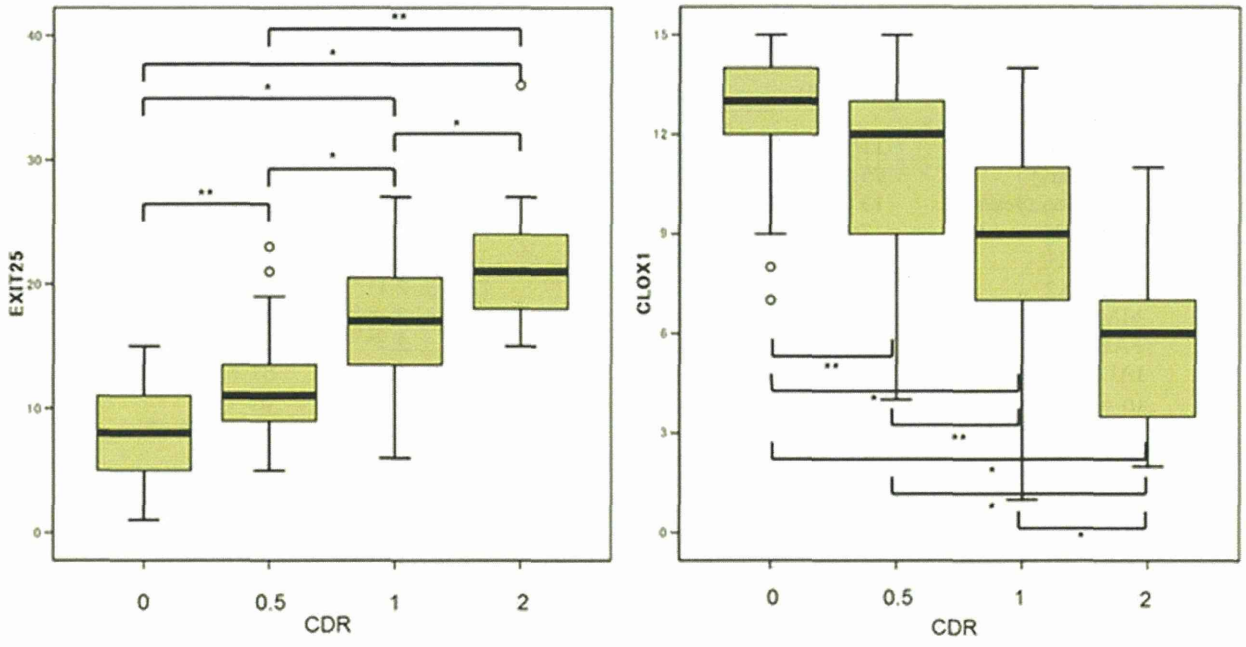

Figure 1. (Colour online) Results of analysis of covariance (ANCOVA) with the Bonferroni *post hoc* tests. In J-EXIT25 and J-CLOX1, ANCOVA showed significant differences among CDR groups. *$p < 0.001$, **$p < 0.05$.

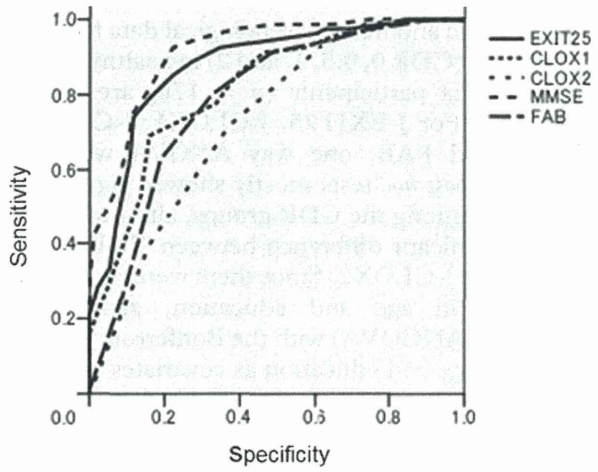

Figure 2. Results of receiver operating characteristic (ROC) analysis. For comparison of diagnostic performance in discriminating between non-dementia and dementia participants, the area under the ROC curve (AUC) of MMSE was the highest, followed by J-EXIT25, J-CLOX1, FAB, and J-CLOX2.

J-EXIT25, 0.818 (CI = 0.756–0.880) for J-CLOX1 ($p < 0.001$), 0.789 (CI = 0.721–0.856) for FAB ($p < 0.001$), and 0.730 (CI = 0.657–0.803) for J-CLOX2.

Scores below the J-EXIT25 cut-off score of 15/16 were obtained for 100% of healthy participants, 93% of MCI participants, and 35% of dementia participants, giving a sensitivity of 65% and specificity of 93% for discriminating between non-dementia and dementia (Youden's index: 0.58). The highest Youden's index was 0.63 with the J-EXIT25 cut-off score of 13/14 (sensitivity: 78%, specificity: 85%). The NPI total score was significantly lower in the participants with the J-EXIT25 score below the cut-off score of 15/16 ($n = 108$) compared with those with the J-EXIT25 score above the cut-off score ($n = 68$) (3.3 ± 6.8 vs. 11.1 ± 12.6, $p < 0.001$). On subscales of the NPI, delusions, agitation, and irritability, scores in the participants with J-EXIT25 scores below the cut-off were significantly lower than for the participants with J-EXIT25 scores above the cut-off (the Bonferroni–Holm corrected $p < 0.05$).

Scores above the J-CLOX1 cut-off of 9/10 were obtained in 89%, 81%, and 39% of healthy, MCI, and dementia participants respectively, giving a sensitivity of 61% and specificity of 85% for discriminating between non-dementia and dementia (the highest Youden's index (0.46)). The NPI total score was significantly lower in the participants with a J-CLOX1 score above the cut-off ($n = 106$) compared with those with a J-CLOX1 score below the cut-off ($n = 70$) (4.8 ± 8.2 vs. 8.8 ± 12.2, $p = 0.018$). No NPI subscales differed significantly between these groups after the Bonferroni–holm correction. For J-CLOX2, scores above the cut-off of 11/12 were obtained for 100%, 97%, and 74% of healthy, MCI, and dementia participants respectively, with a sensitivity of 26% and a specificity of 99% for discriminating between non-dementia and dementia (Youden's

index: 0.25). The highest Youden's index was 0.35 with the J-CLOX2 cut-off score of 13/14 (sensitivity: 63%, specificity: 72%).

Correlation analyses

The J-EXIT25 scores were significantly correlated with age ($r = 0.448$, $p < 0.001$), education ($r = -0.364$, $p < 0.001$), and scores on the MMSE ($r = -0.691$, $p < 0.001$), J-CLOX1 ($r = -0.605$, $p < 0.001$), J-CLOX2 ($r = -0.595$, $p < 0.001$), and PSMS ($r = -0.487$, $p < 0.001$) in healthy, MCI, and dementia participants. These correlations remained significant after the Bonferroni–Holm corrections. Among the 12 items of the NPI, there were significant correlations between J-EXIT25 scores and those for delusions ($r = 0.276$, $p < 0.001$), hallucinations ($r = 0.206$, $p = 0.006$), agitation ($r = 0.299$, $p < 0.001$), apathy ($r = 0.162$, $p = 0.032$), and irritability ($r = 0.241$, $p < 0.001$); however, the significant relationships with hallucinations and apathy disappeared after the Bonferroni–Holm corrections.

J-CLOX1 scores were significantly correlated with age ($r = -0.328$, $p < 0.001$), education ($r = 0.157$, $p = 0.038$), and scores on the MMSE ($r = 0.636$, $p < 0.001$), J-CLOX2 ($r = 0.607$, $p < 0.001$), and PSMS ($r = 0.437$, $p < 0.001$) in healthy, MCI, and dementia participants. These correlations remained significant after the Bonferroni–Holm corrections. On the NPI, there were significant correlations between J-CLOX1 scores and delusions ($r = -0.184$, $p = 0.015$), agitation ($r = -0.211$, $p = 0.005$), and irritability ($r = -0.170$, $p = 0.024$), but these correlations were not significant after the Bonferroni–Holm corrections.

J-CLOX2 scores were significantly correlated with age ($r = -0.218$, $p = 0.004$) and scores on the MMSE ($r = 0.524$, $p < 0.001$) and PSMS ($r = 0.385$, $p < 0.001$), but not with education ($r = 0.05$, $p = 0.454$), in healthy, MCI, and dementia participants. The correlations were also significant after the Bonferroni–Holm corrections. On the NPI, there were significant correlations between J-CLOX2 scores and delusions ($r = -0.153$, $p = 0.043$), agitation ($r = -0.241$, $p = 0.001$), and irritability ($r = -0.223$, $p = 0.003$), but the correlation with delusions was not significant after the Bonferroni–Holm corrections.

IADL scores for men ($n = 52$) were significantly correlated with J-EXIT25 ($r = -0.662$, $p < 0.001$), J-CLOX1 ($r = 0.492$, $p < 0.001$), and J-CLOX2 ($r = 0.485$, $p = <0.001$) scores. IADL scores for women ($n = 124$) were also significantly correlated with J-EXIT25 ($r = -0.580$, $p < 0.001$), J-CLOX1 ($r = 0.548$, $p < 0.001$), and J-CLOX2 ($r = 0.398$, $p < 0.001$) scores. In 61 participants who received Japanese long-term insurance, the care level was significantly correlated with J-EXIT25 ($r = 0.479$, $p < 0.001$), J-CLOX1 ($r = -0.414$, $p = 0.001$), and J-CLOX2 ($r = -0.353$, $p = 0.005$) scores.

The relationship between J-EXIT25 and J-CLOX1 scores is shown in Figure 3. We classified the participants into the following four groups based on their performance on the two tests using the recommended cut-off scores: Group 1: those with high performance on both tests ($n = 82$); Group 2: high performance on J-EXIT25 and low performance on J-CLOX1 ($n = 26$); Group 3: low performance on J-EXIT25 and high performance on J-CLOX1 ($n = 24$); and Group 4: low performance on both tests ($n = 44$).

Regression analyses

The results of stepwise regression analyses in healthy, MCI, and dementia participants are shown in Table 2. In stepwise regression analysis of IADL scores, MMSE and J-EXIT25 scores were significantly independent predictors in men (adjusted $R^2 = 0.565$, $F = 34.058$, $p < 0.001$), and the MMSE score, age, and the J-CLOX1 score were significantly independent predictors in women (adjusted $R^2 = 0.419$, $F = 30.573$, $p < 0.001$). In stepwise regression analysis of PSMS scores, J-EXIT25, MMSE, and J-CLOX1 scores were significantly independent predictors (adjusted $R^2 = 0.281$, $F = 23.796$, $p < 0.001$). In stepwise regression analysis of the care level, the J-EXIT25 score was the only significantly independent predictor (adjusted $R^2 = 0.216$, $F = 17.553$, $p < 0.001$).

Discussion

The results of the study show the satisfactory concurrent validity and reliability of J-EXIT25 and J-CLOX, and of the short versions of EXIT25 (Quick EXIT and EXIT15) in older people. The J-EXIT25 and J-CLOX scores were also associated with ADL, care level, and neuropsychiatric symptoms, which are thought to reflect executive function. These results suggest that J-EXIT25 and J-CLOX are useful for the assessment of executive function in clinical settings. While the J-EXIT25 score was involved specially in IADL in men, PSMS, care level, and delusions, the J-CLOX1 score was specially related to IADL in women and PSMS. Therefore, J-EXIT25 and J-CLOX1 might evaluate different aspects of executive function.

The J-EXIT25 and J-CLOX1 scores showed significant differences among CDR groups, whereas the J-CLOX2 scores did not differ significantly

Table 2. Results of regression analyses

DEPENDENT VARIABLE		INDEPENDENT VARIABLES	β	p-VALUE	VIF	ADJUSTED R^2
IADL	Men (n = 52)	MMSE	0.496	<0.001	1.715	0.565
		J-EXIT25	−0.342	0.007	1.715	
	Women (n = 124)	MMSE	0.347	0.001	2.062	0.419
		age	−0.257	0.001	1.161	
		J-CLOX1	0.211	0.036	2.084	
PSMS (n = 176)		J-EXIT25	−0.238	0.011	2.096	0.281
		MMSE	0.233	0.016	2.233	
		J-CLOX1	0.145	0.098	1.840	
Care level (n = 67)		J-EXIT25	0.479	<0.001	1.000	0.216

Notes: IADL: Instrumental Activities of Daily Living; J-EXIT25: Japanese version of Executive Interview; J-CLOX: Japanese version of Executive Clock Drawing Task; MMSE: Mini-Mental State Examination; PSMS: Physical Self-Maintenance Scale; VIF: Variance Inflation Factor.

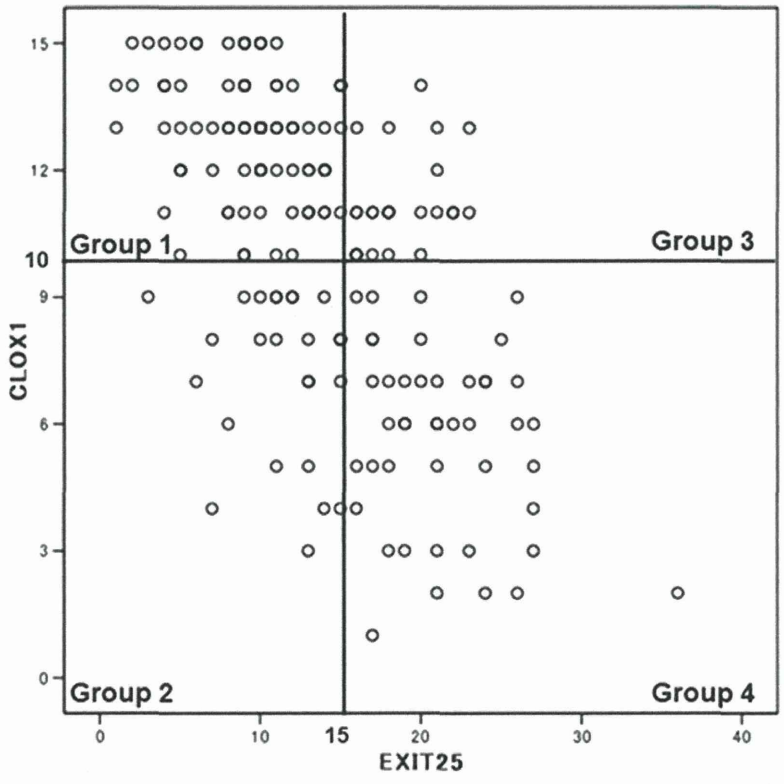

Figure 3. Relationship between J-EXIT25 and J-CLOX1. Participants were classified as those with high performance on both tests (Group 1); high performance on J-EXIT25 and low performance on J-CLOX1 (Group 2); low performance on J-EXIT25 and high performance on J-CLOX1 (Group 3); and low performance on both tests (Group 4).

between the CDR 0 and CDR 0.5 participants. These three scales are thought to assess different cognitive domains: EXIT25 and CLOX1 for executive function and CLOX2 for visuospatial praxis (Royall *et al.*, 1998.). Thus, our findings may indicate that executive function is mildly impaired in the pre-dementia stage.

All the healthy participants in the study had J-EXIT25 scores below the cut-off of 15/16. In older people with cognitive dysfunction with scores below the cut-off score, neuropsychiatric symptoms, including delusions, agitation, and irritability, were significantly milder than in those with scores above the cut-off score. The J-EXIT25 scores were correlated with the neuropsychiatric symptoms measured by the NPI. Previous study showed that the executive function measured by EXIT25 was associated with disruptive behaviors in older people (Royall *et al.*, 1992; Stokholm *et al.*, 2005). Using the original EXIT25, essentially no

disruptive behavior was found in older participants below the cut-off score (Royall *et al.*, 1992). In the Dutch (Stokholm *et al.*, 2005) and Chinese (Chan *et al.*, 2006) versions of EXIT25, scores for normal participants were also below the cut-off of 15/16. The consistent findings among these studies indicate that the cut-off score on the J-EXIT25 is useful for the screening of impairment of executive function.

In discriminating between non-dementia and dementia, the specificities and sensitivities of J-EXIT25 and J-CLOX were high and low respectively. In this study, the mean MMSE score was relatively high and the mean J-EXIT25 and J-CLOX scores were within normal ranges when the recommended cut-off scores were used. The severity in most of the participants with dementia was relatively mild and their executive dysfunction was also suggested to be mild. Therefore, the number of dementia participants with executive dysfunction was relatively low, and this might have caused the low sensitivities of J-EXIT25 and J-CLOX. Previous studies have also shown high specificity and low sensitivity of CLOX in MCI (Forti *et al.*, 2010) and subcortical ischemic vascular disease (Wong *et al.*, 2004). We also found that the CDT-copy task had high specificity and low sensitivity in differentiating AD from MCI or healthy participants (Kato *et al.*, 2013). The J-EXIT25 and J-CLOX cut-off scores might be insufficient to distinguish between non-dementia and dementia, especially mild dementia. However, the J-EXIT25 and J-CLOX1 scores for executive function were superior to the J-CLOX2 score for visuospatial praxis in discriminating between non-dementia and dementia. Screening for executive function may be more useful than for visuospatial praxis in discriminating between non-dementia and dementia.

EXIT25 and CLOX1 have been used to evaluate executive function (Royall *et al.*, 1992; 1998). Both J-EXIT25 and J-CLOX1 scores were associated with age, scores on the MMSE, IADL, and PSMS and care level. However, differences between J-EXIT25 and J-CLOX1 should be noted. For example, J-EXIT25 differentiated the severity of neuropsychiatric symptoms, including delusions, agitation, and irritability, when the recommended cut-off score was used, while J-CLOX1 did not do so. The J-EXIT25 scores were also correlated with severity in delusions, which are considered to be associated with the frontal lobe dysfunction (Matsuoka *et al.*, 2010). In regression analyses, J-EXIT25 was a predictor of IADL in men, PSMS, and care level, and J-CLOX1 was a predictor of IADL in women and PSMS. These findings suggest that J-EXIT25 can better assess tool use and care level, while J-CLOX1 is a good scale to evaluate capacity to perform housework, which is usually done by older women in Japan.

These results are consistent with previous studies showing that the EXIT25 scores are good indicators for inhaler techniques (Allen *et al.*, 2003), functional status (Pereira *et al.*, 2008), problems in self-care (Thabit *et al.*, 2009), and care level (Royall *et al.*, 1992). A previous study also showed that EXIT25 was effective for evaluating decision-making capacity, in contrast to CLOX and MMSE (Schillerstrom *et al.*, 2007). Another study reported that IADL was associated with executive impairment, and that basic ADL was related to apathy, which suggests neuroanatomical differences between these behaviors (Stout *et al.*, 2003). As shown in Figure 3, both J-EXIT25 and J-CLOX1 have common and distinct psychometric properties. Thus, these two scales may assess different aspects of executive function. Since some regions, including the frontal, temporal, and parietal lobes, are involved in CDT (Matsuoka *et al.*, 2013), J-CLOX1 may reflect executive function and other cognitive functions such as visuospatial ability and comprehension. There is a lack of data on this important issue and further studies, including imaging that focuses on differences between EXIT25 and CLOX1, are clearly warranted.

The current study has several limitations despite the inclusion of a large number of participants. First, we could not administer the KWCST in some of the participants, and information on care level was only available for the participants who received long-term care insurance. Since we excluded some of the participants who were reluctant to receive the KWCST and who were not able to understand the instruction of the KWCST in correlation analysis, the J-EXIT25 might be weakly correlated to the KWCST, and the J-CLOX might not be significantly correlated to the KWCST. Second, the dementia participants were heterogeneous, although most had AD. This may have led to relatively low sensitivities of J-EXIT25 and J-CLOX for discriminating non-dementia from dementia. Third, the CDR rater was aware of the MMSE score and this may have caused relatively high AUC for MMSE. Fourth, we did not examine the divergent validity. These limitations should be noted in the interpretation of our results.

In summary, J-EXIT25 and J-CLOX were found to be valid and reliable instruments for the assessment of executive function in older people. J-EXIT25 and J-CLOX have common and distinct psychometric properties in the assessment of executive function. These scales have the potential to contribute to capacity assessment in

various clinical settings in Japan as reported in other countries.

Conflict of interest

None.

Description of authors' roles

T. Matsuoka translated J-EXIT25 and J-CLOX, designed the study, collected and analyzed the data, and wrote the paper. J. Narumoto, H. Koumi, and Y. Kato translated J-EXIT25 and J-CLOX, designed the study, collected the data, and assisted in writing the paper. S. Taniguchi examined the inter-rater reliability, collected the data, and assisted in writing the paper. M. Ogawa, H. Fujimoto, A. Okamura, K. Shibata, and K. Nakamura collected the data and assisted in writing the paper. H. Uchida, S Nakaaki, M. Mimura, and K. Fukui supervised the study and writing of the paper.

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LETTER

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Late-onset psychosis in older outpatients: a retrospective chart review

Late-onset psychosis (LOP) has become increasingly prevalent in the clinical setting, especially in the highly aged society, due to the increasing numbers of older people and its disruptive impact on the lives of patients and caregivers. Although previous studies have identified some of the features of LOP (Webster and Grossberg, 1998; Mitford *et al.*, 2010; Tan and Seng, 2012), some of the previous studies did not include patients with dementia and mood disorders. This study addresses the features of LOP in consecutive outpatients to provide information that supports the differential diagnosis.

We enrolled 1,024 consecutive outpatients over the age of 60 years who were seen at the department of Psychiatry, Kyoto Prefectural University of Medicine, between April 2009 and March 2013. A retrospective chart review of 1,024 outpatients was conducted. The outpatients with LOP were defined as the outpatients who had first manifestations of psychosis, including delusions and hallucinations, at the age of 60 years or older. The early-onset psychosis (EOP) was defined as the first psychosis manifestation below the age of 60 years. The diagnosis was made by psychiatrists, according to the ICD-10. We defined hearing or visual impairment as poor hearing or visual capacity in the clinical examination and daily life. Thought disorder included thought broadcasting, loosening of associations, and blocking of thought, which was usually found in schizophrenia. Negative symptoms included affective flattening and impoverishment of speech. All data were coded and registered anonymously. We used the χ^2 test for the statistical analyses. In post hoc analyses, we used the χ^2 test with pairwise comparison. Differences in age were compared using one-way ANOVA with Bonferroni post hoc test. For the logistic regression analysis, a forward selection method (likelihood ratio) was used to determine the predictors of LOP. Variables, including age, gender, living alone, hearing impairment, visual impairment, and family history, were entered into the logistic regression analysis. Living alone, hearing impairment, visual impairment, and family history were converted into dichotomous variables (0: absence, 1: presence). A p value < 0.05 was used to enter and eliminate variables. Data were analyzed using SPSS Statistics 22 (IBM Corp., USA.). $P < 0.05$ was considered statistically significant. The study was approved by the Ethics Committee of Kyoto Prefectural University of Medicine.

In the 1,024 outpatients, the numbers of outpatients with LOP, EOP, and those without psychosis were 157, 45, and 822, respectively. The mean age (77.8 $\pm$ 7.8 years) and the prevalence of hearing impairment (18.5%) in patients with LOP were the highest in three groups ($P < 0.001$). The prevalences of female gender (73.2%) and visual impairment (7.6%) in patients with LOP were significantly higher than in patients without psychosis ($P = 0.008$ and $P < 0.001$, respectively). The prevalences of thought disorder (4.5%) and negative symptoms (0%) in LOP group were significantly lower than in EOP group ($P < 0.001$). These differences were significant even using a Bonferroni–Holm correction. The prevalences of living alone (28.7%) and family history of psychiatric disorders (14.0%) in LOP group were not significantly different between three groups (Table S1, available as supplementary material attached to the electronic version of this paper at www.journals.cambridge.org/jid_IPG).

Multiple logistic analysis identified four independent predictors of LOP: visual impairment (odds ratio (OR): 13.19; 95% confidence interval (CI): 4.05–43.00; $P < 0.001$), hearing impairment (OR: 3.95; 95% CI: 2.21–7.07; $P < 0.001$), gender (OR: 1.55; 95% CI: 1.03–2.33; $P = 0.035$), and age (OR: 1.08; 95% CI: 1.06–1.11; $P < 0.001$).

In the etiology of LOP ($n = 157$), dementia ($n = 84$) was the most common, followed by delusional disorder ($n = 22$), schizophrenia ($n = 12$), depression ($n = 12$). When the three groups (F0 ($n = 94$), F2 (n = 46), and F3 categories ($n = 13$)) were compared, the type of delusion was different for each group. In the F0 category, the delusions of theft (35.1%), misidentification (28.7%), and persecution (24.5%) were common. In the F2 category, the majority of patients had delusions of persecution (63.0%). In the F3 category, the main types of delusions were of guilt (46.2%), persecution (46.2%), and observation (38.5%). In the F0 category, the family (41.5%) was the main subject of delusions. The neighbor (52.2%) was common in the F2 category, and the strangers (38.5%) and neighbor (30.8%) were common in F3 category. In 157 patients with LOP, 37 patients exhibited the first manifestations of both delusions and hallucinations after the age of 60 years. Among the causes of the first manifestations of both delusions and hallucinations, dementia ($n = 19$) was the most common, followed by schizophrenia ($n = 12$), and depression

($n = 4$), respectively. Delusion of persecution and auditory hallucination ($n = 9$), and delusion of misidentification and visual hallucination ($n = 6$) were common combination in dementia.

In summary, the present study identified 157 patients with LOP among the consecutive outpatients and found that the most common etiology of LOP was dementia, followed by delusional disorder, schizophrenia, and depression. In addition, we found that LOP was associated with a predominance of females, relatively high prevalence of hearing and visual impairment, and a relative lack of thought disorder and negative symptoms. These results were consistent with previous studies (Webster and Grossberg, 1998; Mitford *et al.*, 2010; Tan and Seng, 2012). The combination of persecutory delusion and auditory hallucination was commonly observed, even in patients with dementia. This finding suggests that this combination is present in both schizophrenia and dementia patients; although it is usually regarded as one of the important suggestive features of schizophrenia. Our previous studies have indicated that it is difficult to diagnose when patients with AD exhibit psychosis similar to schizophrenia (Matsuoka *et al.*, 2010; 2011). We should consider the possibility of dementia when older patients exhibit psychosis. Our study has some limitations. First, our study was retrospective in nature, and the information could be insufficient especially about hearing and visual impairment. Second, there might be selection bias because this study was conducted only in a university hospital setting. These limitations should be considered in the interpretation. Further prospective investigations are needed in the community.

Conflict of interest

None.

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Supplementary material

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RESEARCH ARTICLE

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Delayed atrophy in posterior cingulate cortex and apathy after stroke

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Objective: A few studies have been performed on chronic structural changes after stroke. The primary purpose of the present study was to investigate regional cortical volume changes after the onset of stroke and to examine how the cortical volume changes affected neuropsychiatric symptoms.

Methods: Participants were 20 stroke patients and 14 control subjects. T1-MRI was performed twice, once at the subacute stage and again 6 months later, and whole brain voxel-based morphometric (VBM) analysis was used to detect significant cortical gray matter volume changes in patients. We also assessed the correlation between changes in cortical volumes and changes in neuropsychiatric symptoms during the 6 months following a stroke.

Results: In the present study, we found significant volume reductions in the anterior part of the posterior cingulate cortex (PCC) over the 6 months following a stroke by exploratory VBM analysis. We also found that the amount of volume change was significantly correlated with the change in apathy-scale scores during the 6 months poststroke.

Conclusions: The present study suggests that delayed atrophic change is evident in the PCC 6 months after a stroke. There was greater apathetic change in the stroke patients with the larger volume reductions. The delayed atrophy of the PCC may reflect degeneration secondary to neuronal loss due to stroke. Such degeneration might have impaired control of goal-directed behavior, leading to the observed increase in apathy.

Key words: stroke; apathy; magnetic resonance imaging; voxel-based morphometric analysis; posterior cingulate cortex
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Introduction

Stroke is one of the leading contributors to disease burden. A worldwide study in 2010 showed that stroke was the second most prevalent cause of death, representing an estimated 11.1% of all deaths (Lozano *et al.*, 2012). In respect to morbidity, stroke was found to be the fourth leading cause of lost DALYs (disability-adjusted life years) globally in nonpediatric populations (Mukherjee and Patil, 2011). Further, neuropsychiatric symptoms following stroke, such as cognitive impairment, depression and apathy, are associated with excess disability, cognitive impairment, and mortality in stroke patients (Hackett *et al.*, 2005; Pendlebury and Rothwell, 2009; van Dalen *et al.*, 2013).

Evidence concerning stroke has been compiled and is being applied to clinical practice. However, only a few studies on structural changes in the chronic stage

exist. A recent study reported atrophic change in regions anatomically remote from the ischemic lesions (Kraemer *et al.*, 2004), which may reflect degeneration secondary to neuronal loss, possibly Wallerian degeneration. This may mean that degenerative cortical changes appear after an ischemic attack, and that this cortical damage produces a biological vulnerability to neuropsychiatric symptoms after a stroke. However, to our knowledge, there has been no studies that focused on where and how the degenerative cortical changes occurred and whether these affected neuropsychiatric symptoms after a stroke.

The primary purpose of the present study was to investigate regional cortical volume changes after the onset of stroke and to examine how they affected any neuropsychiatric symptoms developing in the patient after the stroke. T1-MRI was performed twice, once at the stage of subacute stroke and again 6 months after the stroke, and whole brain voxel-based morphometric (VBM) analysis was used to quantify cortical gray matter (GM) volume changes in patients during the 6-month period following the stroke. We also assessed the correlation between changes in cortical volumes and any changes in neuropsychiatric symptoms.

We hypothesized that regions, such as cingulate cortex, which have unusually extensive connectivity with other areas, would show especially large degenerative cortical changes in stroke due to simultaneous loss of connections from many spatially distinct sites individually affected by the stroke. The regions of degenerative cortical change might relate to the network abnormalities underlying poststroke depression/apathy, which is a common and serious emotional symptom following stroke.

Methods

Subjects

After the study had been completely described to the subjects, and before enrollment, written informed consent was obtained. The study was approved by the Medical Ethics Committee of the National Cerebral and Cardiovascular Center of Japan. The patients were of Japanese ethnicity and were recruited from the neurology unit of the National Cerebral and Cardiovascular Center hospital. These patients had initially been hospitalized for treatment of acute ischemic stroke.

Stroke is diagnosed by neurologists according to the World Health Organization (WHO) criteria. After the assessment, a group of psychiatrists and neurologists reviewed the data and reached a consensus regarding the presence or absence of psychiatric disease, including dementia, according to DSM-IV criteria. Patients were included if they met the following criteria: (i) a focal lesion of either the right or left hemisphere on MRI; (ii) absence of other neurologic, neurotoxic, or metabolic conditions; (iii) modest ischemic insult (modified Rankin scale ≤ 4) with absence of a significant verbal comprehension deficit; and (iv) occurrence of stroke 10–28 days before the first examinations. Exclusion criteria were the following: (i) transient ischemic attack, cerebral hemorrhage, subdural hematoma, or subarachnoid hemorrhage; (ii) history of a central nervous system disease, such as tumor, trauma, hydrocephalus, Parkinson's disease, etc.; and (iii) any pre-stroke history of depression/apathy. Twenty stroke patients who fulfilled the criteria and completed the series of examinations were included in this study. Fourteen control subjects were recruited who completed a series of examinations for the 6-month follow-up study. Exclusion criterion for the control subjects was a history or present diagnosis of any DSM-IV axis-I or neurological illness.

MRI examinations were conducted twice for all patients and control subjects, once at the subacute stage (10–28 days after onset) and again at the chronic stage (6 months after onset). The lesion location was established from MRI data, and its volume was calculated from a volume of interest manually delineated on the lesion. There were no changes in medication usage between baseline and follow-up, and no patient or control was on antidepressant treatment during the examinations. All patients were subjected to a neurological examination [modified Rankin scale, (mRS) (Brott *et al.*, 1989); National Institutes of Health Stroke Scale, NIHSS (Goldstein and Samsa, 1997)] on the day of the MRI scan. All patients and control subjects were administered a series of standardized, quantitative measurements of depressive symptoms [Zung Self-rating Depression Scale, SDS (Zung, 1965); Apathy scale (Starkstein *et al.*, 1993); and mini-mental state examination (for cognitive function), MMSE (Folstein *et al.*, 1975)] on the day of the MRI scan.

MRI data acquisition

All MRI examinations were performed using a 3.0-Tesla whole-body scanner (Signa Excite HD V12M4; GE Healthcare, Milwaukee, WI, USA) with an 8-channel phased-array brain coil. High-resolution three-dimensional T1-weighted images were acquired using a spoiled gradient-recalled sequence ($TR = 12.8$ ms, $TE = 2.6$ ms, flip angle = 8°, $FOV = 256$ mm; 188 sections in the sagittal plane; acquisition matrix, 256×256; acquired

resolution, $1 \times 1 \times 1$ mm). T2-weighted images were obtained using a fast-spin echo ($TR = 4{,}800$ ms; $TE = 101$ ms; echo train length (ETL) = 8; $FOV = 256$ mm; 74 slices in the transverse plane; acquisition matrix, 160×160, acquired resolution, $1 \times 1 \times 2$ mm).

Image processing

Image preprocessing and statistical analyses were carried out using SPM8 software (Wellcome Department of Imaging, Neuroscience Group, London, UK; http://www.fil.ion.ucl.ac.uk/spm), and VBM was carried out using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html) with default parameters. Images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and nonlinear transformations (warping), within a unified model (Ashburner and Friston, 2005). Subsequently, analyses were performed on GM segments, which were multiplied by the nonlinear components derived from the normalization matrix in order to preserve actual GM values locally (modulated GM volumes). Finally, the modulated volume was smoothed with a Gaussian kernel of 5 mm full-width at half-maximum. The voxel size of the final images was $1.5 \times 1.5 \times 1.5$ mm.

Voxel-wise GM differences before and after a 6-month period beginning shortly after the stroke were examined using paired t-tests. To avoid possible edge effects between different tissue types, we excluded all voxels with GM values of less than 0.2 (absolute threshold masking). As this was a hypothesis-led analysis, we applied a liberal threshold of $p < 0.001$ with an extent of 25 voxels across the whole brain.

Spherical volumes of interest (VOIs) were determined from regions where a significant volume change over the 6-month period was found in patients. The centers of the spherical VOIs were determined from the Montreal Neurological Institute coordinate with peak t-value. The radius of the spherical VOI was determined in accordance with size of the clusters revealed by the analysis. The regional volume was calculated by averaging the values for all voxels within the spherical VOIs.

Statistical analysis

To identify demographic variables distinguishing patients and controls, group differences in demographic characteristics were examined by unpaired t-test and Pearson χ^2-test. To identify changes in neuropsychiatric symptoms and to confirm the SPM8 results on changes in cortical volumes during the first 6 months after a stroke, the psychometric scores and gray matter volumes of spherical VOIs in patients and controls over 6 months were examined by paired t-test. The group differences in changes in the volumes of spherical VOIs over 6 months were examined with repeated-measures analysis of variance.

To examine the relationship between the fractional volume change of VOIs where a significant volume change was found in patients [(volume at 2nd test - volume at 1st test)/volume at 1st test] and the fractional change of depression/apathy scale scores [(scores at 2nd test - scores at 1st test)/scores at 1st test] in patients and controls, we performed Pearson's correlation analysis. Bonferroni correction was applied to avoid type I errors because of the multiplicity of statistical analyses. All statistical tests were 2-tailed and reported at $p < 0.05$. Statistical analysis of the data was performed using SPSS for Windows 21.0 (IBM Japan Inc., Tokyo, Japan).

Results

Demographic and clinical data

Table 1 summarizes the demographic and clinical characteristics of the study subjects. Patients did not differ significantly from controls in age, sex, education, or MMSE scores. On the psychometric scales, patients had worse scores on SDS and apathy scales when compared with controls. Moreover, a history of hypertension was significantly more prevalent in patients than in controls. As shown by the mRS/NIHSS scores, patients showed some disability due to stroke at the time of the initial examination. All of the patients were receiving anticoagulant and/or antiplatelet medication. The mean total volume of infarction was 1.8 ± 1.2 mL.

The locations of the patients' infarctions were restricted to subcortical regions, including the basal ganglia (50.0%), subcortical white matter (40.0%), and thalamus (10.0%). This is because our studies focused on degenerative cortical gray matter changes remote from the primary ischemic lesions therefore, including cases of cortical infarction would make interpretation of the results difficult. In 13 of the patients, the infarction was located in the left hemisphere.

Changes in psychometric scores and regional gray matter volumes over 6 months

As shown in Table 2, we found significant improvement in mRS score, NIHSS score, and MMSE score, while there was no significant change in depression or apathy scale scores overall in patients during the 6 months following the stroke. Two patients at the 1st and one patient

Table 1 Demographic characteristics of patients and control subjects at baseline

Characteristic	Stroke patients ($n=20$)	Control subjects ($n=14$)	t or χ^2	p
Age (y)	69.2 ± 8.5	72.4 ± 3.0	$t=-1.53$	0.14
Female sex (n, %)	4 (20.0)	6 (42.9)	$\chi^2=2.07$	0.15
Education (years)	12.5 ± 3.5	12.3 ± 2.7	$t=0.15$	0.88
MMSE score	27.5 ± 3.4	29.1 ± 1.3	$t=-1.99$	0.06
SDS	27.8 ± 6.1	21.7 ± 1.9	$t=4.17$	<0.001***
Apathy score	9.4 ± 4.0	5.4 ± 4.0	$t=2.84$	0.008**
History of disease, No (%)				
Diabetes mellitus	3 (15.0)	0 (0.0)	$\chi^2=2.30$	0.13
Hyperlipidemia	3 (15.0)	0 (0.0)	$\chi^2=2.30$	0.13
Hypertension	14 (70.0)	1 (0.1)	$\chi^2=13.2$	<0.001**
mRS score	2.1 ± 0.8	—		
NIHSS score	2.5 ± 1.8	—		
Volume of acute infarcts (mL)	1.8 ± 1.2	—		
Acute infarcts (n, %) in:				
Basal ganglia	10 (50.0)	—		
Subcortical white matter	8 (40.0)	—		
Thalamus	2 (10.0)	—		
Laterality of acute hemisphere infarcts				
Left hemisphere (n, %)	13 (65.0)	—		

MMSE, Mini-Mental State examination; SDS, Zung Self-rating Depression Scale; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.
Data are mean ± sd.
*, $p<0.05$;
**, $p<0.01$;
***, $p<0.001$.

Table 2 Changes in psychometry scores and PCC volume over 6 months in patients ($n=20$) and controls ($n=14$)

	10–28 days after stroke	6 months after first exam	paired t-test (t)	p
Patients				
mRS score	2.1 ± 0.8	1.6 ± 0.6	3.68	0.002**
NIHSS score	2.5 ± 1.8	1.0 ± 0.8	4.41	<0.001***
MMSE score	27.5 ± 3.5	28.9 ± 2.1	−2.32	0.03*
SDS	27.8 ± 6.1	28.1 ± 9.8	−0.17	0.87
Apathy score	9.4 ± 4.0	9.4 ± 4.3	−0.05	0.96
Volume of PCC	0.40 ± 0.07	0.38 ± 0.06	5.60	<0.001***
Controls				
MMSE score	29.1 ± 1.3	29.6 ± 0.5	−1.53	0.15
SDS	21.7 ± 1.9	22.2 ± 2.4	−1.20	0.25
Apathy score	5.4 ± 4.0	5.1 ± 3.5	0.64	0.53
Volume of PCC	0.43 ± 0.06	0.43 ± 0.06	−0.44	0.67

mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; MMSE, Mini-Mental State examination; SDS, Zung Self-rating Depression Scale; PCC, posterior cingulate cortex.
Data are mean ± sd.
*, $p<0.05$;
**, $p<0.01$;
***, $p<0.001$.

at the 2nd examination had clinically relevant depression (SDS score >=40), while three patients at the 1st and two at the 2nd examination had clinically relevant apathy (apathy scale score >=14). We found no significant changes in MMSE, depression scale, or apathy scores in control subjects over the 6-month study.

Voxel-based analysis revealed a significant reduction in volume of the anterior part of the PCC in the patients 6 months after the stroke [$(x, y, z)=(-3, -10, 33)$, cluster voxel size = 38, $T=4.77$] (Figure 1). The radius of the spherical VOI was determined to be 3 mm, so that the volume of this size of VOI

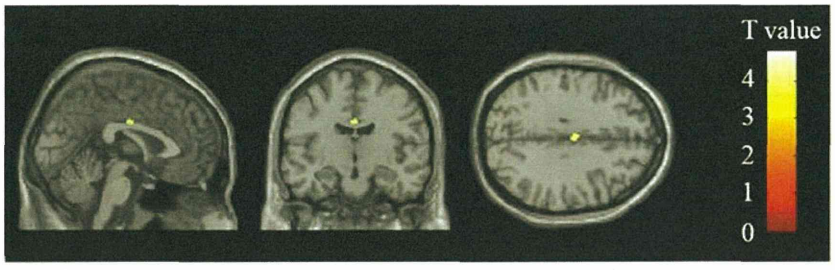

Figure 1 Gray matter volume changes in stroke patients over 6 months, by voxel-based analysis. Images are presented in radiological orientation. Detected areas exceed an uncorrected p-value of 0.001 in 25 or more contiguous voxels. These statistical parametric mapping projections are then superimposed on representative transaxial ($z = 33$), sagittal ($x = -3$), and coronal ($y = -10$) magnetic resonance images.

(113.04 mm^3) almost fit the volume of the cluster (128.25 mm^3). We found a significant reduction of volume of spherical VOIs in the PCC in patients ($p < 0.001$), but not in controls by paired t-test (Table 2; Figure 2). There was no significant difference in VOI volumes between patients and controls at the first examination by unpaired t-test ($t = 1.20$, $p = 0.24$), but the difference became significant after 6 months ($t = 2.36$, $p = 0.024$). We found a significant group effect on the raw volume change in PCC over 6 months by repeated-measures analysis of variance (group-by-volume interaction, $F_{1,32} = 14.2$; $p < 0.001$).

Relation between volume and apathy scale

We found a significant negative relationship between the fractional change of scored apathy and that of volume change in the PCC VOIs in patients ($r = -0.58$, $p = 0.007$), but not in controls ($r = -0.29$, $p = 0.32$) (Figure 3). When we considered the confounding effects of age, sex, laterality of the infarction, and acute stroke size as covariates in a partial correlation analysis, the above negative relationship remained significant in patients ($r = -0.51$, $p = 0.04$). We found no significant relationships between the fractional change of SDS scores and those of any VOIs in patients or controls.

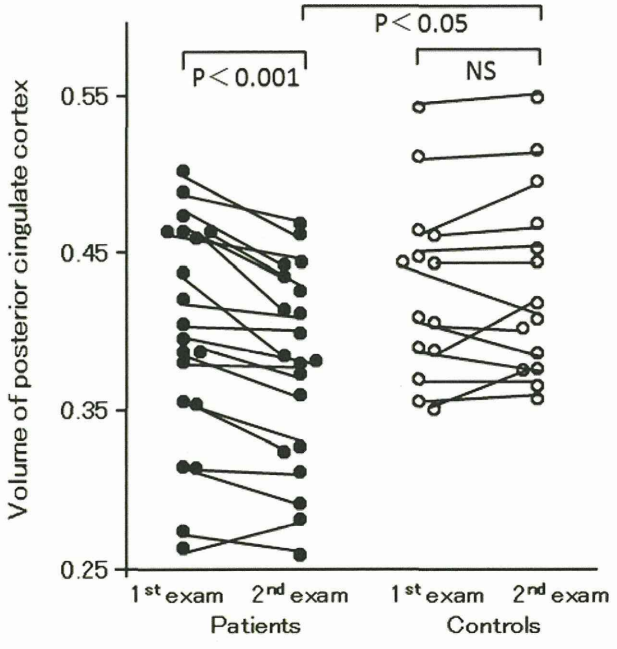

Figure 2 Scatterplots showing volume changes in cingulate cortex over 6 months in patients and controls. We placed spherical VOIs (3-mm radius) on the region where we found significant reduction in volume by voxel-based analysis over 6 months in the patient group. Examining these voxels, we find a significant reduction of gray matter volume in patients ($p < 0.001$) but not in controls by paired t-test. We find a significant group difference in volume only at the 2nd examination.

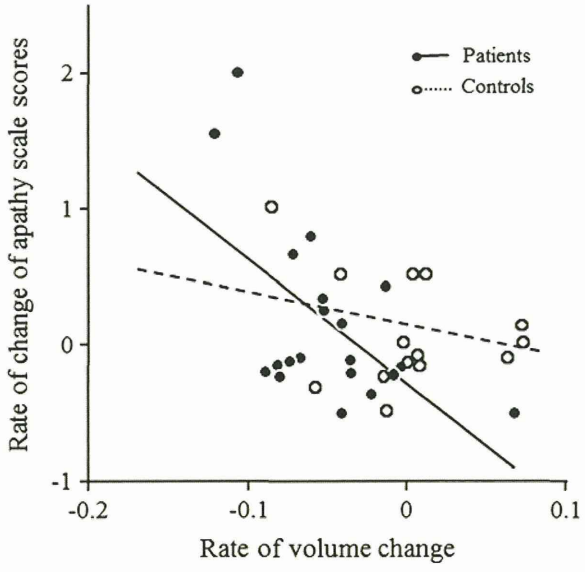

Figure 3 Scatterplots showing the relation between volume change in cingulate cortex and apathy score change over 6 months in patients and controls. A significant correlation is observed between VOI volume change and apathy score change over 6 months in patients ($r = -0.58$, $p = 0.007$), but not in controls ($r = -0.29$, $p = 0.32$) ($y = -9.1 \times x - 0.3$ for patients, $y = -2.6 \times x - 0.1$ for controls). The correlation in patients is still significant after partial correlation analysis with age, sex, laterality of the infarction, and acute stroke size as covariates ($r = -0.51$, $p = 0.04$).

When we divided the patients into two groups whose volume reduction at PCC was less than ($n = 9$) or greater than ($n = 11$) the average (difference in fractional volume change = −0.05), we found a significant difference in the fractional change of scored apathy between the groups (less-than-average group, change = −0.17; greater-than-average group, change = 0.43; $t = 2.41$; $p = 0.03$). When we considered the confounding effects of age, sex, laterality of the infarction, and acute stroke size as covariates in a one-way analysis of covariance the change in the apathy scores between groups showed a trend that did not reach significance ($F_{1, 14} = 3.2$, $p < 0.1$).

Discussion

In the present study, we found a significant volume reduction in the anterior part of the PCC over the 6 months following a stroke, by exploratory VBM analysis. Furthermore, the fractional volume change was observed to be negatively correlated with the apathy scale scores during the 6 months after the stroke. The reduced volume of PCC due to the 6-month interval was associated with increased apathy scores. Our findings indicate that the neuronal changes in PCC after stroke are one of the factors that affect the degree of poststroke apathy.

In the patients, delayed atrophy was observed in a part of the PCC anatomically remote from the respective subcortical infarct site. This finding may reflect degeneration secondary to neuronal loss, possibly due to Wallerian degeneration, which is a degeneration of distal parts of nerve axons after injury of the proximal axon or cell body (Thomalla *et al.*, 2004). Axonal degeneration, in turn, leads to the death of postsynaptic cell bodies (Raff *et al.*, 2002) and should result in a secondary volume reduction in the part of the brain constituting the projection target of the lost axons. From an anatomical perspective, the PCC has dense structural connections to many other brain regions, suggesting a role as a structural hub (Hagmann *et al.*, 2008). Its volume reduction seen here may reflect the simultaneous loss of multiple afferent projections due to stroke in spatially different sites.

We found more apathetic change in the group of stroke patients with larger volume reductions in PCC. A recent meta-analysis showed that apathy occurred in almost every third patient after a stroke (van Dalen *et al.*, 2013). Because poststroke apathy can have a negative effect on the rehabilitation of activities of daily living or quality of life (Samus *et al.*, 2005; Hama *et al.*, 2007), poststroke apathy has attracted considerable attention. Marin has described apathy as a neuropsychiatric syndrome characterized by diminished goal-directed overt behavior, diminished goal-directed cognition, and diminished emotional concomitants of goal-directed behavior (Marin, 1991).

How is the volume reduction of PCC related to the increase in apathy of stroke patients? The PCC is a hub within the brain, connecting networks that function together to support complex behavior (Hagmann *et al.*, 2008). Leech *et al.* (2011) reported that the PCC is subdivided into dorsal and ventral parts differing in the regions to which they functionally connect. The dorsal part of the PCC is consistent with the region showing the volume reduction in stroke patients in the present study. Anatomically, the dorsal part of the PCC has connectivity with the ventral medial prefrontal cortex, part of the default mode network (DMN), and frontal and parietal regions involved in the cognitive control network (CCN). Abnormalities have been identified in CCN and DMN during episodes of late-life depression that have often been characterized as apathy (Alexopoulos *et al.*, 2012), and the PCC was suggested to have an important role in the regulation of these two networks necessary for controlling efficient goal-directed behavior (Leech *et al.*, 2011). We speculate that the degeneration of the PCC following a stroke might impair the function of control of goal-directed behavior, leading to increased apathy scores.

Our study has some limitations. First, we could not find volume reductions in any other regions of the brain than the PCC. However, the sample size in our study was not large enough to reveal moderate-sized differences between groups. Further study with increased numbers of subjects will be necessary for drawing any definitive conclusions. Second, we could not find associations between cognitive scales and the volume reduction at PCC. We assessed cognitive deficits using MMSE scores, but this test is not highly sensitive to differences between persons with normal and higher performances; thus, the possible presence of a ceiling effect must be considered. Extensive neuropsychological testing is needed for the assessment of cognitive dysfunction. Finally, we were not able to control precisely for important variables, such as social support, premorbid personality, and prior medication histories. Further analysis in light of these points is needed to confirm our present findings.

Conclusion

The present study suggests that delayed atrophic change in the PCC is evident 6 months after a stroke. We also found that the fractional volume change during the 6 months following a stroke was negatively correlated with apathy scale scores. The larger the volume reduction in PCC, the

greater was the increase in apathy-scale scores. The delayed atrophy of part of the PCC seen here may reflect degeneration secondary to neuronal loss due to stroke. Damage in this area may damage control of goal-directed behavior, and it is plausible that such a defect would appear clinically as greater apathy. Knowledge of secondary brain degeneration in stroke patients and its impact on the adverse outcome of development of apathy could provide clues for recognizing new therapeutic targets.

Conflict of interest

None declared.

Key points

- We found significant volume reduction in the anterior part of the PCC over 6 months after the incidence of stroke in patients by exploratory VBM analysis.
- We also found that the rate of volume change was significantly correlated with the apathy scale scores during 6 months post-stroke.
- The delayed atrophy of the PCC may reflect degeneration secondary to neuronal loss due to stroke, and it might deteriorate the function of controlling goal-directed behavior related to apathetic change.

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RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Low amyloid-β deposition correlates with high education in cognitively normal older adults: a pilot study

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Objective: Several epidemiological studies have found a lower incidence of Alzheimer's disease in highly educated populations, but the protective mechanism of education against the disease is still unclear. Our objective was to investigate the association between education and ^{11}C-labeled Pittsburgh Compound B (PIB) uptake with positron emission tomography in participants with normal cognitive ability.

Methods: We performed ^{11}C-labeled PIB positron emission tomography and neuropsychological testing in 30 cognitively normal older participants. Of the participants, 16 had a period of education less than 12 years (low-education group) and 14 had more than 13 years (high-education group). Amyloid-β deposition was quantified by binding potential (BP_{ND}) in several brain regions and was compared between the groups with different education levels.

Results: We found significantly higher cortical PIB-BP_{ND} in the cognitively normal participants with low education compared with the ones with high education. None of the brain regions in low-education group showed significantly lower BP_{ND} values. This finding was not affected by the inclusion of possible confounding variables such as age, sex, and general intelligence. Our findings indicated a reduced amyloid pathology in highly educated, cognitively normal, participants.

Conclusions: Our findings lead to the proposal that early-life education has a negative association with Alzheimer's disease pathology. This proposal is not in opposition to the brain reserve hypothesis. People with more education might be prone to a greater inhibitory effect against amyloid-β deposition before the preclinical stage. At the same time, they have a greater reserve capacity, and greater pathological changes are required for dementia to manifest.

Key words: Alzheimer's disease (AD); amyloid-β (Aβ); positron emission tomography (PET); ^{11}C-labeled Pittsburgh Compound B ([^{11}C]PIB); education
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Introduction

In vivo positron emission tomography (PET) studies have shown an increased uptake of the amyloid ligand ^{11}C-labeled Pittsburgh Compound B ([^{11}C]PIB) in Alzheimer's disease (AD) and mild cognitive impairment patients, especially in the frontal, parietal, and temporal cortices and in the posterior cingulate, indicating increased amyloid accumulation in these areas (Klunk *et al.*, 2004; Kemppainen *et al.*, 2006, 2007). Importantly, 20–30% of cognitively normal older individuals also display significant PIB uptake (Pike *et al.*, 2007; Morris *et al.*, 2010), which is consistent with the evidence that some older individuals who had intact cognition during their later life showed substantial numbers of amyloid-β (Aβ) plaques postmortem (Bennett *et al.*, 2006). A greater understanding of the factors associated with Aβ variability in the older population could have important consequences for disease prevention.

Several epidemiological studies have found a lower incidence of AD in highly educated populations, suggesting that education provides protection against

the disease (Stern *et al.*, 1994). This reduced risk for AD in highly educated individuals has been proposed to reflect an increased cognitive reserve that provides greater brain capacity to compensate for disruptions caused by disease pathology and can thus delay the clinical expression of AD (Stern, 2006). This cognitive-reserve hypothesis has been explored in relation to AD pathology (Rentz *et al.*, 2010; Vemuri *et al.*, 2012).

In contrast, individuals with greater early- and middle-life cognitive activity have shown lower [^{11}C]PIB uptake in a previous study (Landau *et al.*, 2012). Greater lifetime cognitive activity has been reported to forestall AD pathology, even in genetically susceptible individuals (Wirth *et al.*, 2014). These studies suggest that people with higher education, who might have more chance of lifetime cognitive activity, have greater inhibitory effects against Aβ deposition. Our objective was to examine the possible association of early-life education with [^{11}C]PIB uptake in later life stage of cognitively normal subjects. We hypothesize that cognitively normal and highly educated participants have lower [^{11}C]PIB uptake, indicating less pronounced pathological brain changes compared with less-educated participants with normal cognitive function. We investigated this hypothesis by performing [^{11}C]PIB-PET and neuropsychological testing in a sample of cognitively normal older participants. Aβ deposition in several cortical brain regions was examined in cognitively normal older participants with different education levels.

Materials and methods

Participants

Thirty cognitively normal older participants were recruited from the local area by poster advertisement. Sixteen participants received education for less than 13 years (low/middle-education group), and 14 had no less than 13 years of education (high-education group). Twelve years' education in Japan corresponds to the education from elementary school to high school, which was regarded as low to middle level of education in Japan. The inclusion criteria were an age of 55–79 years, a Mini-mental state examination (MMSE) score of 26 or higher (Folstein *et al.*, 1975), independent living in the community, normal performance on cognitive tests, and no major structural abnormalities or signs of major vascular pathology on magnetic resonance imaging (MRI). The exclusion criteria included major neurological, psychiatric, or medical illnesses; depression (assessed with the Geriatric Depression Scale) (Yesavage *et al.*, 1982–1983); the use of medications that affect cognition; and MRI contraindications. This study was approved by the institutional review boards of all of the participating institutions, and all participants gave written informed consent.

Neuropsychological testing

All of the participants completed an extensive neuropsychological battery, which was administered up to 1 month before the PET scan to screen for impaired cognition. They were assessed by the MMSE (Folstein *et al.*, 1975), the Alzheimer's Disease Assessment Scale-cognitive subscale (Rosen *et al.*, 1984), and the Raven's Colored Progressive Matrices (RCPM) (Raven, 1958) to measure general cognitive ability and intelligence. They were also assessed by the Wechsler Memory Scale-Revised (Wechsler, 1987) and the Rey Auditory Verbal Learning Test-Revised (Spreen and Strauss, 1991) to measure memory function and by the Frontal Assessment Battery (Dubois *et al.*, 2000) for frontal dysfunction. Attention and executive function were measured by the Trail Making Test (TMT) A and B (Partington and Leiter, 1949).

Probe synthesis

^{11}C-labeled Pittsburgh Compound B was synthesized by the reaction of 2-(40-aminophenyl)-6-hydroxybenzothiazole and [^{11}C]methyl triflate according to a previous method (Price *et al.*, 2005). The product had a radiochemical purity greater than 96.1%. The specific activity ranged from 36.7 to 135.2 GBq/mmol at the time of injection.

Positron emission tomography scanning

Positron emission tomography examinations were performed with a Biograph mCT (Siemens, Knoxville Healthcare/Molecular Imaging, TN, USA). This equipment provides a 40-slice CT, an axial field of view of 218 mm, a coincidence window of 4.1 ns, a timing resolution below 0.6 ns, and an energy window of 435–650 keV. Dynamic emission scan data were acquired in the three-dimensional mode for a period of 70 min. The participants were examined while they were resting in a supine position in a quiet room, and their heads were restrained with a band extending across the forehead that was attached to the headrest. An examiner carefully monitored head movement with laser beams during each scan, and corrections

were made when necessary. [^{11}C]PIB (644 ± 32 MBq) with 50 mL of saline was intravenously injected into the right antecubital vein via an infusion pump for 60 s. A sequence of 33 scans was acquired during 70 min (4 × 15 s, 8 × 30 s, 9 × 1 min, 2 × 3 min, and 10 × 5 min) after the [^{11}C]PIB injection. All data processing and image reconstruction including scatter correction were performed using the standard Siemens software.

Magnetic resonance image acquisition

All MRI examinations were performed on a 3.0-Tesla whole-body scanner (Signa Excite HD V12M4; GE Healthcare, Milwaukee, WI, USA) with an eight-channel phased-array brain coil. High-resolution three-dimensional T1-weighted images were acquired using a spoiled gradient recalled sequence (repetition time = 12.8 ms, echo time = 2.6 ms, flip angle = 8°, field of view = 256 mm; 188 sections in the sagittal plane; acquisition matrix, 256 × 256; and acquired resolution, 1 mm × 1 mm × 1 mm).

Positron emission tomography data analysis

The regions that share a border with lower- or higher-binding structures are susceptible to partial-volume effects due to a blurring caused by the low resolution of PET (Hoffman *et al.*, 1979). Because the gray matter (GM), white matter (WM), and cerebrospinal fluid have different ^{11}C-PIB uptake patterns (Klunk *et al.*, 2004), all GM borders undergo partial-volume effects. Atrophy of a region that increases the amount of neighboring cerebrospinal fluid increases the partial-volume effects, and an effect of education on cortical volume has been reported (Arenaza-Urquijo *et al.*, 2013).

The [^{11}C]PIB-PET data were corrected for partial-volume effects with an algorithm that was implemented in the PMOD software package (PMOD V.3.3; PMOD Technologies GmbH, Adliswil, Switzerland). This correction is based on the assumption that WM uptake is homogeneous. All brain pixels are classified as either WM or GM and are sorted into respective segments. On the basis of these segments and the assumed PET resolution, the spill out from the WM to the GM can be estimated and subtracted. Similarly, the spill out from the GM to the surroundings can be estimated and compensated for. The result is a GM image with corrected activity values in all the pixels. This method was introduced by Müller-Gärtner *et al.* (Müller-Gärtner *et al.*, 1992). The corrections were performed using a point spread function, full-width-half-maximum of 4.0 mm × 4.0 mm × 4.0 mm, correction mode of GM spill out and spill in, WM estimation of regression of 0.95, and GM threshold of 0.5.

The radioactivity concentrations in six brain regions (the prefrontal cortex, lateral temporal cortex, parietal cortex, anterior cingulate cortex, posterior cingulate cortex, and cerebellum) were obtained with a template-based method for defining volumes of interest (Yasuno *et al.*, 2002). Regional time-activity data were analyzed with the Logan graphical method (Logan *et al.*, 1996) from 35 to 70 min of the PET data. The Logan graphical method has been shown to be stable, with a high test–retest reliability (Price *et al.*, 2005) and sensitivity to small changes in ^{11}C-PIB (Lopresti *et al.*, 2005). This method yields binding potential (BP) estimates relative to the non-displaceable (ND) binding, which is denoted by BP_{ND} (Innis *et al.*, 2007).

Analysis methods that used 90 min of PIB-PET data performed better compared with when 60 min was used, but 60 min of PET data also yielded useful data, as judged by the evaluation criteria (Lopresti *et al.*, 2005). Because of considerations of the fatigue of the subjects and the maintenance of the reliability of the analysis, we used the 35–70 min PET data for this analysis.

A voxel-based BP_{ND} was estimated from the [^{11}C]PIB-PET data with a Logan plot graphical analysis, with the cerebellum as the reference region in the PMOD software package. The spatial preprocessing of maps was performed using statistical parametric mapping (SPM, Wellcome Institute of Neurology, University College London, UK). Each T1-weighted MRI scan was coregistered to each PET image, and the spatial normalization of the MRI images to the SPM8 T1-MRI template was applied to the PET images. The normalized BP images were smoothed with a Gaussian filter to 10 mm full-width-half-maximum. We performed a voxel-based analysis of covariance (ANCOVA) on the BP_{ND} images between the low/middle- and high-education groups, while adjusting for differences in age, sex, and RCPM scores (a measure of general intelligence) as possible confounding factors.

Statistical analysis

Statistical analysis was performed with SPSS for Windows 22.0 (IBM Japan, Tokyo, Japan). Regional BP values of the two groups were compared using repeated measures ANCOVA with a Greenhouse–Geisser correction, using age, sex, and RCPM scores as covariates. A follow-up ANCOVA with age, sex, and RCPM score as covariates was performed on the

BP_{ND} values of each volumes of interest. Global cortical mean BP_{ND} values were also compared between groups with ANCOVA using age, sex, and RCPM score as covariates. The correlation between the global cortical mean BP_{ND} values and the duration of education for all of the subjects was evaluated with a Spearman's ρ test. All of the statistical tests were two-tailed and considered significant at $p < 0.05$.

Analysis of the parametric BP images with SPM8 was performed to examine the differences in BP_{ND} between the groups. The statistical test results with an uncorrected p level of 0.001 were considered significant. Clusters of at least 50 contiguous significant voxels were interpreted as significant sites.

Results

Demographic and clinical data

Table 1 summarizes the demographic and clinical characteristics of the participants in the low/middle- and high-education groups. They did not differ significantly in age. The percentage of males was higher in the highly educated group, but the difference in the percentage was not significant between the groups. As for the cognitive functions measured with the MMSE, Alzheimer's Disease Assessment Scale-cognitive subscale, RCPM, and several neuropsychological tests, neither of the groups showed any abnormalities, and all of the scores were within normal ranges. There were no significant between-group differences in the scores of these tests except for the RCPM, which was higher in the highly educated group.

Differences in the Pittsburgh Compound B-binding potential values between the low/middle- and high-education groups

Table 2 shows the PIB-BP_{ND} values between the low/middle- and high-education groups. An ANCOVA of the BP_{ND} values for these groups with age, sex, and RCPM score as covariates revealed a significant main effect of education on the PIB-BP_{ND} values. Follow-up

Table 1 Demographic statistics and neuropsychological performances of the low/middle- and high-education groups

Characteristic/test	Low/middle education	High education	t_{28} or χ^2	p
No.	16	14		
Sex M/F	7/9	11/3	3.77	0.05
Age, y	70.3 ± 5.6	68.7 ± 8.2	0.60	0.55
Education, y	11.4 ± 1.6	16.1 ± 2.0	6.95	0.0001[h]
MMSE[a]	29.3 ± 1.2	29.6 ± 0.6	1.07	0.29
ADAS-C[b]	3.6 ± 1.3	3.7 ± 1.7	0.12	0.90
RCPM[c]	32.5 ± 2.6	34.4 ± 2.2	2.18	0.04[h]
GDS[d]	2.6 ± 2.8	3.8 ± 3.6	1.02	0.32
Neuropsychological tests				
WMS-R[e]				
Verbal memory index	108.3 ± 9.2	113.5 ± 5.7	1.82	0.08
Visual memory index	106.7 ± 11.4	109.1 ± 9.8	0.61	0.55
General memory index	108.6 ± 9.8	113.4 ± 6.6	1.55	0.13
Attention index	104.8 ± 13.1	108.6 ± 13.2	0.80	0.43
Delayed memory index	107.5 ± 9.4	111.9 ± 7.3	1.43	0.17
RAVLT[f]				
Maximum of the correct immediate recall	12.4 ± 1.3	12.9 ± 1.1	1.26	0.22
Delayed recall	10.5 ± 2.1	11.1 ± 2.1	0.83	0.41
Delayed recognition	47.2 ± 3.2	48.1 ± 1.9	0.91	0.37
FAB[g]	17.2 ± 0.8	17.3 ± 0.9	0.32	0.75
Trail making test (second)				
A	36.8 ± 15.4	36.6 ± 10.6	0.02	0.98
B	93.6 ± 36.2	92.4 ± 23.2	0.11	0.92

Data are mean ± standard deviation (SD).
[a]Mini-mental state examination.
[b]Alzheimer's Disease Assessment Scale-cognitive subscale.
[c]Raven's Colored Progressive Matrices.
[d]Geriatric Depression Scale.
[e]Wechsler Memory Scale-Revised.
[f]Rey Auditory Verbal Learning Test-Revised.
[g]Frontal Assessment Battery.
[h]$p < 0.05$.

Table 2 Comparison of binding potential (BP_{ND}) values between the groups with low/middle and high education

Region	BP_{ND} values (mean ± SD)[a,b]		Analysis of covariance	
	Low/middle education ($n = 16$)	High education ($n = 14$)	F ($df = 1, 25$)	p
Prefrontal cortex	0.24 ± 0.18	0.11 ± 0.19	3.40	0.08
Lateral temporal cortex	0.12 ± 0.16	−0.03 ± 0.16	5.64	0.03[c]
Parietal cortex	0.19 ± 0.18	0.06 ± 0.18	3.40	0.08
Anterior cingulate cortex	0.30 ± 0.18	0.14 ± 0.18	4.82	0.04[c]
Posterior cingulate cortex	0.30 ± 0.18	0.16 ± 0.18	3.87	0.06
Global cortical mean	0.23 ± 0.16	0.09 ± 0.16	4.90	0.04[c]

[a]BP_{ND} values were adjusted for age and sex.
[b]Repeated measures of analysis of covariance with age, sex, and RCPM score as covariates revealed a significant main effect of education (Regions: $F = 0.73$, $df = 2.3, 58.2$, $p = 0.51$; region × education: $F = 0.16$, $df = 2.3, 58.2$, $p = 0.88$; education: $F = 4.90$, $df = 1, 25$, $p = 0.04$).
[c]$p < 0.05$

analysis revealed that the BP_{ND} values of the low/middle-education group were significantly higher in the lateral temporal and anterior cingulate cortices. The BP_{ND} values of the low/middle-education group in other regions showed a trend toward an increase compared with the high-education group ($p < 0.1$). The global mean BP_{ND} values were significantly higher in the low/middle-education group than the high-education group (Table 2, Figure 1(a)). Four of the "low/middle education" group showed relatively high BP values (>0.3), which were high enough to suggest that the PIB binding is positive. However, when we removed these subjects from the data, the low/middle-education group remained to show higher global mean BP_{ND} values ($F_{1, 21} = 8.59$, $p = 0.008$). When we applied a nonparametric analysis with the Mann–Whitney U test, the result was not changed ($Z = 2.99$, $p = 0.002$). There was a significant correlation between the duration of education and the global mean BP_{ND} values for all the subjects ($r = -0.58$, $p = 0.001$; Figure 1(b)).

In the voxel-based ANCOVA of the PIB-BP_{ND} values, the low/middle-education group showed higher BP_{ND} values in the broad cortical areas shown in Table 3 and Figure 2. There were no significantly lower BP_{ND} values in any region in the low/middle-education group.

Discussion

This study demonstrated significantly higher cortical PIB-BP_{ND} in the cognitively normal participants with low/middle levels of education compared with those with high levels of education. Neither group showed a significant difference in the cognitive measurements, except for the RCPM score, which is a measure of

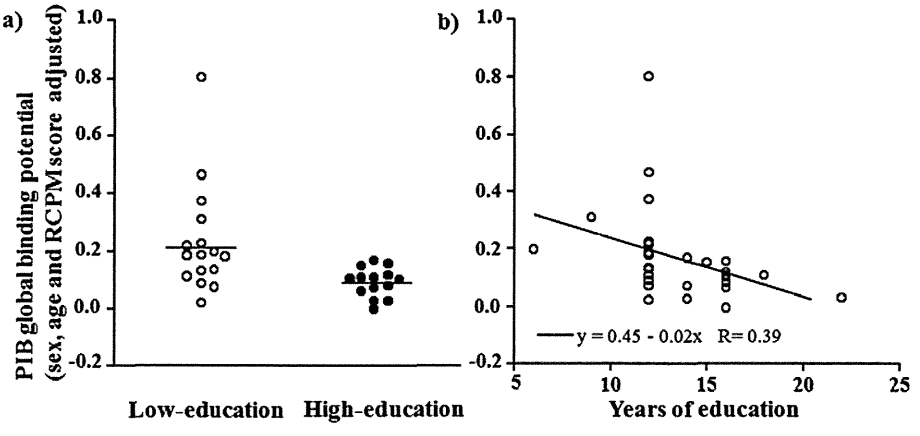

Figure 1 (a) The scatter plot of global cortical mean Pittsburgh Compound B-binding potential (PIB-BP_{ND}) of the participants in the low/middle- and high-education groups, and (b) the plot between PIB-BP_{ND} and the duration of education for all subjects. The PIB-BP_{ND} values were adjusted for the variables of age, sex, and Raven's Colored Progressive Matrices (RCPM) score.