(i.e. levodopa equivalent dose), the scores of UPDRS part III (motor part), and the scores of MMSE—all of which are possible confounding factors for regional metabolism—were controlled by entering these variables into the model.

Results

Standard neuropsychological tests

Table 1 lists the results of the standard neuropsychological tests and statistical comparison between the Parkinson's disease patients and normal controls, as well as the demographic data. The *t*-test was used to assess the statistical significance for all the variables between the two groups except for sex ratio, for which the chi-squared test was used. The patients performed significantly worse than the controls on the digit span test (backward), the verbal fluency task related to syllables and category, and the trail-making test, indicating that Parkinson's disease patients had executive dysfunction. The patients also performed marginally worse than controls on the ADAS word recall test. No significant difference was found between the two groups in the Stroop task and the Go/No-go task, possibly due to ceiling effects resulting from the level of difficulty of these tests, which were specifically designed for the present study. Also, no difference was found between the patients and controls in the digit span test (forward) and the spatial span tests (forward and backward).

The experimental deception task

During the encoding phase, animate–inanimate judgment was virtually 100% correct for all the Parkinson's disease patients and normal controls, indicating that the participants paid sufficient attention to the stimuli.

For the retrieval session, collapsing across item type (i.e. studied and unstudied items), the data related to mean accuracy were analysed. For the patients, mean accuracies were 80.4% (SD = 9.5) for the Truth condition and 71.5% (SD = 17.1) for the Lie condition. For the normal controls, mean accuracies were 84.8% (SD = 5.1) for the Truth condition and 83.8% (SD = 11.9) for the Lie condition. A 2 (Group: Parkinson's disease patients, normal controls) × 2 (Task: Truth, Lie) analysis of variance (ANOVA) revealed a significant main effect of Group [$F(1,50) = 7.25$, $P = 0.010$], a significant main effect of Task [$F(1,50) = 9.22$, $P = 0.004$] and a significant Group × Task interaction [$F(1,50) = 5.77$, $P = 0.020$]. *Post hoc* tests revealed the reason for this interaction: the Parkinson's disease patients showed a decreased number of correct responses in the Lie condition relative to the Truth condition [$t(31) = 4.06$, $P = 0.0003$], whereas the controls showed no difference in scores between these two conditions [$t(19) = 0.47$, $P = 0.641$]. The results are shown in Fig. 1.

Although one patient stated in the middle of the task that she was not sure of the target person to deceive, the remaining patients stated with confidence after the experiment that they could easily and immediately recognize the target person to deceive throughout the task. However, in the forced-choice recognition test, all the patients, including the patient who had expressed uncertainty, correctly chose the target person

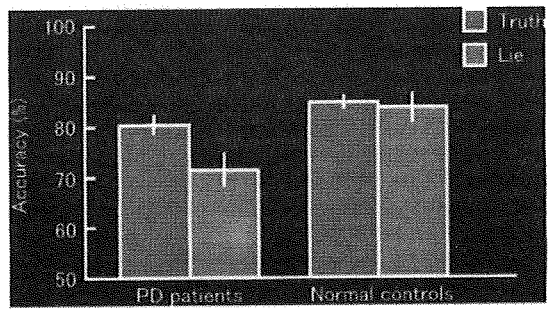

Figure 1 Proportion of correct honest (Truth condition) and deceptive (Lie condition) responses during the deception task in the Parkinson's disease patients and normal controls. Error bars represent standard error. PD = Parkinson's disease.

to deceive. This indicates that the patients' impaired ability to lie cannot be attributable to forgetting who to deceive. In addition, analysis of error pattern during the Lie condition in Parkinson's disease patients revealed that they often made errors by telling the truth (91.8% of all the error responses, but note that this rate includes errors for basic recognition memory performance). More importantly, there were few errors of no response (0.9%) and dual response (7.3%). The extremely low rate for these types of errors indicates that the patients understood sufficiently and performed the task without any difficulty resulting from motor dysfunction. Together, these findings support the view that the patients' deteriorated performance was definitely derived from a failure to inhibit true responses and make deceptive responses.

To clarify the effect of set shifting on the deception task in Parkinson's disease patients, we also compared the accuracy of Truth trials that were preceded by Lie trials with that of the remaining Truth trials that were not preceded by Lie trials in Parkinson's disease patients. If the set-shifting deficits affected the deception task performance, the patients should show worse performance for the Truth trials preceded by Lie trials than for those not preceded by Lie trials. Mean accuracies were 79.1% (SD = 10.3) for the Truth trials preceded by Lie trials and 81.1% (SD = 10.3) for the Truth trials not preceded by Lie trials. We found that there was no significant difference between the two types of trials [$t(31) = 1.32$, $P = 0.198$], suggesting that there was no effect of set-shifting deficits on the deception task.

We further conducted correlation analyses to investigate the relationship between performance of the deception task and cognitive dysfunctions detected by the standard neuropsychological tests in Parkinson's disease patients (i.e. the backward digit span task, the verbal fluency for category and syllables, and the trail-making test). The deception task index was significantly correlated with the performance of verbal fluency for syllables ($r = -0.429$, $P = 0.013$) and with the performance (i.e. time required) of the trail-making test ($n = 30$, because of missing data for two patients, $r = 0.372$, $P = 0.042$). We also found a trend between the deception task index and the performance of verbal fluency for category ($r = -0.303$, $P = 0.092$). However, there was no significant correlation between the deception task index and performance of the digit span (backward) task ($r = -0.245$, $P = 0.179$).

Table 2 **Brain regions showing a significant correlation between deception task performance and regional metabolism**

Regions (Brodmann's Area)	Coordinates			Z-value	Cluster size
	x	y	z		
Controlling for age and sex (shown in Figure 2)					
Right anterior prefrontal cortex (10)	10	66	−6	4.03	426
Left dorsolateral prefrontal cortex (10/46)	−32	58	10	3.99	261
Controlling for age, sex and disease duration					
Right anterior prefrontal cortex (10)	8	68	−6	4.00	396
Left dorsolateral prefrontal cortex (10/46)	−32	58	10	3.84	198
Controlling for age, sex and levodopa equivalent dose					
Right anterior prefrontal cortex (10)	8	68	−6	4.14	455
Left dorsolateral prefrontal cortex (10/46)	−18	58	12	3.91	225
Controlling for age, sex and UPDRS motor scores					
Right anterior prefrontal cortex (10)	10	68	−6	4.06	588
Left dorsolateral prefrontal cortex (10/46)	−32	60	10	3.91	214
Controlling for age, sex and MMSE scores					
Right anterior prefrontal cortex (10)	8	66	−4	3.56	102
Left dorsolateral prefrontal cortex (10/46)	−32	58	10	3.40	23

The results were masked with the contrast of normal controls versus Parkinson's disease patients.

Cognitive-metabolic correlations

The results are shown in Table 2 and Fig. 2. Significant negative correlations were found between the deception task index and the metabolic rates of the right anterior prefrontal cortex (BA10) and the left dorsolateral prefrontal cortex (BA10/46). Note that the results were masked with the contrast of normal controls versus Parkinson's disease patients, indicating that these two regions were found within the regions showing hypometabolism in the patients relative to the normal participants. Furthermore, the confounding effects of age and sex were also controlled. If the effect of disease duration was further controlled, the results remained virtually unchanged, suggesting that they are not affected by duration of the disease. Similarly, if the effect of medication (i.e. levodopa equivalent dose) was further controlled, the results again remained virtually unchanged, suggesting that they are not affected by Parkinson's disease medication. If the UPDRS scores part III (motor part) were further controlled ($n=31$, because of missing data for one patient), the results again remained virtually unchanged, suggesting that they are not affected by severity of motor symptoms. If the MMSE scores were further controlled, the results for these two regions remained significant ($P<0.001$ at the voxel level, uncorrected, but with smaller cluster size; 102 voxels for the right anterior prefrontal cortex and 23 voxels for the left dorsolateral prefrontal cortex), suggesting that the main findings of this study cannot simply be explained in terms of the severity of general cognitive deficits.

Discussion

In the present study, we tested our hypothesis that patients with Parkinson's disease have difficulty making deceptive responses due to dysfunction of the prefrontal cortex. As predicted, the patients could not successfully make deceptive responses compared with the healthy controls. Furthermore, consistent with previous neuroimaging studies with healthy individuals that have indicated an association between deception and the prefrontal cortex, FDG-PET imaging revealed that the patients' failure in the deception task was significantly correlated with hypometabolism in the prefrontal cortex, regardless of age, sex and other possible confounding factors. To our knowledge, this is the first neuropsychological evidence that dysfunction of the prefrontal cortex is involved in the inability to inhibit true responses and produce deceptive responses in Parkinson's disease patients.

The results of the present study raise two important points. First, certain personality traits of Parkinson's disease patients (Menza, 2000; Ishihara and Brayne, 2006) might be at least partly explained by neuropsychological deficits. In other words, the cognitive deficits may have an influence on ostensible personality traits in Parkinson's disease patients. More specifically, the present results indicate that honesty in Parkinson's disease patients might result from impairment of the executive functions necessary for the processes involved in telling lies. Indeed, the patients showed worse performance in the verbal fluency task and the trail-making test (generally used as measures of executive function) compared with the normal controls. Although these tests are different from the deception task in terms of how the subjects respond (e.g. open-ended responses in verbal fluency and forced-choice responses in the deception task), and therefore are not likely to have direct impact on deception task performance, there is still a possibility that these tests partially share the cognitive and neural mechanisms of deception in terms of higher-order cognitive processes including executive function. In line with this idea, these task performances were significantly correlated with deception task performance. Future studies using an approach similar to that of the present study might further clarify the relationships between cognitive dysfunction and characteristic personality and behavioural traits in Parkinson's disease patients.

Second, the results reveal a direct association between a cognitive control system subserving deception and function of the prefrontal cortex. It is known that brain imaging of healthy people

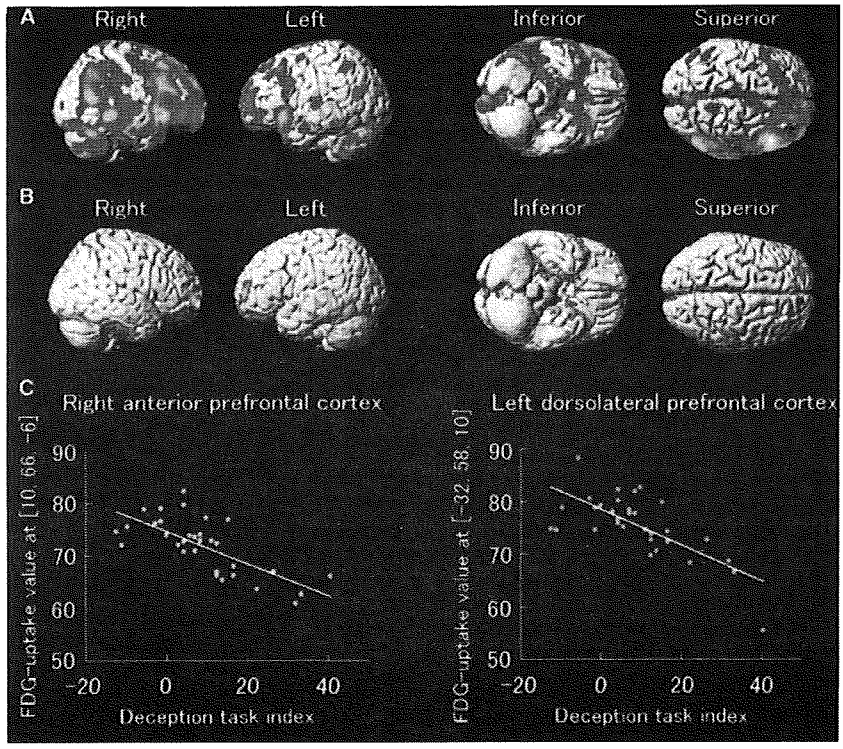

Figure 2 (A) Brain regions showing hypometabolism in the Parkinson's disease patients compared with the normal controls. Note that the statistical threshold was relatively liberal in this group comparison ($P<0.05$, uncorrected), since this analysis was done only for generating a mask image included in the cognitive-metabolic correlation analysis within the group of Parkinson's disease patients. The regions are displayed on a surface-rendered standard brain. (B) Brain regions showing a significant correlation between performance in the deception task and regional cerebral glucose metabolism in the Parkinson's disease patients ($P<0.001$, uncorrected). Note that the results were masked with the above contrast of the normal controls versus the Parkinson's disease patients to confine our analysis to the regions showing hypometabolism in the Parkinson's disease patients. The possible confounding effects of age and sex were also controlled. (C) Scatter plots of the correlations between the deception task indices and the FDG-uptake values in the right anterior prefrontal cortex ($r=-0.719$, $P<0.001$) and the left dorsolateral prefrontal cortex ($r=-0.709$, $P<0.001$). FDG = fluorodeoxyglucose; PD = Parkinson's disease.

cannot provide direct evidence that a certain brain region is necessary for the performance of a specific cognitive task (Frackowiak *et al.*, 1997). That is, some activation in functional brain imaging studies may reflect brain activity that is not essential for the function of interest. Therefore, direct evidence is derived from loss-of-function studies. In the present study, we revealed that the right anterior prefrontal cortex and left dorsolateral prefrontal cortex, which have been activated during deception in a number of carefully designed imaging studies (for reviews, see Spence *et al.*, 2004; Sip *et al.*, 2008; Christ *et al.*, in press), are associated with making deceptive responses. In line with our results, a recent study using transcranial direct current stimulation provided evidence that manipulation of functions in the dorsolateral prefrontal cortex altered the speed and efficiency of deceptive responses (Priori *et al.*, 2008). Furthermore, the association between deception and the left dorsolateral prefrontal cortex in the present study is highly consistent with the findings of a series of neuroimaging studies that we have conducted with healthy individuals (Abe *et al.*, 2006, 2007, 2008).

Based on the previous findings and the present results, we propose that the left dorsolateral prefrontal cortex, the region implicated in a wide range of higher-level cognitive operations such as working memory (D'Esposito *et al.*, 1995; Salmon *et al.*, 1996) and resolution of response conflict (MacDonald *et al.*, 2000; Badre and Wagner, 2004), plays a pivotal role in telling lies. The right anterior prefrontal cortex is also likely to play a critical role in integrating the multiple cognitive processes (Ramnani and Owen, 2004) in deception. One might think that set-shifting deficits, one of the well-known cognitive deficits in Parkinson's disease (Ravizza and Ciranni, 2002; Monchi *et al.*, 2004; Moustafa *et al.*, 2008; Nagano-Saito *et al.*, 2008), affect the results. However, our analysis of set-shifting effect on the response accuracy in Truth trials did not support this interpretation. We believe that our task does not simply measure set shifting, and that dysfunction of the left dorsolateral and right anterior prefrontal cortices specifically prevents Parkinson's disease patients from inhibiting true responses and producing deceptive responses.

It is important to determine how frontal executive dysfunction, possibly disrupting deceptive behaviour, is derived from the neuropathological changes observed in Parkinson's disease patients. One possibility is that prefrontal hypometabolism in Parkinson's disease patients results from degeneration of the substantia nigra pars compacta with subsequent depletion of dopamine in the striatum. A recent study suggests that the dorsolateral prefrontal circuit consisting of the dorsolateral prefrontal cortex, caudate nucleus, globus pallidus, substantia nigra, and thalamus (Cummings, 1993; McPherson and Cummings, 2002) is specifically associated with executive dysfunction in Parkinson's disease patients (Zgaljardic *et al.*, 2006). Alternatively, the executive dysfunction may reflect a functional disturbance of the frontal cortex itself caused by locally impaired mesocortical dopaminergic transmission (Mattay *et al.*, 2002). Although these two models are not mutually exclusive, there is controversy in the recent literature in that some researchers have argued that both the nigrostriatal and mesocortical pathways are disrupted in Parkinson's disease (Monchi *et al.*, 2007), whereas others have shown impaired nigrostriatal dopaminergic function with preserved mesocortical dopaminergic transmission in early Parkinson's disease (Sawamoto *et al.*, 2008). As for dopaminergic transmission, a study in which the 'on' and 'off' medication states are directly compared would also be useful. We can predict that dopaminergic medication would have a beneficial effect on the regions affected by depletion of dopamine, such as the caudate nucleus and thereby its connections to the dorsolateral prefrontal cortex, and that the ability to make deceptive responses would improve in Parkinson's disease patients. In fact, some previous studies have reported the beneficial effects of levodopa on cognitive performance, although it should be noted that the effects depend on the nature of the task (Gotham *et al.*, 1988; Cools *et al.*, 2001; Lewis *et al.*, 2005).

In conclusion, our results provide new evidence that damage to the prefrontal cortex disrupts the processes involved in making deceptive responses in Parkinson's disease patients. It appears that the 'honesty' of patients is caused by an impaired ability to deceive others that results from brain dysfunction caused by the disease. However, there are some limitations of the present study that should be borne in mind for future studies. First, the present study examined only the processes associated with executive control during deception. The participants were instructed to tell a lie, which cannot be viewed as being the same as deception in real life. The neural bases of genuine deception or immoral lying should be investigated further in both healthy individuals and brain-damaged patients. Second, it remains a possibility that the association between difficulty deceiving others and prefrontal dysfunction may not be specific to Parkinson's disease patients, and further studies are needed to examine whether patients with other neurological disorders affecting the prefrontal cortex show similar deficits (see Spence and Kaylor-Hughes, 2008). Third, the present study investigated only patients with mild Parkinson's disease of short duration. Whether our claim is true of patients in general is an important issue to be pursued. Finally, it is also important to determine how (and when) the brain pathology derived from Parkinson's disease causes specific personality traits together with explicit cognitive deficits. A longitudinal assessment with detailed neuropsychological assessment and multimodal neuroimaging in Parkinson's disease patients is required.

Acknowledgements

We are grateful to Takafumi Hasegawa, Akio Kikuchi, Shigenori Kanno, Yoichi Sawada, Kazue Okada, and Kaori Tachibana for their constant support and insightful comments. We also thank the patients and their families for sparing their valuable time to participate in this study.

Funding

Japan Society for the Promotion of Science for Young Scientists Research Fellowships (05J04930 to N.A.); Grant-in-Aid for Scientific Research on Priority Areas—System study on higher-order brain functions—from the Ministry of Education, Culture, Sports, Science and Technology of Japan (18020003 to E.M.). Funding to pay the Open Access publication charges for this article will be provided by 'Grant-in-Aid for Young Scientists (Start-up) from the Japan Society for the Promotion of Science (20800006 to N.A.)'.

References

Abe N, Okuda J, Suzuki M, Sasaki H, Matsuda T, Mori E, et al. Neural correlates of true memory, false memory, and deception. Cereb Cortex 2008; 18: 2811–9.

Abe N, Suzuki M, Mori E, Itoh M, Fujii T. Deceiving others: distinct neural responses of the prefrontal cortex and amygdala in simple fabrication and deception with social interactions. J Cogn Neurosci 2007; 19: 287–95.

Abe N, Suzuki M, Tsukiura T, Mori E, Yamaguchi K, Itoh M, et al. Dissociable roles of prefrontal and anterior cingulate cortices in deception. Cereb Cortex 2006; 16: 192–9.

Anderson SW, Tranel D. Neuropsychological consequences of dysfunction in human dorsolateral prefrontal cortex. Handbook of neuropsychology. 2nd edn. Vol. 7. Amsterdam: Elsevier; 2002. p. 145–56.

Badre D, Wagner AD. Selection, integration, and conflict monitoring; assessing the nature and generality of prefrontal cognitive control mechanisms. Neuron 2004; 41: 473–87.

Bhatt S, Mbwana J, Adeyemo A, Sawyer A, Hailu A, Vanmeter J. Lying about facial recognition: an fMRI study. Brain Cogn 2009; 69: 382–90.

Browndyke JN, Paskavitz J, Sweet LH, Cohen RA, Tucker KA, Welsh-Bohmer KA, et al. Neuroanatomical correlates of malingered memory impairment: event-related fMRI of deception on a recognition memory task. Brain Inj 2008; 22: 481–9.

Camp CD. Paralysis agitans, multiple sclerosis and their treatment. In: White WA, Jelliffe SE, Kimpton H, editors. Modern treatment of nervous and mental disease. Philadelphia: Lea & Febiger; 1913. p. 651–7.

Carbon M, Marie RM. Functional imaging of cognition in Parkinson's disease. Curr Opin Neurol 2003; 16: 475–80.

Carter CS, Macdonald AM, Botvinick M, Ross LL, Stenger VA, Noll D, et al. Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. Proc Natl Acad Sci USA 2000; 97: 1944–8.

Christ SE, Van Essen DC, Watson JM, Brubaker LE, McDermott KB. The contributions of prefrontal cortex and executive control to deception: evidence from activation likelihood estimate meta-analyses. Cereb Cortex (in press).

Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in Parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 2001; 11: 1136–43.

Cummings JL. Frontal-subcortical circuits and human behavior. Arch Neurol 1993; 50: 873–80.

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M. The neural basis of the central executive system of working memory. Nature 1995; 378: 279–81.

Davatzikos C, Ruparel K, Fan Y, Shen DG, Acharyya M, Loughead JW, et al. Classifying spatial patterns of brain activity with machine learning methods: application to lie detection. Neuroimage 2005; 28: 663–8.

Desgranges B, Baron JC, Lalevee C, Giffard B, Viader F, de La Sayette V, et al. The neural substrates of episodic memory impairment in Alzheimer's disease as revealed by FDG-PET: relationship to degree of deterioration. Brain 2002; 125: 1116–24.

Eustache F, Piolino P, Giffard B, Viader F, De La Sayette V, Baron JC, et al. 'In the course of time': a PET study of the cerebral substrates of autobiographical amnesia in Alzheimer's disease. Brain 2004; 127: 1549–60.

Fahn S, Elton R. Vol 2. Unified Parkinson's Disease Rating Scale. Fluhum Park, NJ: Macmillan Healthcare Information; 1987.

Fellows LK, Farah MJ. Is anterior cingulate cortex necessary for cognitive control? Brain 2005; 128: 788–96.

Frackowiak RS, Friston KJ, Frith CD, Dolan RJ, Mazziotta J, editors. Human brain function. San Diego: Academic Press; 1997.

Gamer M, Bauermann T, Stoeter P, Vossel G. Covariations among fMRI, skin conductance, and behavioral data during processing of concealed information. Hum Brain Mapp 2007; 28: 1287–301.

Ganis G, Kosslyn SM, Stose S, Thompson WL, Yurgelun-Todd DA. Neural correlates of different types of deception: an fMRI investigation. Cereb Cortex 2003; 13: 830–6.

Ganis G, Morris RR, Kosslyn SM. Neural processes underlying self- and other-related lies: an individual difference approach using fMRI. Soc Neurosci (in press).

Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1988; 51: 745–52.

Gotham AM, Brown RG, Marsden CD. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain 1988; 111: 299–321.

Hakun JG, Ruparel K, Seelig D, Busch E, Loughead JW, Gur RC, et al. Towards clinical trials of lie detection with fMRI. Soc Neurosci (in press).

Hakun JG, Seelig D, Ruparel K, Loughead JW, Busch E, Gur RC, et al. fMRI investigation of the cognitive structure of the Concealed Information Test. Neurocase 2008; 14: 59–67.

Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. Neurology 1967; 17: 427–42.

Ishihara L, Brayne C. What is the evidence for a premorbid parkinsonian personality: a systematic review. Mov Disord 2006; 21: 1066–72.

Kozel FA, Johnson KA, Grenesko EL, Laken SJ, Kose S, Lu X, et al. Functional MRI detection of deception after committing a mock sabotage crime. J Forensic Sci 2009; 54: 220–31.

Kozel FA, Johnson KA, Laken SJ, Grenesko EL, Smith JA, Walker J, et al. Can simultaneously acquired electrodermal activity improve accuracy of fMRI detection of deception? Soc Neurosci (in press).

Kozel FA, Johnson KA, Mu Q, Grenesko EL, Laken SJ, George MS. Detecting deception using functional magnetic resonance imaging. Biol Psychiatry 2005; 58: 605–13.

Kozel FA, Padgett TM, George MS. A replication study of the neural correlates of deception. Behav Neurosci 2004a; 118: 852–6.

Kozel FA, Revell LJ, Lorberbaum JP, Shastri A, Elhai JD, Horner MD, et al. A pilot study of functional magnetic resonance imaging brain correlates of deception in healthy young men. J Neuropsychiatry Clin Neurosci 2004b; 16: 295–305.

Langleben DD, Loughead JW, Bilker WB, Ruparel K, Childress AR, Busch SI, et al. Telling truth from lie in individual subjects with fast event-related fMRI. Hum Brain Mapp 2005; 26: 262–72.

Langleben DD, Schroeder L, Maldjian JA, Gur RC, McDonald S, Ragland JD, et al. Brain activity during simulated deception: an event-related functional magnetic resonance study. Neuroimage 2002; 15: 727–32.

Lee TM, Au RK, Liu HL, Ting KH, Huang CM, Chan CC. Are errors differentiable from deceptive responses when feigning memory impairment? An fMRI study. Brain Cogn 2009; 69: 406–12.

Lee TM, Liu HL, Chan CC, Ng YB, Fox PT, Gao JH. Neural correlates of feigned memory impairment. Neuroimage 2005; 28: 305–13.

Lee TM, Liu HL, Tan LH, Chan CC, Mahankali S, Feng CM, et al. Lie detection by functional magnetic resonance imaging. Hum Brain Mapp 2002; 15: 157–64.

Lewis SJ, Slabosz A, Robbins TW, Barker RA, Owen AM. Dopaminergic basis for deficits in working memory but not attentional set-shifting in Parkinson's disease. Neuropsychologia 2005; 43: 823–32.

Lissek S, Peters S, Fuchs N, Witthaus H, Nicolas V, Tegenthoff M, et al. Cooperation and deception recruit different subsets of the theory-of-mind network. PLoS ONE 2008; 3: e2023.

Lozza C, Baron JC, Eidelberg D, Mentis MJ, Carbon M, Marie RM. Executive processes in Parkinson's disease: FDG-PET and network analysis. Hum Brain Mapp 2004; 22: 236–45.

MacDonald AW 3rd, Cohen JD, Stenger VA, Carter CS. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science 2000; 288: 1835–8.

Magistretti PJ, Pellerin L, Rothman DL, Shulman RG. Energy on demand. Science 1999; 283: 496–7.

Mattay VS, Tessitore A, Callicott JH, Bertolino A, Goldberg TE, Chase TN, et al. Dopaminergic modulation of cortical function in patients with Parkinson's disease. Ann Neurol 2002; 51: 156–64.

McPherson S, Cummings JL. The frontal lobes and frontal-subcortical circuits in neuropsychiatric disorders. In: Grafman J, editor. Handbook of neuropsychology. 2nd edn. Amsterdam: Elsevier; 2002. p. 99–116.

Mendelsohn GA, Dakof GA, Skaff M. Personality change in Parkinson's disease patients: chronic disease and aging. J Pers 1995; 63: 233–57.

Mentis MJ, McIntosh AR, Perrine K, Dhawan V, Berlin B, Feigin A, et al. Relationships among the metabolic patterns that correlate with mnemonic, visuospatial, and mood symptoms in Parkinson's disease. Am J Psychiatry 2002; 159: 746–54.

Menza M. The personality associated with Parkinson's disease. Curr Psychiatry Rep 2000; 2: 421–6.

Mesulam MM. Behavioral neuroanatomy: large-scale networks, association cortex, frontal syndromes, the limbic system, and hemispheric specializations. In: Mesulam MM, editor. Principles of behavioral and cognitive neurology. New York: Oxford University Press; 2000. p. 1–120.

Mohamed FB, Faro SH, Gordon NJ, Platek SM, Ahmad H, Williams JM. Brain mapping of deception and truth telling about an ecologically valid situation: functional MR imaging and polygraph investigation–initial experience. Radiology 2006; 238: 679–88.

Monchi O, Petrides M, Doyon J, Postuma RB, Worsley K, Dagher A. Neural bases of set-shifting deficits in Parkinson's disease. J Neurosci 2004; 24: 702–10.

Monchi O, Petrides M, Mejia-Constain B, Strafella AP. Cortical activity in Parkinson's disease during executive processing depends on striatal involvement. Brain 2007; 130: 233–44.

Monteleone GT, Phan KL, Nusbaum HC, Fitzgerald D, Irick JS, Fienberg SE, et al. Detection of deception using fMRI: better than chance, but well below perfection. Soc Neurosci (in press).

Moustafa AA, Sherman SJ, Frank MJ. A dopaminergic basis for working memory, learning and attentional shifting in Parkinsonism. Neuropsychologia 2008; 46: 3144–56.

Nagano-Saito A, Leyton M, Monchi O, Goldberg YK, He Y, Dagher A. Dopamine depletion impairs frontostriatal functional connectivity during a set-shifting task. J Neurosci 2008; 28: 3697–706.

Nunez JM, Casey BJ, Egner T, Hare T, Hirsch J. Intentional false responding shares neural substrates with response conflict and cognitive control. Neuroimage 2005; 25: 267–77.

Owen AM. Cognitive dysfunction in Parkinson's disease: the role of frontostriatal circuitry. Neuroscientist 2004; 10: 525–37.

Parkinson J. An essay on the shaking palsy. London: Sherwood Neely & Jones; 1817.

Phan KL, Magalhaes A, Ziemlewicz TJ, Fitzgerald DA, Green C, Smith W. Neural correlates of telling lies: a functional magnetic resonance imaging study at 4 Tesla. Acad Radiol 2005; 12: 164–72.

Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. Ann Neurol 1979; 6: 371–88.

Pillon B, Boller F, Levy R, Dubois B. Cognitive deficits and dementia in Parkinson's disease. In: Boller F, Cappa SF, editors. Handbook of neuropsychology. 2nd edn. Vol. 6. Amsterdam: Elsevier; 2001. p. 311–71.

Piolino P, Chetelat G, Matuszewski V, Landeau B, Mezenge F, Viader F, et al. In search of autobiographical memories: a PET study in the frontal variant of frontotemporal dementia. Neuropsychologia 2007; 45: 2730–43.

Priori A, Mameli F, Cogiamanian F, Marceglia S, Tiriticco M, Mrakic-Sposta S, et al. Lie-specific involvement of dorsolateral prefrontal cortex in deception. Cereb Cortex 2008; 18: 451–5.

Ramnani N, Owen AM. Anterior prefrontal cortex: insights into function from anatomy and neuroimaging. Nat Rev Neurosci 2004; 5: 184–94.

Ravizza SM, Ciranni MA. Contributions of the prefrontal cortex and basal ganglia to set shifting. J Cogn Neurosci 2002; 14: 472–83.

Salmon E, Van der Linden M, Collette F, Delfiore G, Maquet P, Degueldre C, et al. Regional brain activity during working memory tasks. Brain 1996; 119: 1617–25.

Sawamoto N, Piccini P, Hotton G, Pavese N, Thielemans K, Brooks DJ. Cognitive deficits and striato-frontal dopamine release in Parkinson's disease. Brain 2008; 131: 1294–302.

Sip KE, Roepstorff A, McGregor W, Frith CD. Detecting deception: the scope and limits. Trends Cogn Sci 2008; 12: 48–53.

Spence SA, Farrow TF, Herford AE, Wilkinson ID, Zheng Y, Woodruff PW. Behavioural and functional anatomical correlates of deception in humans. Neuroreport 2001; 12: 2849–53.

Spence SA, Hunter MD, Farrow TF, Green RD, Leung DH, Hughes CJ, et al. A cognitive neurobiological account of deception: evidence from functional neuroimaging. Philos Trans R Soc Lond B Biol Sci 2004; 359: 1755–62.

Spence SA, Kaylor-Hughes CJ. Looking for truth and finding lies: the prospects for a nascent neuroimaging of deception. Neurocase 2008; 14: 68–81.

Spence SA, Kaylor-Hughes C, Farrow TF, Wilkinson ID. Speaking of secrets and lies: the contribution of ventrolateral prefrontal cortex to vocal deception. Neuroimage 2008; 40: 1411–18.

Swick D, Jovanovic J. Anterior cingulate cortex and the Stroop task: neuropsychological evidence for topographic specificity. Neuropsychologia 2002; 40: 1240–53.

Zgaljardic DJ, Borod JC, Foldi NS, Mattis P. A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. Cogn Behav Neurol 2003; 16: 193–210.

Zgaljardic DJ, Borod JC, Foldi NS, Mattis PJ, Gordon MF, Feigin A, et al. An examination of executive dysfunction associated with frontostriatal circuitry in Parkinson's disease. J Clin Exp Neuropsychol 2006; 28: 1127–44.

Original Research Article

Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 269972
DOI: 10.1159/000269972

Accepted: November 17, 2009
Published online: ■■■

Transition of Distinctive Symptoms of Semantic Dementia during Longitudinal Clinical Observation

Tetsuo Kashibayashi[a] Manabu Ikeda[b] Kenjiro Komori[a] Shunichiro Shinagawa[c] Hideaki Shimizu[a] Yasutaka Toyota[a] Takaaki Mori[a] Tomohisa Ishikawa[a] Ryuji Fukuhara[a] Shu-ichi Ueno[a] Satoshi Tanimukai[a]

[a]Department of Neuropsychiatry, Neuroscience, Ehime University Graduate School of Medicine, Toon, [b]Department of Psychiatry and Neuropathobiology, Faculty of Medical and Pharmaceutical Science, Kumamoto University, Kumamoto, and [c]Department of Psychiatry, Jikei University School of Medicine, Tokyo, Japan

Key Words
Behavioral symptoms · Cognitive decline · Frontotemporal lobar degeneration · Semantic dementia

Abstract
Background/Aims: The aim of this study is to examine the clinical symptoms in a number of semantic dementia (SD) patients and to reveal the longitudinal progression and clinical course of these distinctive symptoms of SD. ***Methods:*** 19 consecutive SD patients were examined. Symptoms were classified into 23 distinct categories: behavioral symptoms, language and cognitive symptoms and symptoms concerning the impairment of activities of daily living (ADL). We divided patients into two subgroups, left- and right-dominant SD, and compared the onset of each symptom. ***Results:*** Language impairments occurred as the initial symptom in 16 cases. At the first examination, all cases showed both anomia and impairment of word comprehension. By around 3 years after onset, almost all language impairments were observed. Approximately 3–5 years after onset, prosopagnosia and behavioral symptoms appeared. Around the period when the loss of the language faculty and apathy became remarkable, impairment of ADL appeared. Patients spent all day in bed at this stage. Moreover, prosopagnosia appeared significantly earlier in right-dominant SD. ***Conclusion:*** Our findings clarify the progression of distinctive symptoms of SD patients. It is necessary to create a treatment strategy for SD patients with such a disease-specific course of SD.

Introduction

Semantic dementia (SD) is a group of disorders included in a family of disorders called frontotemporal lobar degeneration (FTLD) [1]. Patients with SD present with selective and progressive loss of semantic memory associated with focal atrophy of the anterior temporal lobes [2–4]. Their most prominent feature is a profound breakdown in semantic memory, such as that associated with the naming and conceptual knowledge of objects. SD patients present with severe anomia, impairment in the production and recognition of single words, and surface dyslexia, a condition in which the patient has difficulty reading words with irregular pronunciations. These language

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1420–8008/10/0000–0000$26.00/0

Accessible online at:
www.karger.com/dem

Satoshi Tanimukai
Department of Neuropsychiatry, Neuroscience
Ehime University Graduate School of Medicine
Shitsukawa, Toon-City 791-0295 (Japan)
Tel. +81 89 960 5315, Fax +81 89 960 5317, E-Mail satanimu@m.ehime-u.ac.jp

symptoms are known more generally as 'Gogi (word meaning) aphasia' in Japan [5–8]. There also exist several case reports on patients presenting with prosopagnosia, i.e. deficits in recognizing faces of familiar persons [9–11]. Those patients demonstrated greater atrophy on the right temporal lobe, while language symptoms were typically observed in the cases with left temporal lobe atrophy.

In addition to these cognitive and language impairments, the decrease in the control exerted by the frontal lobe cortex and posterior cortical hyperactivity leads to marked changes in personality and behavior, such as disinhibition, stimulus-bound behavior and stereotypic behavior [12–14] similar to patients with frontotemporal dementia. Behavioral and psychological symptoms in dementia (BPSD) lead to early hospitalization and admittance into skilled nursing facilities; this adversely affects the quality of life of the patients and caregivers. Therefore, it is necessary to provide appropriate treatment and care for BPSD. A few pharmacological or nonpharmacological treatments aimed at reducing BPSD in FTLD [12, 15–17] have been attempted, but appropriate treatment for each stage of SD has not been developed yet.

Investigation into the unique clinical symptoms of SD over a period of several years provides an important way to determine the appropriate treatment and care for each stage of SD and to improve the prognosis for SD patients as much as possible.

Therefore, we examined the onset of these clinical symptoms in a number of SD patients based on longitudinal clinical observations. The aim of this study is to clarify the time points at which distinctive symptoms appear during the clinical course of SD, in order to create appropriate treatment strategies for each stage of SD.

Materials and Methods

Patients

Patients were recruited from a total of 1,045 consecutive patients in the Higher Brain Function Clinic of the Department of Neuropsychiatry at Ehime University Hospital between January 1997 and June 2007, and were examined by senior neuropsychiatrists. All patients underwent physical and neurological examinations, laboratory blood tests including those for vitamin B_1, B_{12}, folic acid and thyroid function, magnetic resonance imaging (MRI) or computed tomography (CT) of the brain, and HMPAO-SPECT. A standard psychiatric evaluation was used to exclude patients with major functional psychiatric disorders such as schizophrenia and mood disorders.

Patients were assessed with a comprehensive battery of neuropsychiatric and neuropsychological tests, including the Mini-Mental State Examination (MMSE) [18], the Short-Memory Questionnaire (SMQ) [19, 20], Raven's Colored Progressive Matrices (RCPM) [21] and the Neuropsychiatric Inventory (NPI) [22, 23]. Activities of daily living (ADL) were evaluated by the Physical Self-Maintenance Scale and the Instrumental Activities of Daily Living Scale [24]. Language function was evaluated by a semantic test battery [25]. The semantic test battery was comprised of the Japanese Standard Language Test of Aphasia consisting of 26 subtests, each assigned to 1 of 5 linguistic functions (listening, speaking, reading, writing, and calculating) [26], and Object Naming from 80 line drawings of common everyday objects and 10 colors, as well as Word-Picture Matching with spoken word targets and 10 line drawing choices: the target plus 9 within-category distracters using the same 90 items as in the naming test [27].

Among all of the patients, 64 patients were diagnosed with FTLD, and 23 patients were diagnosed with SD according to consensus criteria [1]. Four patients were excluded because we could not follow up on these cases for 1 year, so 19 patients remained. This study was conducted with the informed consent of all patients or their caregivers.

Selection of Clinical Symptoms

After reviewing the existing literature on the subject and identifying frequently cited symptoms, 9 behavioral symptoms and 6 cognitive symptoms were selected based on the clinical criteria for FTLD. In addition, 8 symptoms associated with ADL were selected on the basis of the subcategories of the Instrumental Activities of Daily Living Scale, Physical Self-Maintenance Scale and earlier studies [1, 3, 17, 28–30]. We evaluated clinical symptoms of SD using these 23 symptoms divided into 3 categories.

Language and Cognitive Symptoms

Language symptoms examined included anomia, impairment of word comprehension, reading or writing difficulties, paraphasia, and mutism. The first episode of each symptom was counted mainly based on patient history information obtained from the patients or their caregiver, and confirmed by the semantic test battery. Sometimes the semantic test battery disclosed certain symptoms for the first time. Late-stage symptoms, for example mutism, were scored on the basis of a direct examination or an interview with the caregivers. The cognitive symptom closely associated with semantic impairment in recognizing faces of familiar persons is treated as prosopagnosia (inability to recognize relatives' and acquaintances' faces). We conducted the test to identify photographs of relatives' faces if any information was obtained from the patient or informant concerning difficulty identifying a familiar person from his or her face. The patients were defined as having prosopagnosia when they could not identify themselves and/or their family from the photograph.

Behavioral Symptoms

The behavioral symptoms examined included loss of social awareness (lack of empathy, acting without regard for others' opinions), loss of personal awareness (difficulty applying makeup or washing one's own hair, no interest in one's own clothes), disinhibition (tendency to lick dishes, inability to wait one's turn, talking to others at inappropriate times), apathy or social withdrawal of spontaneity (ceasing to pursue hobbies), stereotypic behavior (tendency to always walk the same route or buy the same products), mental rigidity and inflexibility (lack of flexibility about time, money management or abdominal symptoms), irrita-

Table 1. Demographic variables of patients

Sex (M:F)	7:12
Age at consultation, years	65.5 ± 9.1 (53–83)
Untreated duration, years	2.8 ± 1.4 (0.3–6.4)
MMSE score (max. 30)	20.1 ± 7.7
NPI score (max. 120)	13.2 ± 15.3
RCPM score (max. 36)	30.5 ± 4.3
SMQ score (max. 46)	29.0 ± 7.8
Follow-up duration after consultation, years	4.3 ± 1.9 (1.5–7.4)

Data are given as the number of patients or mean ± SD. Figures in parentheses indicate ranges.

bility or aggression (tendency to become angry or complain when unable to communicate), changes in food preferences (tendency to prefer sweet foods) and increase in appetite. Most of these behavioral symptoms were revealed by an interview with caregivers at every examination reported as a troublesome event that occurred in daily life. Some of them were already found in the patient history information at the first examination. A few of them were disclosed at the time of administering the NPI and neurological examination.

ADL and Other Symptoms

Impairments in ADL examined included incontinence, dressing disorder, need for regular help to eat, tendency to spend all day in bed, decrease in efficiency (work or housework), ceasing to perform work or housework, getting lost and decline in daily activities. Dressing disorder is a condition where patients need help changing their clothes. These ADL symptoms were all reported in an interview with caregivers.

Interview Methods

Disease onset was defined as the time of the appearance of each initial symptom among 23 symptoms. It was emphasized that the initial symptom should be the first change the caregiver noticed and should reflect a substantive change from the patient's premorbid state, rather than a longstanding character trait. The untreated duration was defined as the time period from the disease onset to the first examination. Symptoms that appeared during the untreated duration were reported by the caregiver and were carefully confirmed by a senior neuropsychiatrist. For example, if a caregiver mentioned that the patient had begun to say the same phrases repeatedly, further clarification was sought to ascertain whether this represented repetitive questioning in the context of a memory disorder versus stereotypic catch phrase usage. In addition, if a caregiver or patient complained of memory disturbances, the symptom was carefully scrutinized to determine whether or not it involved word finding difficulties. During the follow-up duration, the examinations and interviews were performed every month or every 2 weeks by a senior neuropsychiatrist, and the appearance of each of the 23 symptoms was described. In 1 case (case 17), however, the caregiver had visited our hospital alone every 2 months for the last 3 years because of her strong refusal to attend the clinic after deprivation of her driving opportunity.

We determined the duration from the disease onset to the time of the occurrence of each symptom and calculated the mean values and standard error of these durations. Observations for this study were performed over the period from January 1997 to May 2008. Nineteen patients were classified into two subgroups, left- or right-dominant cases, based on the predominance of temporal lobe atrophy observed on the CT or MRI and the predominance of temporal lobe cerebral blood flow (CBF) hypoperfusion on HMPAO-SPECT. We compared the mean intervals from disease onset for 14 language, cognitive, and behavioral symptoms between the predominant left temporal lobe atrophy (left-dominant) and the predominant right temporal lobe atrophy (right-dominant).

Statistical Analyses

SPSS version 15.0 was used for statistical calculations. Mann-Whitney U tests were employed to determine the significance of the difference between the mean values for the left-dominant and right-dominant subgroups of SD patients.

Results

Patient Profiles

The demographics of the 19 cases, including sex, age at consultation, the untreated duration, MMSE score, SMQ score, RCPM score and NPI score, are summarized in table 1. The mean follow-up duration was 4.7 years (min. 1.5, max. 7.4). The mean total follow-up period from the onset of initial symptoms to the last follow-up examination was 7.1 years (min. 1.8, max. 11.2). Table 2 shows the data obtained at the first examination of each patient including sex, age at consultation, the untreated duration, MMSE score, SMQ score, NPI score and RCPM score, in addition to the follow-up duration and the outcome of the last examination.

All cases showed focal atrophy of the anterior temporal lobe on a CT or MRI in addition to either predominantly left or right temporal lobe CBF hypoperfusion on HMPAO-SPECT. There was no case whose CBF hypoperfusion was restricted to one side only. Fourteen cases had left-dominant SD while 5 cases had right-dominant SD. The mean duration of the follow-up periods from the first examination and the total follow-up period for each case are shown in table 2.

Clinical Symptoms

Among the 19 cases, language impairments occurred as the initial symptom in 16 cases. By the time of the first examination, some language impairments including anomia, impaired word comprehension, reduction of speech and paraphasia had already appeared. Among language impairments, anomia was the earliest symptom and was observed an average of 1.3 years after disease on-

Table 2. Demographics, neuropsychological test results at first examination and follow-up duration

Case No.	Sex	Education years	Dominancy	Age years	MMSE total (max. 30)	RCPM (max. 36)	Picture naming (max. 90)	Picture matching (max. 90)	SMQ (max. 46)	NPI (max. 120)	Untreated duration years	Follow-up duration years	Total follow-up duration, years	Course
1	M	16	left	57.4	26	35	30	74	30	8	3.4	7.4	10.8	under course
2	M	12	left	57.6	28	34	49	78	42	4	1.6	6.7	8.3	under course
3	F	9	left	58.5	6	28	17	28	23	36	4.5	5.5	10.0	under course
4	F	8	left	81.4	16	29	27	37	28	1	6.4	4.8	11.2	under course
5	M	9	left	76.9	25	28	33	65	26	45	3.9	4.5	8.5	hospitalization
6	M	16	left	58.8	23	33	53	77	37	11	1.8	4.3	6.1	under course
7	F	12	left	67.6	28	33	43	64	32	49	3.6	3.7	7.2	under course
8	M	13	left	56.6	18	36	17	58	17		2.7	3.3	5.9	hospitalization
9	F	9	left	70.7	20	31	32	51	32	5	4.7	3.3	8.1	under course
10	F	9	left	56.0	8	27	36	64	34	0	1.4	3.1	4.5	under course
11	M	12	left	56.7	27	35	29	74	32	0	1.7	2.6	4.3	under course
12	F	9	left	65.2	5	30	10	27	20	8	3.8	2.5	6.3	nursing facility
13	M	15	left	78.2	28	30	64	80	35	0	2.2	2.0	4.3	under course
14	F	10	left	82.8	12	26	30	68	12	0	0.3	1.5	1.8	under course
15	M	9	right	52.5	21	34	39	64	19	6	2.0	7.4	9.4	death
16	F	12	right	64.4	28	34	67	82	35	15	1.2	6.8	8.0	under course
17	F	12	right	65.4	27	28	43	58	40	4	2.8	6.4	9.2	under course
18	F	9	right	63.9	23	17	52	60	31	19	2.2	3.1	5.3	under course
19	F	11	right	73.8	13	32	21	45	26	26	3.2	2.1	5.3	nursing facility

Individual data for patients with left-dominant atrophy (n = 14) and right-dominant atrophy (n = 5). CDR = Clinical dementia rating; untreated duration = the duration from onset to first consult; total follow-up duration = untreated duration + follow-up duration; F = female; M = male.

set. The next symptom to appear was impaired word comprehension which presented at an average of 2.1 years after disease onset. Afterwards, paraphasia and reading and writing difficulties appeared at an average of 2.5 and 2.6 years, respectively, after disease onset. In 15 of the 19 cases, prosopagnosia appeared at an average of 3.3 years after disease onset. At the first examination, 11 cases complained of memory disturbances. We confirmed that these symptoms were the result of difficulty in recognition, difficulty in recall of words and deficits in face recognition. Four patients developed mutism at an average of 7.1 years after onset (min. 5.6, max. 8.9).

Approximately 3–5 years after onset, behavioral and psychiatric symptoms including stereotypic behavior, disinhibition, mental rigidity, inflexibility or aggression, loss of personal awareness, loss of social awareness and apathy appeared, and patients had difficulty with their work or housework. Among the behavioral symptoms, stereotypic behavior was the earliest symptom to appear. It appeared an average of 3.1 years (min. 1.2, max. 5.5) after disease onset and was present in 18 cases. The only patient who did not show stereotypic behavior had a total follow-up period of only 1.8 years. All patients presented with changes in food preferences and the mean duration from the occurrence of this symptom to disease onset was 3.5 years (min. 0.7, max. 7.0), followed by an appetite increase at an average of 5.1 years (min. 2.2, max. 7.5) after disease onset (table 3; fig. 1).

During clinical observation, 14 cases showed a decline in daily activities at an average of 5.4 years (min. 3.1, max. 9.4), 4 cases showed a tendency to get lost at an average of 5.6 years (min. 4.7, max. 8.0), and 4 cases began to need regular help to eat at an average of 6.6 years (min. 5.0, max. 8.0) after disease onset. Eight cases presented with incontinence at an average of 7.0 years (min. 4.5, max. 10.4) after onset and 6 cases presented with dressing disorder at an average of 7.1 years (min. 5.0, max. 9.4) after onset. Eight cases began to show a tendency to sleep all day in bed at an average of 7.4 years (min. 4.7, max. 10.9) after onset (table 3; fig. 1).

Among all of the patients, 6 cases have already finished the longitudinal follow-up program. One patient died of hepatocellular carcinoma 9.4 years after the onset of SD. Two patients were admitted to hospitals for physical diseases 8.5 and 5.9 years after the onset of SD. The other 2 patients were admitted to nursing facilities 6.3 and 5.3 years after disease onset. One case dropped out of the study as a result of the caregiver's decision 5.3 years after onset. The other 13 cases were followed to the end of this study (table 2).

Table 3. The number of patients and the duration from disease onset to the occurrence of each symptom

Symptom	n	Mean duration
Anomia	19	1.3 (0.4)
Impaired word recognition	19	2.1 (0.4)
Paraphasia	16	2.5 (0.4)
Reading or writing difficulties	18	2.6 (0.4)
Stereotypic behavior	18	3.1 (0.3)
Prosopagnosia	15	3.3 (0.6)
Changing food preferences	19	3.5 (0.3)
Disinhibition	18	3.6 (0.4)
Decrease in efficiency (work or housework)	15	3.8 (0.5)
Mental rigidity and inflexibility	15	3.9 (0.5)
Irritability or aggression	17	3.9 (0.4)
Loss of personal awareness	12	4.1 (0.4)
Loss of social awareness	14	4.2 (0.4)
Apathy	15	4.3 (0.5)
Increase in appetite	13	5.1 (0.4)
Retirement (work or housework)	14	5.1 (0.6)
Decline in daily activities	14	5.2 (0.6)
Getting lost	4	5.4 (1.1)
Regular help to eat	4	6.6 (0.7)
Incontinence	8	7.0 (0.8)
Mutism	4	7.1 (0.8)
Dressing impairment	6	7.1 (0.7)
Spends all day in bed	8	7.4 (0.8)

Observations are ranked according to the length of the mean duration in decreasing order. Figures in parentheses indicate SE.

Table 4 shows data comparing left-dominant SD and right-dominant SD. There were no significant differences between the two groups in age, untreated duration, MMSE scores, SMQ scores, NPI scores, RCPM scores and the length of time from disease onset to the occurrence of language symptoms. Prosopagnosia, irritability, or aggression appeared significantly earlier in right-dominant SD. Mutism and ADL symptoms were not compared because few patients revealed these symptoms.

Discussion

In this study, we revealed the onset period of each distinctive symptom of SD by analyzing longitudinal clinical observations. Cross-sectional studies have been able to confirm the prevalence of each symptom, but have not determined the onset period and development order of each symptom. We clarified the common course of SD in several patients. SD patients initially showed cognitive impairment manifested as characteristic language symptoms, followed by gradual but profound personality and behavioral changes. This accompanied the progression of severe semantic memory impairment, and finally impairment of the ADL with a loss of language function and a remarkable decrease in spontaneity. SD patients who present with cognitive impairment as an early symptom

Table 4. The duration from disease onset to the occurrence of each symptom in left- and right-dominant SD

	Left-dominant SD		Right-dominant SD	
	n	mean duration	n	mean duration
Anomia	14	1.4 (0.5)	5	1.0 (0.6)
Impaired word recognition	14	2.0 (0.5)	5	2.4 (0.3)
Paraphasia	13	2.5 (0.5)	3	2.4 (0.6)
Reading or writing difficulties	13	2.8 (0.5)	5	2.2 (0.4)
Stereotypic behavior	13	3.3 (0.4)	5	2.5 (0.2)
Prosopagnosia**	10	4.5 (0.6)	5	0.9 (0.4)
Changing food preferences	14	3.5 (0.4)	5	3.8 (0.6)
Disinhibition	13	3.8 (0.4)	5	3.0 (0.8)
Mental rigidity and inflexibility	10	4.1 (0.6)	5	3.3 (0.2)
Irritability or aggression*	12	4.4 (0.6)	5	2.9 (0.5)
Loss of personal awareness	8	4.6 (0.4)	4	3.1 (0.3)
Loss of social awareness	11	4.1 (0.4)	3	4.6 (0.6)
Apathy	11	4.4 (0.6)	4	4.2 (1.0)
Increase in appetite	11	5.2 (0.5)	3	4.8 (0.8)

* $p < 0.05$; ** $p < 0.01$. Figures in parentheses indicate SE.

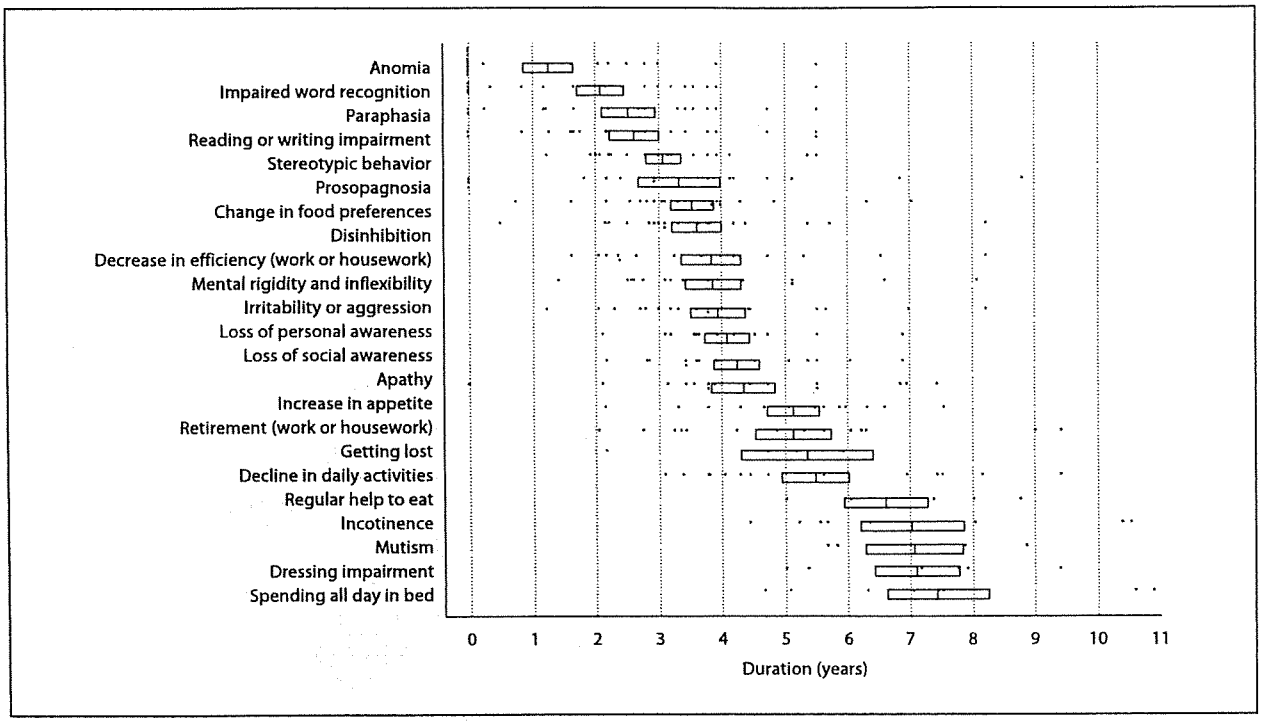

Fig. 1. The duration from disease onset to the occurrence of each clinical symptom in SD. The bars indicate the mean ± SE of the duration from disease onset to the occurrence of each symptom. Each dot shows the onset point of each symptom.

are often misdiagnosed with AD and given inappropriate treatment. For example, donepezil used in treating AD was actually found to worsen behavioral symptoms in patients with FTLD [31]. Consequently, they developed BPSD and their ADL were impaired, increasing the caregiver's burden. Information about the onset period of each symptom is important in enabling accurate diagnosis in the early stages of the disease and in determining appropriate treatment for behavioral problems in the later stages.

Language and cognitive symptoms appeared in all cases as manifestations of semantic memory impairment, and also appeared earlier than behavioral symptoms or ADL impairment. The initial symptoms of the SD patients were anomia, paraphasia and impairment of the ability to understand word meaning. Prosopagnosia seems to be a common symptom in SD patients. This symptom appeared at an average of 3.3 years after onset, later than language symptoms, and at a point when semantic memory impairment had progressed. Most cases presented with this symptom along with many behavioral symptoms. As we will describe later, it is important to note the time at which some symptoms appear because of differences in onset related to atrophic laterality.

Three to five years after onset, behavioral symptoms involving both increases and decreases in activity appeared. Symptoms involving increases in activity included disinhibition, stereotypic behavior, inflexibility, irritability and aggression. Symptoms involving decreases in activity included apathy and loss of personal awareness. Almost all cases presented with stereotypic behavior which was also the earliest behavioral symptom to appear. As a result of the progression of semantic memory impairment, the patients' range of interests narrowed and repetitive behavior became simpler and remarkable. Irritability or aggression seemed to develop when the repetitive behavior was prevented [32]. Some studies have reported that SD patients present with behavioral symptoms in the early stages [32, 33], but the precise time at which each symptom appeared was not described in detail. We revealed that behavioral symptoms appeared later than language symptoms.

In our study, we confirmed the hypothesis for abnormal eating behaviors in SD proposed in a cross-sectional study [34] reporting that first changes in food preferences occur, followed by increases in appetite. An increase in appetite and a decline in daily activities require appropriate treatment because these changes can lead to other health issues like an increase in body weight or diabetes. Of 4 cases who began to need regular help to eat, 3 patients were admitted to a hospital and 1 patient entered a group home. These 4 patients presented an increase in appetite at the early stage, and later became indifferent to eating, never to eat on their own initiatives.

In addition, a decrease in the efficiency of work or housework was noted during the period 3–5 years after onset. At more than 5 years after onset, many patients retired from their work. Among the 14 cases who retired from their work, 7 patients retired from their outside duty at an average of 3.8 years (min. 2.0, max. 6.1) after disease onset and 7 patients retired from their simple housekeeping at an average of 6.5 years (min. 3.4, max. 9.4). The occupation which could be continued considerably longer than other outside duty was simple agriculture (6.1 years after onset). Close support from their family might allow these patients a relatively long-term engagement with agriculture or housekeeping. In this advanced stage, semantic memory impairment progressed further, communication using language became difficult, and mutism appeared in 4 cases at an average of 7.1 years after onset. In this period, ADL disturbances such as requiring regular help to eat, incontinence, and dressing impairment appeared. Among 6 cases who presented with dressing impairment, 3 patients were admitted to a hospital, 2 patients entered a group home and 1 patient lived at home.

In our study, there were no significant differences in the time appearance of the language symptoms appearing in left- and right-dominant cases at an early stage. However, prosopagnosia was observed significantly earlier in right-dominant cases than in left-dominant cases, and among 5 cases with right-dominant atrophy, 2 cases presented with prosopagnosia before language symptoms. Alternatively, among 14 cases with left-dominant atrophy, 10 cases presented with prosopagnosia at an average of 4.5 years after onset, around the time when behavioral symptoms appeared. As reported in a previous study, left-dominant cases did not present with behavioral symptoms in the early stage, while right-dominant cases presented with irritability or aggression significantly earlier than left-dominant cases [35]. These results suggest that the left and right temporal lobes might have different functions in semantic memory and that visual perception associated with semantics such as prosopagnosia, as well as mood instability are mainly associated with the right temporal lobe. However, we do not think that the left and right temporal lobes take completely independent roles and create completely different clinical concepts. Instead, we suggest that these differences between left- and right-dominant cases are the result of the gradual collapse of central semantic memory, which involves both the left and right temporal lobes, in the early stage of SD [36, 37]. In our longitudinal study, not only language impairment and prosopagnosia but also behavioral symptoms appeared in almost all cases regardless of whether atrophy occurred predominantly in the left or right temporal lobe. Previous studies emphasizing the difference between left- and right-dominant SD might probably have missed the opportunity for longitudinal observation of those patients. Statistical comparisons of the differences in impairment of ADL between left- and right-dominant cases were difficult to perform in this study. Few right-dominant cases were followed until the appearance of ADL impairment, so in further studies, it is necessary to observe more right-dominant cases.

Following selective cognitive impairments, SD patients presented with remarkable behavioral and personality changes such as stereotypic behavior, mental rigidity, apathy and social withdrawal of spontaneity. These symptoms also lead to tendencies to be persistent with some habits and reject other behaviors, tendencies which are difficult to modify. Since BPSD associated with these symptoms increase the caregivers' burden, some type of intervention is necessary. In a previous study, pharmacological treatment was attempted to treat the stereotypic behavior of SD patients in the early stage [16]. These treatments may contribute to the ease of long-term home care. It is also important to provide the patient's health care environment before the appearance of BPSD so that interventions can be carried out promptly if necessary. Therefore, we recommend a combination of pharmacotherapy using SSRIs and nonpharmacologic management such as behavior modification and environmental manipulation, which can enable caregivers to decrease their burden and maintain the long-term care at home [17, 38]. Moreover, the introduction of rehabilitation programs, which works with preserved cognitive functions and motivates the patient to continue treatment after the early stage, is an important way to ensure the quality of the treatment in the advanced stages [28, 39]. Continuing language rehabilitation exercises and jigsaw puzzle activities introduced in the early stage can decrease the burden of BPSD [12, 40–42]. For these interventions to be effec-

tive, early and accurate diagnosis is needed. At more than 5 years after onset, several patients require specialized care for ADL disturbances, including eating disturbances, dressing impairments and incontinence. In our study, patients were still capable of physical functions such as standing and walking in almost all cases in this advanced stage. Therefore, the ADL disturbances observed in SD patients might be caused by severe loss of semantic memory and decreasing spontaneity; appropriate treatment can enable caregivers to maintain the long-term care at home. In this study, 3 patients were followed for over 10 years. Their total follow-up periods were 11.2, 10.8 and 10.0 years. Among these 3 patients, 2 patients live at home and still visit our hospital regularly.

There are a few methodological issues that should be taken into consideration to fully appreciate our results. As this study is based on the retrospective recall of caregivers, it is possible that the informants' memories may be inaccurate [43]. For example, in some cases we could not confirm anomia during the early stage despite detailed accounts from the caregivers. In those cases, paraphasia or impairment in word comprehension was reported as an initial symptom. We believe that anomia is often an initial symptom of SD. However, a medical history obtained through a clinical interview is the common way of diagnosing dementia, so any possible bias introduced by the current methods is likely to be similar to that in routine clinical practice. Secondly, we investigated the symptoms of each case for as long as possible in our study, and as a result, the follow-up durations were different for each subject. We found the mean duration from the onset of SD to the occurrence of each symptom by only using data from the cases which presented with each symptom. To confirm the prevalence of each symptom, cross-sectional studies with larger cohorts are needed.

Our findings clarify the progression of distinctive symptoms that have previously been unclear and also suggest clinical characteristics of SD. In addition, our study can serve as a guide for establishing staging measures for SD and the longitudinal clinical observations performed in our study may support the recently reported FTLD clinical dementia rating (CDR) [44]. We think that because SD patients initially show language symptoms followed by gradual but remarkable personality and behavioral changes, the two new rating domains included in the FTLD CDR, language and behavior, and comportment and personality, reflect the severity of SD more precisely than the original CDR [45]. Because the various approaches to treatment for FTLD are rapidly evolving [17, 38, 46] and FTLD, including SD, is a progressive disease, understanding the clinical characteristics of SD is important to ensure appropriate treatment and care during each stage of SD. Moreover, by investigating the clinical course found in this study in combination with brain imaging, it may be possible to clarify the regions responsible for each symptom. Also, it may be useful to investigate the clinico-anatomical basis of each symptom of SD by correlating the results of this study with the functional imaging or the statistical image analysis of the brain.

Acknowledgements

We wish to thank the late Professor Hirotaka Tanabe for his instruction. Without it this study could not have been undertaken. The present study was undertaken with the support of grants provided by the Ministry of Education, Culture, Sports, Science and Technology for M.I. (Grant No. 20591414) and for K.K. (Grant No. 21500260) and the Ministry of Health, Labor and Welfare (research on dementia) for M.I. and R.F.

References

1 Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF: Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998;51:1546–1554.

2 Snowden JS, Goulding PJ, Neary D: Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 1989;2:167–182.

3 Hodges JR, Patterson K, Oxbury S, Funnell E: Semantic dementia. Progressive fluent aphasia with temporal lobe atrophy. Brain 1992;115:1783–1806.

4 Lladó A, Sánchez-Valle R, Rey MJ, Ezquerra M, Tolosa E, Ferrer I, Molinuevo JL: Clinicopathological and genetic correlates of frontotemporal lobar degeneration and corticobasal degeneration. J Neurol 2008;255:488–494.

5 Imura T: Aphasia: characteristic syndrome in Japanese language. Psychiatr Neurol Jpn 1943;47:196–218.

6 Sasanuma S, Monoi H: The syndrome of Gogi (word meaning). Selective impairment of kanji processing. Neurology 1975;25:627–632.

7 Tanabe H, Ikeda M, Nakagawa Y, Yamamoto H, Ikejiri Y, Kazui H, Hashikawa K, Harada K: Gogi (word meaning) aphasia and semantic memory for words (in Japanese). Higher Brain Function Res 1992;12:153–167.

8 Tanabe H, Nakagawa Y, Ikeda M, Hashimoto M, Yamada N, Kazui H, Nishikawa T, Okuda J: Selective loss of semantic memory for words; in Ishikawa K, McGaugh JL, Sakata H (eds): Brain Processes and Memory. Amsterdam, Elsevier Science, 1996, pp 141–152.

9 Tyrrell PJ, Warrington EK, Frackowiak RS, Rossor MN: Progressive degeneration of the right temporal lobe studied with positron emission tomography. J Neurol Neurosurg Psychiatry 1990;53:1046–1050.

10 Evans JJ, Heggs AJ, Antoun N, Hodges JR: Progressive prosopagnosia associated with selective right temporal lobe atrophy. A new syndrome? Brain 1995;118:1–13.
11 Gainotti G, Barbier A, Marra C: Slowly progressive defect in recognition of familiar people in a patient with right anterior temporal atrophy. Brain 2003;126:792–803.
12 Tanabe H, Ikeda M, Komori K: Behavioral symptomatology and care of patients with frontotemporal lobe degeneration – based on the aspects of the phylogenetic and ontogenetic processes. Dement Geriatr Cogn Disord 1999;10:50–54.
13 Shigenobu K, Ikeda M, Fukuhara R, Maki N, Hokoishi K, Nebu A, Yasuoka T, Komori K, Tanabe H: The Stereotypy Rating Inventory for frontotemporal lobar degeneration. Psychiatry Res 2002;110:175–187.
14 Rosen HJ, Allison SC, Ogar JM, Amici S, Rose K, Dronkers N, Miller BL, Gorno-Tempini ML: Behavioral features in semantic dementia vs other forms of progressive aphasias. Neurology 2006;67:1752–1756.
15 Swartz JR, Miller BL, Lesser IM, Darby AL: Frontotemporal dementia: treatment response to serotonin selective reuptake inhibitors. J Clin Psychiatry 1997;58:212–216.
16 Ikeda M, Shigenobu K, Fukuhara R, Hokoishi K, Maki N, Nebu A, Komori K, Tanabe H: Efficacy of fluvoxamine as a treatment for behavioral symptoms in frontotemporal lobar degeneration patients. Dement Geriatr Cogn Disord 2004;17:117–121.
17 Ikeda M: Frontotemporal dementia; in Ritchie CW, Ames D, Master CL, Cummings J (eds): Therapeutic Strategies in Dementia. Oxford, Oxford University Press, 2006, pp 287–299.
18 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr 1975;12:189–198.
19 Koss E, Patterson MB, Ownby R, Stuckey JC, Whitehouse PJ: Memory evaluation in Alzheimer's disease. Caregivers' appraisals and objective testing. Arch Neurol 1993;50:92–97.
20 Maki N, Ikeda M, Hokoishi K, Nomura M, Torikawa S, Fujimoto N, Komori K, Hirono N, Tanabe H: Interrater reliability of the short-memory questionnaire in a variety of health professional representatives. Int J Geriatr Psychiatry 2000;15:373–375.
21 Raven JC, Court JH, Raven J: Manual for Raven's Coloured Progressive Matrices. Oxford, Oxfords Psychologists Press, 1990.
22 Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J: The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–2314.
23 Hirono N, Mori E, Ikejiri Y, Imamura T, Shimomura T, Hashimoto M, Yamashita H, Ikeda M: Japanese version of the Neuropsychiatric Inventory – a scoring system for neuropsychiatric disturbance in dementia patients (in Japanese). No To Shinkei 1997; 49:266–271.
24 Lawton MP, Brody EM: Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist 1969; 9:179–186.
25 Fushimi T, Komori K, Ikeda M, Patterson K, Ijuin M, Tanabe H: Surface dyslexia in a Japanese patient with semantic dementia: evidence for similarity-based orthography-to-phonology translation. Neuropsychologia 2003;41:1644–1658.
26 SLTA Committee: Standard Language Test of Aphasia Manual. Tokyo, Shinkou Igaku Shuppan-sha, 1997.
27 Ito K, Nakagawa Y, Ikeda M, Yamada N, Hashimoto M, Tanabe H: Category-specific word meaning impairment in Gogi aphasics (in Japanese). Higher Brain Function Res 1994;14:221–229.
28 Snowden JS, Neary D, Mann D: Frontotemporal Lobar Degeneration: Frontotemporal Dementia, Progressive Aphasia, Semantic Dementia. New York, Churchill Livingstone, 1996.
29 Shinagawa S, Ikeda M, Fukuhara R, Tanabe H: Initial symptoms in frontotemporal dementia compared with Alzheimer's disease. Dement Geriatr Cogn Disord 2006;21:74–80.
30 Mioshi E, Kipps CM, Dawson K, Mitchell J, Graham A, Hodges JR: Activities of daily living in frontotemporal dementia and Alzheimer disease. Neurology 2007;68:2077–2084.
31 Mendez MF, Shapira JS, McMurtray A, Licht E: Preliminary findings: behavioral worsening on donepezil in patients with frontotemporal dementia. Am J Geriatr Psychiatry 2007;15:84–87.
32 Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D: Distinct behavioural profiles in frontotemporal dementia and semantic dementia. J Neurol Neurosurg Psychiatry 2001;70:323–332.
33 Bozeat S, Gregory CA, Ralph MA, Hodges JR: Which neuropsychiatric and behavioural features distinguish frontal and temporal variants of frontotemporal dementia from Alzheimer's disease? J Neurol Neurosurg Psychiatry 2000;69:178–186.
34 Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR: Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002;73:371–376.
35 Chan D, Anderson V, Pijnenburg Y, Whitwell J Barnes J, Scahill R, Stevens JM, Barkhof F, Scheltens P, Rossor MN, Fox NC: The clinical profile of right temporal lobe atrophy. Brain 2009;132:1287–1298.
36 Patterson K, Hodges JR: Semantic dementia: one window on the structure and organization of semantic memory; in Cermak L (eds): Handbook of Neuropsychology (Memory and Its Disorders), ed 2. Amsterdam, Elsevier, 2000, pp 313–334.
37 Thompson SA, Patterson K, Hodges JR: Left/right asymmetry of atrophy in semantic dementia: behavioral-cognitive implications. Neurology 2003;61:1196–1203.
38 Ikeda M, Tanabe H: Reducing the burden of care in dementia through the amelioration of BPSD by drug therapy. Expert Rev Neurother 2004;4:921–922.
39 Graham KS, Simons JS, Pratt KH, Patterson K, Hodges JR: Insights from semantic dementia on the relationship between episodic and semantic memory. Neuropsychologia 2000;38; 313–324.
40 Graham KS, Patterson K, Pratt KH, Hodges JR: Relearning and subsequent forgetting of semantic category exemplars in a case of semantic dementia. Neuropsychology 1999;13: 359–380.
41 Snowden JS, Neary D: Relearning of verbal labels in semantic dementia. Neuropsychologia 2002;40:1715–1728.
42 Green HA, Patterson K: Jigsaws – a preserved ability in semantic dementia. Neuropsychologia 2009;47:569–576.
43 Oppenheim G: The earliest signs of Alzheimer's disease. J Geriatr Psychiatry Neurol 1994;7:116–120.
44 Knopman DS, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, Mendez MF, Miller BL, Mercaldo N: Development of methodology for conducting clinical trials in frontotemporal lobar degeneration. Brain 2008; 131:2957–2968.
45 Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL: A new clinical scale for the staging of dementia. Br J Psychiatry 1982; 140:566–572.
46 Vossel KA, Miller BL: New approaches to the treatment of frontotemporal lobar degeneration. Curr Opin Neurol 2008;21:708–716.

8. 前頭側頭型認知症の脱抑制
——特に自動車運転について

はじめに

近年，認知症の自動車運転について，社会的に注目されるようになった．2002年に改正道路交通法*1が施行され，認知症患者は相対的免許制限を受けるものとして法的に明文化され，Alzheimer病（Alzheimer disease：AD）と血管性認知症（vascular dementia：VD）が実質的に運転免許の更新ができなくなった．しかし，実際は認知症患者の大多数が自動車運転を継続している現状も存在する[1,2]．さらに2009年から75歳以上の免許更新予定者に認知機能検査の導入*2が義務化された．これまで認知症と自動車運転の医学的研究の多くはADに関する社会医学的研究や対策が中心であった．しかしながら認知症のなかでも，前頭側頭型認知症（frontotemporal dementia：FTD）は初老期認知症の背景疾患として大きな比率を占め，疫学調査でもADの1/5〜1/10の頻度でみられると報告されている[3,4]．そこで本項では，これまで医学的にほとんど検討されていないFTDの自動車運転について，筆者の検討を中心に紹介し，今後の課題について述べることとする．FTDは現在，前頭側頭葉変性症（frontotemporal lobar degeneration：FTLD）の下位分類としての症候群に位置づけられている疾患である．

FTDの精神症状・行動障害と症候学

FTDはその特徴的な行動異常のため，処遇やケアが困難な認知症であり，特に初老期発症の認知症のなかでは抗精神病薬の使用や精神科病棟への入院も余儀なくされる場合もありうる主要な疾患群である．FTDは主として大脳前方部が萎縮し，病初期から脱抑制，食行動異常，衝動性，常同行為，反社会的行動などの行動障害を主とした臨床症状を呈する疾患群である．

本書中の別項からも明らかなように，FTDでは記憶やその他の認知機能の障害は病初期には目立たないが，一方で病初期から比較的よくみられる脱抑制や，常同行為，衝動性などの前頭葉性の行動障害のため社会生活上では，他の認知症と比較しても介護やケア，社会的対応が困難である．また，自動車運転や運転能力についても疾患特異的な行動障害の大きな影

＊1　2002年の改正道路交通法
2002（平成14）年6月から施行された道路交通法で，'痴呆'が免許更新の相対的制限を受け，都道府県公安委員会の責任で免許停止をすることができるようになった．警察庁ホームページ．改正道路交通法の概要
http://www.npa.go.jp/koutsuu/doukouhou/doukouhou/PAGE020.HTM

＊2　認知機能検査の導入
2009年から75歳以上の免許更新者は認知機能検査の受検が義務化された．本制度により，認知症ドライバーに対する国家的な対策が一歩前進したと考えられている．

響がみられ，臨床現場でも大きな問題となりうる．

FTD と自動車運転

FTD と自動車運転に関するこれまでの検討について紹介する．

Miller らは FTD 患者 22 人と AD 患者 22 人を対象として脱抑制，衝動性，反社会的行動を比較検討した結果，FTD 患者では 22 人中 10 人，AD 患者では 22 人中 1 人と FTD に有意に反社会的な行動が多くみられ（p=0.004），また FTD 患者では，ひき逃げ事故（hit-and-run accident）が 2 人であったように，AD よりも脱抑制に関連した反社会的な運転行動が認められたと報告[5] している．

De Simone らは，FTD 患者における運転能力および精神症状・行動障害と運転行動との関係を検討するため FTD と診断された 15 人の患者（評価時 10 人が運転を継続）と健常対照者 15 人の運転行動について運転シミュレーター課題を施行し，比較した．また同時に精神症状・行動障害を Neurobehavioral Rating Scale（NBRS）を用いて評価した．その結果，FTD 患者は対照群と比較しより多くの交通違反カードを渡され，停止信号でも止まることをせず，道路から外れての激突や衝突をより頻回に起こしていた．また，FTD 群では平均速度が有意に速く，シミュレーターの運転成績が（落ち着きのなさ，脱抑制，敵意を含んだ）興奮に関連した行動と関連性を認めたが，認知症の重症度とは関連を認めなかったと報告している．これらの結果から FTD 患者に特徴的な行動変化は，不適切な運転行動に影響しうると述べている（**表 1**）[6]．

これらの報告から考察すると，FTD 患者の運転は AD 患者の運転よりも危険であり，認知症と自動車運転を検討する際に決して見過ごせないと考えられる．

症例提示

ここで，FTD 患者の自動車運転で精神医学的管理のうえで問題となった自験例について提示する．

症例 1

74 歳，男性．右利き．自損事故を繰り返しても運転中断，診断書提出につながらない FTD 症例．

病前性格はまじめで几帳面．70 歳代から物忘れに加え，妻に怒りっぽくなり，車で道を間違うことがあった．X－2 年，当科物忘れ外来初診．X－1～X 年初旬にかけて自損事故や，タイヤを溝に落とすことが繰り返されたが，反省もなく運転を継続するため，認知症の精査および運転継続

表 1　FTD 患者の運転能力・運転行動の比較検討

評価項目	FTD 群	対照群	p 値
平均速度	31 ± 9 (16~47.2)	25.6 ± 3 (19~30)	< 0.05
標準偏差(平均速度)	14.2 ± 2 (8.4~14.2)	8 ± 1 (6~10)	< 0.001
路上検査事故	1.6 ± 2.5 (0~8)	(0~1)	NA
総合追突事故	1.3 ± 1.7 (0~5)	0	NA
停止標識無視	2 ± 3.6 (0~10)	0	NA
歩行者事故	1 ± 2 (0~6)	(0~2)	NS
交通違反カード	1 ± 1 (0~3)	1 ± 1 (0~3)	NS
速度違反カード	11 ± 11 (0~33)	1 ± 2 (0~5)	0.003

NA：nonapplicable, NS：nosignificant.

(De Simone V, et al. *Dement Geriatr Cogn Disord* 2007[6] より一部改変)

の危険性の評価目的に X 年 7 月当科入院.

粗大なエピソード記憶障害はなかった. 自損事故のことについて深刻味はなく, 反省することもまったくなかった. 入院主治医には自損事故を起こしているにもかかわらず「事故はない」と主張した. 神経学的に異常なく, 神経心理学的検査では, MMSE (Mini-Mental State Examination) 26/30, レーヴン色彩マトリックステスト (Raven's Coloured Progressive Matrices：RCPM) 29/36 であった. 画像では前頭葉 (左優位) の萎縮を認め, FTD と診断した.

その後, 入院中に免許センターの協力を得て運転実車評価を行った. 運転評価内容では,

① 確認行為の不備,
② 停止線越え停止,
③ 赤信号の見落とし,
④ バック時の後方確認見落とし,
⑤ 急発進, 急ブレーキ,

これら多数の安全運転上の問題を指摘され, 同席した家族も驚いていた. 所見を本人に説明したが, へらへらとし, 深刻な様子はまったくみられなかった. そのため, 本人と家族に対し, 実車テスト結果をもとに運転免許返納および運転中断を勧告したが, 患者本人は「わかった」という反面, すぐに「大丈夫やろ」と言ったり, 家族も「本人がゆうこと聞かないからあきません」と述べ, 公安委員会への主治医診断書提出に至らず, 運転中断には至らなかった.

Memo
主治医の運転能力に関する診断書
この診断書は, 基本的な臨床診断, ICD-10 コードのほか, 運転能力評価として, 原則, 現状での運転能力を 5 段階, 将来の運転能力を 4 段階で評価し, 公安委員会がその結果を参考に, 免許の停止を判断する診断書である. 診断書であるため原則本人による診断書作成要請と提出が必要であり, 認知症患者では, 本診断書の提出に結びつきにくい現状がある.

症例 2

58 歳, 女性. 右利き. 反社会的行動, 脱抑制, 当て逃げ事故により精神科病院入院となった FTD 症例 (**表 2**)[7].

表2　症例2の実車テスト結果

- 確認動作の不備
- 停止線を越えての停止
- 赤信号の見落とし
- 反対車線への乗り入れ
- 障害物の回避不備
- 方向指示器を出すタイミングの遅れ
- コース侵入間違いと無理な侵入
- バック時の後方確認見落とし
- 急発進，急ブレーキ
- 脱輪走行継続
- 本人は自覚に乏しい

（上村直人，ほか．老年精神医学雑誌 2005[7]）

X－2年（56歳）頃から健忘，清潔観念の低下，人格変化が認められた．X－1年，注意散漫となり，頻回の事故や当て逃げを起こし，事故処理が一人ではできないことがあった．本人は交通事故の反省はなく，病識もない状態で車に乗り続けるため，家族が免許を取り上げようとした．しかし他の親族が「かわいそうだ．生き甲斐を取り上げたら，余計に混乱する」と家族間でも患者の運転に関する評価が異なった．その後も車で出かけて交通事故を繰り返し起こすため，X年7月，精査目的で当科に入院．

MMSE 27/30，RCPM 16/36．頭部CTで，両側前頭葉（左優位）の萎縮を認めた．臨床経過，画像検査，神経心理学的検査から，FTDと診断した．

運転中断に納得せず，運転継続の訴えが主治医に頻回あり，運転能力評価として免許センターでの実車テストを行った．実車テストは，主治医同伴で免許センターに赴き，患者の許可を取ったうえで，その模様をビデオ撮影した．実車テストの判定では，

① 運転動作が粗雑で，指示したコースが覚えられていない，
② 各場所での確認動作ができていない，
③ 停止線を越えての停止，赤信号の見落とし，線路内への一時停止なしの乗り入れ，中央線のはみ出し，反対車線への乗り越え，障害物の回避不十分，方向指示器の出し遅れ，
④ 間違ったコースへの強引な侵入，およびバックするときの確認なし，
⑤ 前方車両発見時のスピードダウンができない，また上記失敗に対する自覚が欠如している，

などの点が指摘された．患者本人にも運転中断を勧告したが，「自分は上手と言われた」「免許を返せ」「運転をする，生き甲斐を取るな」など運転継続へのこだわりがみられた．そのため，ビデオ撮影の様子を患者本人に見せ，運転中断を試みた．しかし本人は納得できず，ビデオの様子を見ても自分の失敗に自覚がなかった．

その後，不安・焦燥感が高まり，当科での入院継続が困難となり，単科精神科病院に転院となった．その後，自動車運転継続へのこだわりは転院先の病院でも強い状態が続いた．

Memo
運転適性検査／運転適性試験／運転適性診断
運転適性検査とは通常，臨時運転適性検査のことを指し，免許交付後，交通安全上問題があると判断された場合に都道府県の公安委員会の命令で専門医（通常，精神疾患では精神保健指定医）が任命されて診察を行うことを指す．運転適性試験とは，道路交通法第97条に規定されている免許の新規申請や更新時に行われる，視力検査，聴力検査や色覚識別試験，四肢体幹の異常の有無を評価するものを指す．運転適性診断とは，運転シミュレーターを用いた運転適性の評価を指し，高齢者講習や免許センター，および自動車教習所において行う検査であり，それらの運転適性結果に基づいて，受講者の安全運転に対して指導や教示がなされる．

FTLDと自動車運転に関する検討[8]

認知症の原因疾患による運転行動の違いと交通安全上の危険性を検討するため，FTLD群とAD群の運転行動について比較検討を行った．なお，本検討では対象がFTLDのため，語義失語や意味記憶障害，および相貌失認を主症状とする意味性認知症（semantic dementia：SD）患者2人が対象に入っていることを断わっておく．対象は1995～2002年に高知大学神経科精神科外来，および関連病院を受診し，調査期間中の初診時において運転を継続している者で，FTLDの国際診断基準[9]を満たした8人とNINCDS-ADRDA[*3]のprobable ADの診断基準[10]を満たした23人の連続症例である．評価内容は，発症後の運転行動の変化，交通事故や違反の有無について，半構造化面接により家族情報から得た．FTLD群は男性5人，女性3人で平均年齢65.8 ± 8.4歳，平均MMSE 19.8 ± 7.2，平均罹病期間1.75 ± 1.0年であった．AD群は男性13人，女性10人で平均年齢68.5 ± 7.6歳，平均MMSE 17.0 ± 6.8，平均罹病期間1.87 ± 1.2年で，両群間で性別，年齢，MMSE，CDR（clinical dementia rating：臨床認知症評価尺度）に有意な差はなかった．

運転行動の差異（**図1**）では，FTLDでは車間距離の調整困難が62.5％，接触事故が87.5％，信号・道路標識の無視が62.5％，わき見・注意散漫運転が62.5％に認められた．一方ADでは，行き先忘れが95.6％，車庫入れの失敗が17.6％に認められた．交通事故や重大な交通違反の危険性は，FTLD群が87.5％（7/8），AD群が21.7％（5/23）で，FTLD群のほうが有意に危険性は高かった（$p < 0.001$，Fisher's exact test）．さらに，認知症の発症から初回交通事故までの期間は，FTLD群（1.28 ± 0.49年）のほうがAD群（3.0 ± 1.2年）より有意に短かった（Mann-Whitney U test，$p < 0.05$）．

以上から，FTLD群が有意に交通事故や交通違反の危険性が高いことが示された．したがって，医師はFTLDが，ADよりも公共の交通安全という点ではより深刻な運転危険性を有することをふまえて，運転に関する指導をする必要があると考えられた．

FTDと自動車運転に関する検討のまとめ

これまでの認知症と運転行動に関するRegerらのメタ解析[11]では，視空間技能が運転能力の予測と関連している指標であったと報告している（**図2**）．これは主として検討された論文の対象患者がADかもしくは認知症の原因が特定されていないことが影響している可能性がある．今回の筆者らの検討でも，AD群では行き先忘れや車庫入れの失敗が多くみられた．

＊3 NINCDS-ADRDA
National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association.