion domain ($p = 0.013$), and the difference remained significant even after adjustment for age ($p = 0.036$, ANCOVA), and age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.049$, ANCOVA). In addition, patients with SVD had significantly higher scores than those without SVD in the depression domain after adjustment for age, sex, years of education, disease duration, cholinesterase inhibitor usage and CDR ($p = 0.044$, ANCOVA).

## Discussion

The most remarkable finding of this study was that patients with AD and SVD had significantly more delusions than those without SVD. In the present

Table 2 Neuropsychological performances of subjects

| | SVD present ($n = 93$) | SVD absent ($n = 70$) | $p$ | Adjusted $p1$ | Adjusted $p2$ |
|---|---|---|---|---|---|
| MMSE scores | 19.7 ± 4.5 | 20.2 ± 4.1 | 0.425[a] | 0.232 | 0.633 |
| ADAS-J cog | | | | | |
| Word recall (correct response) | 4.1 ± 1.6 | 3.9 ± 1.4 | 0.415[a] | 0.456 | 0.166 |
| Word recognition (correct response) | 7.7 ± 3.0 | 8.2 ± 2.8 | 0.285[a] | 0.522 | 0.888 |
| LFT scores ('Ka') | 5.3 ± 3.0 | 6.5 ± 3.1 | 0.013[a*] | 0.021* | 0.065† |
| CFT scores (animals) | 9.0 ± 4.0 | 9.8 ± 3.3 | 0.210[a] | 0.317 | 0.571 |

Values are presented as mean ± SD.
SVD, small vessel disease; MMSE, Mini mental state examination; ADAS-J cog, Alzheimer's Disease Assessment Scale—Cognitive subscale (Japanese version); LFT, letter fluency task; CFT, category fluency task.
[a]$t$ test; age adjustment was performed using analysis of covariance and is represented as adjusted $p1$. Adjustment of age, sex, years of education, disease duration, cholinesterase inhibitor usage and Clinical Dementia Rating scale using analysis of covariance is represented as adjusted $p2$.
$^{*}p < 0.05$; $^{\dagger}p < 0.10$.

Table 3 Prevalence of behavioural and psychological symptoms of dementia and mean composite scores (frequency × severity) of individual Neuropsychiatric Inventory symptoms in patients

| | SVD present ($n = 93$) | SVD absent ($n = 70$) | $p$ | Adjusted $p1$ | Adjusted $p2$ |
|---|---|---|---|---|---|
| NPI total scores ≥1 | 84 (90.3) | 64 (91.4) | 0.809[b] | | |
| NPI scores | | | | | |
| Total score | 11.7 ± 11.4 | 8.3 ± 9.2 | 0.036[a*] | 0.053[†] | 0.042* |
| Delusion | 1.5 ± 3.0 | 0.5 ± 1.6 | 0.013[a*] | 0.036* | 0.049* |
| Hallucination | 0.3 ± 1.0 | 0.1 ± 0.6 | 0.288[a] | 0.421 | 0.839 |
| Agitation/aggression | 0.9 ± 1.9 | 0.9 ± 2.1 | 0.912[a] | 0.938 | 0.860 |
| Depression/dysphoria | 1.5 ± 2.8 | 0.9 ± 1.6 | 0.075[a†] | 0.062[†] | 0.044* |
| Anxiety/indifference | 0.9 ± 2.6 | 0.8 ± 2.0 | 0.726[a] | 0.749 | 0.828 |
| Euphoria | 0.0 ± 0.0 | 0.1 ± 0.5 | 0.321[a] | 0.471 | 0.358 |
| Apathy | 3.9 ± 4.0 | 3.2 ± 3.2 | 0.202[a] | 0.248 | 0.332 |
| Disinhibition | 0.6 ± 2.0 | 0.3 ± 1.6 | 0.373[a] | 0.528 | 0.354 |
| Irritability/lability | 1.0 ± 1.8 | 0.8 ± 1.9 | 0.521[a] | 0.536 | 0.304 |
| Aberrant motor behaviour | 1.2 ± 2.8 | 0.7 ± 1.9 | 0.222[a] | 0.210 | 0.478 |

Values are presented as mean ± SD or $n$ (%).
SVD, small vessel disease; NPI, Neuropsychiatric Inventory.
[a]$t$ test; [b]$\chi^2$ test; age adjustment was performed using analysis of covariance and is represented as adjusted $p1$. Adjustment of age, sex, years of education, disease duration, cholinesterase inhibitor usage and Clinical Dementia Rating scale using analysis of covariance is represented as adjusted $p2$.
*$p < 0.05$; †$p < 0.10$.

study, patients with SVD were significantly older than those without SVD. Both WMH and lacunes have been shown to be associated with aging (Fazekas *et al.*, 1988; Longstreth *et al.*, 1998). Some studies have found a significant association between psychosis in AD and age (Levy *et al.*, 1996; Bassiony *et al.*, 2000) and age at onset of AD (Hwang *et al.*, 1996; Gormley and Rizwan, 1998). However, delusions in patients with AD and SVD were significantly more severe than in those without SVD after adjustment for age in this study. Therefore, the present results cannot be explained by the differences of age between the two groups.

Previous studies have reported relationships between delusions and severity of white matter changes observed on MRI (Lee *et al.*, 2006) and between delusions and lacunar infarcts of white matter observed on computed tomography (Binetti *et al.*, 1995) in patients with AD. Furthermore, one study reported that a history of hypertension increased the risk of delusions in patients with AD (Treiber *et al.*, 2008), and another showed an association between delusions and the use of antihypertensives in patients with AD (Bassiony *et al.*, 2000). Thus, it can be suggested that SVD is a risk factor of delusions in patients with AD.

Mechanisms underlying delusions in patients with AD remain unclear. However, some neuroimaging studies have suggested an association between psychotic symptoms in AD and frontal lobe dysfunction (Sultzer *et al.*, 1995; Mega *et al.*, 2000; Sultzer *et al.*, 2003). Mentis *et al.* (1995) suggested that delusional misidentification in patients with AD are caused because of the abnormal integration of perceptual information from multimodal association cortices with affective information from paralimbic–limbic structures. White matter changes may result in a disruption of the functional connections between the frontal cortex and other related cortices or paralimbic–limbic structures, thus resulting in delusions. Furthermore, white matter changes in basal ganglia may alter connections between the frontal cortex and subcortical regions, resulting in development of delusions (Mentis *et al.*, 1995; McMurtray *et al.*, 2008). Further studies are needed to localise areas on MRI and single-photon emission computed tomography and support this hypothesis.

In this study, there was a trend for patients with SVD to be more impaired on the letter fluency task (for evaluating executive dysfunction) compared with those without SVD. No significant differences were observed in MMSE (for evaluating general cognitive functioning) and ADAS-J cog word recall and recognition subtests (for evaluating memory function) between both groups. In older people, appearance of SVD and incident lacunes on MRI have been reported to be associated with decreases in executive function and processing speed but not in memory or global cognition (Prins *et al.*, 2005; Jokinen *et al.*, 2011). In patients with AD, white matter lesions observed on MRI have been reported to be associated with impaired frontal lobe function, regardless of their

location (Tullberg *et al.*, 2004). These findings were consistent with our results, which suggest that SVD was associated with the impairment of executive function but not to impairments of global cognitive and memory functions. In a study examining the association between cognitive function and BPSD assessed by NPI, the letter fluency task and the category fluency task scores were significantly associated with changes in the psychosis subdomain but not in other subdomains (Tsai *et al.*, 2010). In addition, Swanberg *et al.* (2004) reported that symptoms of psychosis were more frequent in patients with AD with executive dysfunction than in those without. The lesions of the dorsolateral prefrontal circuit mainly involved in executive function are associated with performances of verbal fluency (Duffy and Campbell, 1994; Tekin and Cummings, 2002). In addition, lesions in the dorsolateral prefrontal circuit are associated with psychosis in patients with AD (Sultzer *et al.*, 1995). These previous neuroimaging and cognitive findings and the present result suggest that executive dysfunction due to SVD may be associated with delusions in patients with AD.

In the present study, patients with AD with SVD had significantly more depression than those without SVD after adjustment estimated covariates. Previous study suggests that white matter lesions confer an increased risk for depression in AD (O'Brien *et al.*, 2000). In this study, we did not find evidence to support the previously reported association of WMH with apathy (Scheltens *et al.*, 1992), aberrant motor behaviour (Hirono *et al.*, 2000) as well as anxiety and aberrant motor behaviour (Berlow *et al.*, 2010) in patients with AD. Unlike our study, previous studies failed to find any association between WMH and BPSD (Harrell *et al.*, 1991; Lopez *et al.*, 1992; Staekenborg *et al.*, 2008). Results obtained in our and previous studies may have differed because of the small sample sizes of the previous studies. An advantage of our study is the relatively large study cohort.

This study had some limitations. First, despite the exclusion of patients with any evidence suggestive of VaD, probably a few patients with VaD was included. However, patients with AD have been reported to have more delusions than patients with VaD (Lyketsos *et al.*, 2000; Ikeda *et al.*, 2004), suggesting that a combination of AD pathology and SVD may contribute to delusions. Second, WMH and lacunes are collectively treated as SVD. In this study, 40 patients (43.0% of patients with SVD) had both WMH and lacunes. Because our main aim was to investigate the effect of SVD on clinical symptoms in patients with AD, we analysed the two major representations of SVD together. In the future, WMH and lacunes need to be evaluated separately in order to investigate their independent effect on BPSD of patients with AD in a larger population. Third, in order to measure the extent of WMH, we used a visual rating scale, which may not be as accurate as the MRI volumetric method. However, the Fazekas rating scale, which was used in the present study, is widely accepted and has been shown to provide good global assessments of WMH. In an overview of 26 rating scales used to evaluate WMH on MRI, it was suggested that the simplicity of the Fazekas scale might make it robust, even for images of poorer quality (Scheltens *et al.*, 1998). In addition, simple rating scales, such as the Fazekas scale, have been shown to be comparable with complex measures of WMH in terms of associations with clinical outcome measures (Gouw *et al.*, 2006). Importantly, histopathological analyses have been used to validate this rating scale (Fazekas *et al.*, 1991; Fazekas *et al.*, 1993). Fourth, the study results might be able to be biased because all patients were recruited in only one dementia clinic.

## Conclusion

Our results suggest that cerebral SVD observed on MRI is associated with symptoms of delusions and depression in patients with AD.

Key points

- Cerebral SVD in patients with AD is associated with symptoms of delusions and depression.
- No significant differences were observed in other neuropsychiatric symptoms, memory or global cognition between patients with AD with SVD and those without SVD.

## Conflict of interest

None declared.

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# Do parkinsonian patients have trouble telling lies? The neurobiological basis of deceptive behaviour

**Nobuhito Abe,[1] Toshikatsu Fujii,[1] Kazumi Hirayama,[1] Atsushi Takeda,[2] Yoshiyuki Hosokai,[1] Toshiyuki Ishioka,[1] Yoshiyuki Nishio,[1] Kyoko Suzuki,[1] Yasuto Itoyama,[2] Shoki Takahashi,[3] Hiroshi Fukuda[4] and Etsuro Mori[1]**

1 Department of Behavioral Neurology and Cognitive Neuroscience, Tohoku University Graduate School of Medicine, Sendai, Japan
2 Department of Neurology, Tohoku University Graduate School of Medicine, Sendai, Japan
3 Department of Diagnostic Radiology, Tohoku University Graduate School of Medicine, Sendai, Japan
4 Department of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

Correspondence to: Nobuhito Abe,
Department of Behavioral Neurology and Cognitive Neuroscience,
Tohoku University Graduate School of Medicine,
2-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan
E-mail: abe-n@mail.tains.tohoku.ac.jp

Parkinson's disease is a common neurodegenerative disorder with both motor symptoms and cognitive deficits such as executive dysfunction. Over the past 100 years, a growing body of literature has suggested that patients with Parkinson's disease have characteristic personality traits such as industriousness, seriousness and inflexibility. They have also been described as 'honest', indicating that they have a tendency not to deceive others. However, these personality traits may actually be associated with dysfunction of specific brain regions affected by the disease. In the present study, we show that patients with Parkinson's disease are indeed 'honest', and that this personality trait might be derived from dysfunction of the prefrontal cortex. Using a novel cognitive task, we confirmed that patients with Parkinson's disease ($n = 32$) had difficulty making deceptive responses relative to healthy controls ($n = 20$). Also, using resting-state $^{18}$F-fluorodeoxyglucose PET, we showed that this difficulty was significantly correlated with prefrontal hypometabolism. Our results are the first to demonstrate that the ostensible honesty found in patients with Parkinson's disease has a neurobiological basis, and they provide direct neuropsychological evidence of the brain mechanisms crucial for human deceptive behaviour.

Keywords: Parkinson's disease; prefrontal cortex; neuropsychology; PET; executive function

Abbreviations: ADAS = Alzheimer's Disease Assessment Scale; FDG = $^{18}$F-fluorodeoxyglucose; MMSE = Mini-Mental State Examination; OSEM = ordered subset expectation maximization; WMS-R = Wechsler Memory Scale-Revised

## Introduction

Parkinson's disease, or paralysis agitans, was first described in 1817 by James Parkinson as 'shaking palsy' (Parkinson, 1817). It is a neurodegenerative disease characterized by clinical symptoms that include bradykinesia, rigidity, resting tremor and postural instability. In addition, it has been acknowledged that Parkinson's disease patients have impairments in cognitive functions (e.g. frontal executive dysfunction), which have a profound impact on quality of life for some of them (Pillon *et al.*, 2001).

Certain personality traits have long been noted as being characteristic of Parkinson's disease patients. In 1913, Carl Camp wrote 'It would seem that paralysis agitans affected mostly those persons whose lives had been devoted to hard

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work... The people who take their work to bed with them and who never come under the inhibiting influences of tobacco or alcohol are the kind that are most frequently affected. In this respect, the disease may be almost regarded as a badge of respectable endeavor' (Camp, 1913). Since the publication of Camp's report, many researchers have investigated the association of Parkinson's disease with personality or behavioural traits, and have consistently shown that Parkinson's disease patients have characteristic personality traits such as industriousness, seriousness and inflexibility (Ishihara and Brayne, 2006).

Parkinson's disease patients have also been described as 'honest' (Menza, 2000), in the sense that they tend not to tell lies. Although the possibility that honest people are particularly vulnerable to this disease cannot be ruled out, insidious neuropathological changes in the course of the illness might underlie this specific trait. In relation to this idea, a previous study reported that the personality change in Parkinson's disease patients was primarily the result of the disease rather than aging (Mendelsohn *et al.*, 1995), and some researchers have suggested the possibility that the personality traits are associated with Parkinson's disease-specific brain damage (Menza, 2000; Ishihara and Brayne, 2006). However, it may not be the case that Parkinson's disease patients choose not to tell lies, but rather that they actually have difficulty lying due to cognitive deficits resulting from pathological changes in certain brain regions.

One potentially critical contender for the role of mediator in complex cognitive processes such as deception is the prefrontal cortex, a structure known to support executive function. In particular, it is widely assumed that the lateral (especially dorsolateral) prefrontal cortex supports cognitive processes requiring executive function such as response inhibition and cognitive control (Mesulam, 2000; Anderson and Tranel, 2002). Some clinical studies have already implicated the prefrontal cortex as being responsible for executive dysfunction in Parkinson's disease patients (Carbon and Marie, 2003; Zgaljardic *et al.*, 2003; Owen, 2004). Impairment in the prefrontal executive system can prevent people exhibiting flexible and goal-directed behaviours, which are regarded as essential features of human deceptive behaviour. In support of the clinical findings mentioned above, recent neuroimaging studies involving healthy individuals have provided substantial evidence that the prefrontal cortex is consistently active during the making of deceptive responses relative to honest responses (Spence *et al.*, 2001; Langleben *et al.*, 2002, 2005; Lee *et al.*, 2002, 2005; Ganis *et al.*, 2003; Kozel *et al.*, 2004*a*, *b*, 2005, 2009; Davatzikos *et al.*, 2005; Nunez *et al.*, 2005; Phan *et al.*, 2005; Abe *et al.*, 2006; Mohamed *et al.*, 2006; Abe *et al.*, 2007, 2008; Gamer *et al.*, 2007; Browndyke *et al.*, 2008; Hakun *et al.*, 2008; Lissek *et al.*, 2008; Spence *et al.*, 2008; Bhatt *et al.*, 2009; Ganis *et al.*, in press; Hakun *et al.*, in press; Kozel *et al.*, in press; Lee *et al.*, 2009; Monteleone *et al.*, in press).

The available evidence allows us to hypothesize that Parkinson's disease patients have difficulty making deceptive responses due to dysfunction of the prefrontal executive system, and that this is the reason why they seem to be relatively honest compared with healthy individuals. To test our hypothesis, we developed a novel cognitive task for measuring the ability of Parkinson's disease patients to give deceptive responses, and assessed the correlation between their ability to tell a lie and their resting brain metabolism using PET with $^{18}$F-fluorodeoxyglucose (FDG). Unlike the activation paradigm with normal participants, which assesses neural response during the actual performance of a task, resting-state studies of metabolic rate with FDG-PET in brain-damaged patients can reveal regional dysfunction associated with their cognitive impairments. Resting-state FDG-PET is considered to be especially useful in the context of the neuropsychological investigation of patients with neurodegenerative disease (Desgranges *et al.*, 2002; Mentis *et al.*, 2002; Eustache *et al.*, 2004; Lozza *et al.*, 2004; Piolino *et al.*, 2007), because regional metabolic rate is a marker of integrated local synaptic activity and is sensitive to both direct neuronal/synaptic damage and secondary functional disruption at synapses distant from the primary site of pathology (Magistretti *et al.*, 1999). To our knowledge, the present study is the first to provide direct neuropsychological evidence that the prefrontal cortex plays a critical role in human deceptive behaviour.

# Materials and Methods

## Participants

The participants were 32 idiopathic Parkinson's disease patients and 20 normal controls matched for age, sex and score on the Mini-Mental State Examination (MMSE). The demographics of the Parkinson's disease patients and normal controls are shown in Table 1. All the patients were recruited from the Tohoku University Hospital. Normal controls with no history of neurological or psychiatric disease were recruited from local communities via an advertisement. The diagnosis of Parkinson's disease was made by board-certified neurologists according to the UK Parkinson's Disease Society Brain Bank criteria (Gibb and Lees, 1988). The patients' motor symptoms were evaluated using Hoehn-Yahr staging (Hoehn and Yahr, 1967) and the Unified Parkinson's Disease Rating Scale (UPDRS) part III (Fahn and Elton, 1987). The scores of UPDRS part III were recorded while the patients were 'on' medication. The inclusion criteria for patients in this study were as follows: age between 50 and 75 years, age at onset above 40 years, Hoehn-Yahr stage from 1 to 3, and a score of 24 or higher on the MMSE. The exclusion criteria were: a medical history of disease of the central nervous system not directly related to Parkinson's disease (e.g. stroke, head injury, epilepsy), concurrent psychiatric illness such as schizophrenia or manic depression, a documented or suspected history of drug abuse and/or alcoholism, diabetes mellitus and major abnormalities on brain MRI scans such as cerebral infarction or tumour. Of the 32 patients with Parkinson's disease, 14 were taking drugs for Parkinson's disease (i.e. levodopa and/or dopamine agonists), and they were asked not to take these drugs for at least 5 h before PET scanning.

Because we intended to conduct correlation analysis between the ability to tell lies and resting regional glucose metabolism within the group of patients, none of the control subjects who participated in the neuropsychological assessments was included in the PET study. However, even if correlation analysis within the group of patients identified the specific regions responsible for disability to tell lies, this would not prove that these findings were caused by the disease. To draw a definite conclusion, we needed to demonstrate explicitly that the regions identified in the correlation analysis were hypometabolic in the patients relative to the normal controls, i.e. lesioned. Therefore, we obtained PET data from another group consisting of 14 healthy participants without psychiatric or neurological disease (seven women,

Table 1 **Demographic and neuropsychological data (mean ± SD) of the Parkinson's disease patients and controls**

| Variable | Parkinson's disease patients ($n=32$) | Controls ($n=20$) | *P*-values |
|---|---|---|---|
| Demographics | | | |
| Age | 65.9 (6.7) | 65.5 (4.8) | 0.807 |
| Sex (Female/Male) | 19/13 | 11/9 | 0.756 |
| Education | 11.7 (2.1) | 12.7 (2.4) | 0.127 |
| Duration of Parkinson's disease | 4.1 (4.6) | – | – |
| Levodopa equivalent dose (mg/day) | 507.0 (825.6) | – | – |
| UPDRS part III (motor part)[a] | 18.1 (7.2) | – | – |
| Hoehn-Yahr stage (median/range) | 2.5/1.0-3.0 | – | – |
| Cognitive function | | | |
| MMSE | 28.3 (1.7) | 28.6 (1.1) | 0.386 |
| Digit span | | | |
| Forward | 5.7 (0.9) | 5.6 (1.0) | 0.693 |
| Backward | 4.1 (1.0) | 4.8 (1.0) | 0.035 |
| Spatial span | | | |
| Forward | 5.7 (0.9) | 5.6 (1.1) | 0.546 |
| Backward | 5.0 (1.0) | 4.9 (0.9) | 0.588 |
| ADAS word recall | | | |
| Total score | 19.3 (4.3) | 21.3 (3.5) | 0.089 |
| Verbal fluency | | | |
| Category: animal | 16.4 (5.3) | 22.1 (5.8) | 0.001 |
| Syllables: 'fu', 'a', 'ni' | 22.1 (8.2) | 29.4 (8.7) | 0.004 |
| Trail-making test (time required)[b] | | | |
| Part B - Part A | 83.0 (41.0) | 59.1 (33.7) | 0.035 |
| Stroop task (accuracy) | | | |
| Congruent | 98.0 (11.0) | 100.0 (0.0) | 0.424 |
| Incongruent | 93.5 (14.9) | 95.6 (8.8) | 0.565 |
| Go/No-go task (accuracy) | | | |
| Go condition | 99.9 (0.5) | 100 (0) | 0.184 |
| No-go condition | 99.6 (1.2) | 99.6 (1.3) | 0.942 |

Chi-square test was used for sex ratio, and *t*-test was used for the remaining variables.
a One patient was not assessed ($n=31$).
b Two patients could not complete this test ($n=30$).
ADAS = Alzheimer's Disease Assessment Scale.

seven men; mean age 64 years; mean education 12.3 years; mean MMSE score 29.1). There was no significant difference in age, sex, education and MMSE score between the patients and these healthy participants (all $P>0.1$). The PET data obtained from our sample of 32 patients were contrasted with those obtained from this normative group, and a resulting mask image was used in the correlation analysis in order to confine our analysis to regions showing hypometabolism in the Parkinson's disease patients. All the PET images were obtained with the same machine (see below).

After being given a detailed description of the study, written informed consent was obtained from all participants in accordance with guidelines approved by the Ethical Committee of Tohoku University and the Declaration of Helsinki.

## Standard neuropsychological tests

For all the patients and controls, in addition to the MMSE, a set of standard neuropsychological tests was used to identify any explicit cognitive deficits. Attention was assessed by digit span and spatial span subtests from the Wechsler Memory Scale-Revised (WMS-R). Memory function was assessed by a word recall task from the Alzheimer's Disease Assessment Scale (ADAS). Frontal lobe function was assessed by verbal fluency tasks, the trail-making test and computerized versions of the Stroop task and the Go/No-go task.

In the computerized version of the Stroop task, the subjects were required to name the colour of the ink in which single words were printed, as each word was shown on the screen. Four ink colours were used, and all the words in the test were the names of these four colours. Therefore, trials were either congruent (colour and word the same) or incongruent (colour and word different). Each stimulus was presented for 2000 ms, with 2000-ms interstimulus intervals. The entire session consisted of 72 congruent and 24 incongruent trials. The verbal response was recorded on a digital sound-recording machine.

In the computerized version of the Go/No-go task, when a single digit appeared with the illustration of a dog in the centre of the screen, the subjects were required to read the digit aloud. When the number appeared with the illustration of a cat, the subjects were required to make no response. Each stimulus was displayed for 2000 ms, with 2000-ms interstimulus intervals. The entire session consisted of 72 Go trials and 24 No-go trials. The verbal response was recorded on a digital sound-recording machine.