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ORIGINAL ARTICLE

Classification of delusions in Alzheimer's disease and their neural correlates

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Abstract

Background: Previous findings on neural correlates of delusion in Alzheimer's disease (AD) have been inconsistent because of methodological issues, such as treating multiple delusions as a single entity. In this retrospective study, we classified AD delusions and investigated their neural correlates by using single-photon emission computed tomography data.

Methods: We selected AD patients with delusions from our consecutive outpatients from 2004 to 2010. In this study, eight types of delusions were evaluated with Neuropsychiatric Inventory and classified by factor analysis. Twenty-five of the patients also had single-photon emission computed tomography data, which we used to assess the relationships between cerebral regions of hypoperfusion and hyperperfusion and each classified delusion. The relations were assessed using Statistical Parametric Mapping with normalization to the white matter cerebral blood flow.

Results: The delusions were classified into three factors. Factor 1 consisted of a belief that his/her house is not his/her home, phantom boarder symptom, delusion of abandonment, and belief that one's spouse or others are not who they claim to be. Factor 1 was related to hypoperfusion in the right temporal pole and hyperperfusion in the medial frontal and precentral regions. Factor 2 consisted of delusion relating to the television and delusion of persecution. Factor 2 was related to hypoperfusion in the precuneus and hyperperfusion in the insula and thalamus. Factor 3 consisted of delusion of abandonment and delusional jealousy. Factor 3 was related to hypoperfusion in the right inferior temporal and frontal regions and hyperperfusion in the middle frontal gyrus, insula and posterior cingulate gyrus. Delusion of theft was not included in any factors, and it was related to hypoperfusion in the bilateral thalami and left posterior cingulate gyrus and hyperperfusion in the left inferior frontal regions and anterior cingulate gyrus.

Conclusions: Delusions in AD were classifiable, and each classified delusion was related to different neural networks.

Key words: *Alzheimer's disease, delusions, factor analysis, neuroanatomical basis, regional cerebral blood flow, single-photon emission computed tomography.*

INTRODUCTION

A wide range of neuropsychiatric symptoms and behavioural changes, known as behavioural psychological symptoms of dementia (BPSD), can emerge in the course of Alzheimer's disease (AD).[1,2] BPSD can encompass delusions, hallucinations, agitation, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability and aberrant motor behaviours.[1] Among BPSD, delusions are more likely to appear at the earlier stage and are one of the common symptoms.[3–6] The occurrence of delusions in AD is generally a sign of a worsening prognosis.[7,8] Delusions increase a patient's sense of distress and the burden on the caregivers,[9] and can be a predictor of the need for

institutionalization.[10–12] Current neuroleptic drugs for delusions are not very effective.[10,13] Designing more effective drugs would be easier if the mechanisms by which delusions in AD develop were better understood.

Although many studies have investigated the neural correlates of delusion in AD with single-photon emission computed tomography (SPECT) and positron emission tomography (PET), there is no consensus on these findings.[4,6,14–18] The lack of consensus could be the result of methodological differences, which fall into four categories.

First, previous AD delusion studies considered the delusions as a single entity. However, many types of delusions have been described in AD. The most common types are delusion of persecution,[4–6,11,14,16,17,19–21] delusion of theft,[4–6,11,17,19–22] delusion of abandonment,[4–6,19–21] phantom boarder symptoms (PBS) (belief that some people are in his/her house although the no one is actually there),[4–6,19,20,23] misidentification of people,[6,17,20] including Capgras phenomenon,[14,16,20,21,24,25] belief that his/her house is not his/her home,[4–6,11,17,20,21,24] delusions relating to the television (i.e. the belief that television or magazine images or reports are actually present in the home),[4–6,19,20,23,26] and delusional jealousy.[4–6,14,20,21] Other delusions, such as misidentification of mirror image and the belief that a deceased family member is still alive,[17,19,20,23] can be also observed in AD. Patients with AD often experience more than two types of delusions at the same time.[5] However, AD patients with delusions do not experience all kinds of delusion in the course of the disease, and the frequency of each type of delusion differs.[4–6] Therefore, we thought that delusions in AD may be classifiable and distinguishable neuropsychiatric symptoms.

Second, among the three accumulative radiopharmaceuticals used to assess regional cerebral blood flow (rCBF) with SPECT (technetium-99-labelled hexamethylpropyleneamine oxime, technetium-99-labelled ethyl cysteinate dimer, and iodine-123-labelled N-isopropyl-p-iodoamphetamine (^{123}I-IMP)),[27] ^{123}I-IMP shows the best linearity between the cerebral radioactivity and cerebral blood flow (CBF).[28] Furthermore, ^{123}I-IMP is more sensitive to abnormalities in brain perfusion than the others.[29] However, no studies have yet used ^{123}I-IMP SPECT to investigate the relationship between AD delusions and rCBF. We expected that ^{123}I-IMP SPECT would detect minor alterations of rCBF that previous studies have missed.

Third, most previous neuroimaging studies investigating AD delusions used the regions of interest (ROI) technique to evaluate alterations in rCBF or regional cerebral metabolic rate.[4,14,16,18,24] The ROI technique is not user-independent and cannot evaluate the whole brain. Moreover, the ROI technique does not take individual variations in brain size and shape into account, so it is not suitable for assessing AD brains, which are atrophic. Statistical parametric mapping (SPM) has recently supplanted the ROI technique. SPM analyzes the obtained spatially normalized brain images on a voxel-by-voxel comparison without any priori assumptions and evaluates the whole brain.[22]

Fourth, in statistical analyses, normalization is required to reduce intra-individual variation and to sensitively detect disease-dependent patterns of rCBF and regional cerebral metabolic rate in the SPM.[30,31] Usually, the counts per voxel are normalized to the global mean, which normalizes a global CBF for each subject to 50 mL/100 g/min.[30,31] However, the normalization to the global mean falsely increases CBF and cerebral metabolic rate, which are in fact unchanged.[30] Recently, it has been found that normalization to the white matter produced much less biased patterns of CBF than normalization to the global mean.[30,31]

The aims of this study were to classify delusions in AD with a factor analysis (Study 1) and to investigate the neural correlates of each classified delusion with ^{123}I-IMP SPECT (Study 2). We analyzed the SPECT data with SPM and normalized the counts per voxel to the white matter for statistical analyses.

STUDY 1 AND STUDY 2

These studies were carried out in accordance with the World Medical Association's Declaration of Helsinki (2008) and approved by the Research Ethical Committee of Osaka University (Suita, Japan).

Study 1: classification of delusions in AD

Methods

Participants. Eighty-seven AD patients with delusion were entered into this study. None of them lived in a nursing home. They were consecutive outpatients of the neuropsychological clinic in the Department of Neuropsychiatry of Osaka University Medical Hospital

between December 2004 and December 2010. All patients met the following criteria: (i) met the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria for probable AD;[32] (ii) showed evidence of diffuse cerebral atrophy and possible atrophy in the medial temporal lobes on a cranial magnetic resonance imaging (MRI) or a cranial computed tomography; (iii) had no history of other neurological or psychiatric disorders, serious cerebral vascular disorders, brain tumours, brain injuries, or alcohol abuse; (iv) were at least 60 years old at the first visit; and (v) had a reliable caregiver who could evaluate the BPSD. This study carefully excluded patients who showed indication of dementia with Lewy bodies, such as notable fluctuating cognition with pronounced variations in attention and alertness, recurrent visual hallucinations, or spontaneous motor features of parkinsonism.[33]

The mean age of the patients with delusions was 75.7 ± 6.8 years (range: 63–90 years). The number of women exceeded the number of men (65 vs 22). The mean years of education were 11.5 ± 2.8 (range: 6–18 years). Fifty-five patients (63.2%) were receiving donepezil and nine others (10.3%) were receiving antipsychotics (risperidone: four; tiapride: two; quetiapine: two; sulpiride: one). The mean Mini-Mental State Examination score was 17.4 ± 5.3 (range: 3–26).[34] The Clinical Dementia Rating (CDR) was used to evaluate disease stage.[35] The CDR is a five-point scale with the following grades: 0, no symptoms; 0.5, very mild; 1, mild; 2, moderate; 3, severe.[35] The numbers of patients with CDR grades of 0.5, 1, 2 and 3 were 19, 37, 25 and 6, respectively.

Assessment of delusions. The Neuropsychiatric Inventory (NPI) was employed to evaluate BPSD.[36] The NPI has been frequently used in clinical settings and has been shown to be valid and reliable in both Western countries and Japan.[36,37] The NPI contains 10 subscales of BPSD, including delusion. For those symptoms, the caregiver was asked to rate severity from 0 to 3 and frequency from 0 to 4 for each subscale. The NPI composite scores were calculated by multiplying the severity and frequency scores, so the possible composite scores ranged from 0 to 12 for each subscale. In the delusion subscale, eight different types of delusion, which have been reported to be the most frequent in AD,[20,21] can be evaluated in a manner of present or absent. The eight delusions were: delusion of persecution, delusion of theft, delusional jealousy, PBS, belief that one's spouse or others are not who they claim to be, belief that his/her house is not his/her home, delusion of abandonment, and delusion relating to the television (i.e. the belief that television or magazine images and reports are actually present in the home).[36,37] Although the original NPI defines PBS as a belief that unwelcome guests are living in his/her house,[36,37] we also considered the complaint PBS if a patient complained that family members or acquaintances who had already died or left home were in his/her house. We evaluated the eight delusions within the preceding 30 days by interviewing each patient's main caregiver.

Statistical analysis for clinical data and classification of delusions. The eight types of delusions were analyzed with exploratory factor analysis. Before carrying out a principal component analysis, we assessed the suitability of data and the factorability of the correlation matrix by calculating the Kaiser-Meyer-Olkin measure of sampling adequacy and Bartlett's test of sphericity. The principal component analysis was used to analyze the inter-item relationship and to extract the initial factors, and then a Varimax rotation was performed. The number of factors to be retained was determined by examining the eigenvalues exceeding 1.0 and by examining a scree plot. Items with factor loadings ≥0.30 were entered as a factor. In general, dichotomous responses are not appropriate for a factor analysis. However, if a factor analysis is employed to investigate a general clustering of variables and if the underlying correlations among variables are moderate, a factor analysis for dichotomous variables is allowed.[38] A factor analysis accompanies factor scores, which can be used as variables in subsequent statistical modelling, for each factor. We used the factor scores for Study 2. All statistical analyses of the demographic and neuropsychological data were performed with SPSS v. 17.0 (SPSS Inc. Chicago, IL, USA). An alpha level less than 0.05 was considered to be significant for all statistical analyses.

Results

Frequencies of different types of delusion. The mean composite scores of NPI delusion was 4.4 ± 3.4 (range: 1–12). The most common type of delusion was delusion of theft ($n = 47$, 54.0%), followed by PBS

Table 1 Factor loadings for delusions according to Neuropsychiatric Inventory in patients with Alzheimer's disease

	Factor 1	Factor 2	Factor 3
Eigenvalues	1.83	1.28	1.10
Variance explained (%)	22.8	16.0	13.7
His/her house is not his/her home	**0.687**	0.069	–0.010
Phantom boarder symptom	**0.605**	–0.095	–0.113
Delusion of abandonment	**0.590**	0.004	**0.579**
Spouse or others are not who they claim to be	**0.352**	–0.676	–0.199
Delusion relating to the television	0.038	**0.579**	–0.469
Delusion of persecution	0.225	**0.487**	0.054
Delusional jealously	–0.221	0.087	**0.738**
Delusion of theft	–0.610	–0.416	0.188

Significant loadings (≥0.30) were entered into the factor and are displayed in boldface.

(n = 29, 33.3%) and belief that his/her house is not his/her home (n = 29, 33.3%), and delusion of persecution (n = 26, 29.9%). Delusion relating to the television (n = 11, 12.6%), belief that one's spouse or others are not who they claim to be (n = 8, 9.2%), delusional jealousy (n = 7, 8.0%), and delusion of abandonment (n = 6, 6.9%) were less common delusions. In this study, the subject of patients' PBS was mostly people closely related to the patients such as a child, sibling, grandparent, cousin, or acquaintance, even though the person had already died or left home. Although these people were not living with the patients, the patients felt as if they were present. Of the 87 patients, 51 patients (58.6%) presented more than two types of delusion.

Classification of delusions. The results of the exploratory factor analysis are shown in Table 1. The value of the Kaiser-Meyer-Olkin measure of sampling adequacy was 0.555, and Bartlett's test of sphericity reached statistical significance (χ^2 = 45.798, d.f. = 28, P = 0.018). The principal component analysis found three components with eigenvalues exceeding 1.0, explaining 22.8%, 16.0%, and 13.7% of the variance respectively. Moreover, a plain break after the third component was seen by visual inspection of the scree plot. The delusions that were loaded into Factor 1 were belief that his/her house is not his/her home, PBS, delusion of abandonment, and belief that one's spouse or others are not who they claim to be. The delusions that were loaded into Factor 2 were delusion relating to the television and delusion of persecution. The delusions that were loaded into Factor 3 were delusion of abandonment and delusional jealousy. The factor loadings of delusion of abandonment for Factor 1 and 3 were almost equivalent (0.590 and 0.579, respectively). Delusion of theft was not loaded into any of these three factors, and it was negatively loaded into Factors 1 and 2.

Study 2: Neural correlates of each classified delusions

Methods

Participants. Among the 87 patients, 25 patients underwent a ^{123}I-IMP SPECT examination. None of them had bad smoking or drinking habits nor reported complications or histories of severe heart and pulmonary diseases. Severe ischemic changes were not observed on head MR images, and motion artefacts were not observed on the head MR images and SPECT images. In Study 2, the mean age of the patients with delusions was 74.0 ± 7.2 years (range: 63–86 years). The numbers of men and women were 4 and 21, respectively. The mean years of education were 10.8 ± 2.5 (range: 8–17 years). Donepezil was prescribed to 18 patients (72.0%), and antipsychotics were prescribed to two patients (8.0%), one of whom received tiapride and the other received sulpiride. A potent vasodilator, which was nicergoline, was prescribed to four patients. The mean Mini-Mental State Examination score was 18.3 ± 4.3 (range: 8–26). The numbers of patients with CDR grades of 0.5, 1, 2, and 3 were six, ten, eight and one, respectively. The mean factor scores for each factor were 0.1449 ± 1.0141 (range: –1.53–2.32) for Factor 1, –0.2113 ± 0.9446 (range: –2.15–1.55) for Factor 2, and –0.0258 ± 0.9646 (range: –1.29–2.15) for Factor 3.

SPECT image acquisition. Patients were each administered 167-MBq ^{123}I-IMP intravenously and asked to lie supine on the scanning bed with their eyes closed in a quiet examination room while the SPECT images were acquired. The SPECT scans were performed with a four-head rotating gamma camera (Gamma View SPECT 2000H; Hitachi Medical Corporation, Tokyo, Japan) with a low-energy, medium-resolution parallel-hole collimator that allows a spatial resolution of 13 mm full width at half maximum. After each patient's head was fixed on the headrest, a laser-assisted device equipped with the gamma camera determined the orbitomeatal line.

The acquisition protocol was 20 s per step with 64 collections over 360°, and the final data set was recorded in a 64 × 64 matrix. The raw SPECT data were transferred to a nuclear medicine computer (HARP3; Hitachi Medical Corporation, Tokyo, Japan). A Butterworth filter (cut-off frequency; 0.20 cycles per pixel; order 10) pre-filtered the projection data to minimize noise, and then the data were reconstructed into transaxial sections of 4.0-mm thick slices in planes parallel to the orbitomeatal line. Chang's attenuation correction with an optimized effective attenuation coefficient of 0.08/cm was applied to the reconstructed images.

SPECT image analysis. The SPECT data were analyzed using the SPM 5 (Wellcome Department of Cognitive Neurology, London, UK) in MATLAB software (MathWorks, Natick, MA). In the pre-processing steps, each image was spatially normalized to the stereotactic 3-D space of the Montreal Neurological Institute brain and then was smoothed with an 8 mm full width at half maximum Gaussian filter to increase the signal-to-noise ratio. The relationship between each classified delusion and rCBF was examined with multiple regression models, which are covariate only design matrices, and a two sample *t*-test was employed for the delusion of theft. In the multiple regression models, the factor scores of each factor were entered into the covariate. In both statistical models, the age, the score of the Mini-Mental State Examination, and the mean of the tracer uptake in the white matter were entered into the models as nuisance covariates. Whether the other types of delusions, except delusion of theft, were present was added to the model of the two sample *t*-test. The multiple regression models identified cerebral regions that were positively or negatively correlated with factor scores. The two sample *t*-test model identified cerebral regions that were more hyperperfused or hypoperfused in the patients with the delusion of theft than the patients without the delusion of theft. Expediently, in this study, we defined the positively correlated and more hyperperfused regions as cerebral regions of hyperperfusion and the negatively correlated and more hypoperfused regions as cerebral regions of hypoperfusion. The statistical tests were performed with thresholds of uncorrected $P < 0.01$, and the normalization to the white matter was employed. We report the significant results, in which the extent threshold was more than 100 voxels, with the Montreal Neurological Institute coordinates.[39] However, descriptions of the anatomical location also relied on visual inspection of the normalized structural MR image.

Results

Factor 1, consisting of belief that his/her house is not his/her home, PBS, delusions of abandonment, and belief that one's spouse or others are not who they claim to be, was related to hypoperfusion in the right temporal pole and hyperperfusion in the bilateral medial frontal regions and the precentral gyrus (Table 2, Fig. 1). Factor 2, consisting of delusion relating to the television and delusion of persecution, was related to hypoperfusion in the bilateral precuneus and hyperperfusion in the left insula and right thalamus (Table 3, Fig. 2). Factor 3, consisting of delusion of abandonment and delusional jealousy, was related to hypoperfusion in the right inferior temporal gyrus and inferior frontal gyrus and hyperperfusion in the left middle frontal gyrus, insula, and posterior cingulate gyrus (Table 4, Fig. 3). Finally, delusion of theft was related to hypoperfusion in the bilateral thalami and left posterior cingulate gyrus, and hyperperfusion in the left inferior frontal regions and anterior cingulate gyrus was detected (Table 5, Fig. 4).

DISCUSSION

The present study classified eight delusions in 87 AD patients through a factor analysis and then investigated the relationship between each classified delusion and alterations of rCBF by using ^{123}I-IMP SPECT. When analyzing the SPECT data, we employed SPM and normalization to the white matter CBF for the statistical analyses. Furthermore, this study revealed some hypoperfused cerebral regions related to the classified delusions. Factor 1 consisted of belief that his/her house is not his/her home, PBS, delusion of abandonment, and belief that one's spouse or others are not who they claim to be. Belief that his/her house is not his/her home and belief that one's spouse or others are not who they claim to be are a form of delusional misidentification, which refers to a false belief that an identify of a place or person has been altered,[24,40] so that those two delusions have been equated.[24,40] Furthermore, PBS has been reported to be related to belief that his/her house is not his/her home and belief that one's spouse or others are not

who they claim to be.[20,24,41–43] The present study confirmed that these three types of delusions are correlated with each other and first revealed that delusion of abandonment was also related to these three delusions.

Patients with PBS in this study probably recall a person who used to live or stay with them in the home. Delusional misidentification was found to be associated with paramnesia,[40] which is a false recollection of memory that is caused by biographical memory impairment, and losing the sense of familiarity with one's environment.[44] Therefore, PBS as well as the belief that his/her house is not his/her home and the belief that one's spouse or others are not who they claim to be are probably caused by biographical memory impairment and loss of the sense of familiarity. In Study 2, these three delusions were related to hypoperfusion in the right temporal pole, indicating that dysfunction in this region causes these three delusions. Our interpretation is consistent with the findings in previous studies that delusional misidentification was associated with right cerebral hemisphere dysfunction,[23,40] that the temporal lobes are involved in both biographical memory and experiencing feelings of familiarity,[45–47] and that the right temporal pole is involved in discriminating familiar faces and scenes from unfamiliar ones on the basis of memory.[48] As for the association between the delusional misidentifications including the three delusions and delusion of abandonment, if patients have lost senses of familiarity, they ought to be uncomfortable about and alienated from their family, home, and belongings, which subsequently brings about delusion of abandonment. Hyperperfusion in the bilateral medial frontal and precentral regions, including the primary motor cortex, was associated with the delusions in Factor 1. The primary motor cortex has been reported to play an important role in action preparation, which is induced by worry and anxiety.[49] Therefore, hyperperfusion might reflect the patients' unsettled state of mind.

Delusion relating to the television and delusion of persecution were loaded into Factor 2. These related to hypoperfusion in the precuneus and hyperperfusion

Table 2 Brain regions showing significant relative hypoperfusion and hyperperfusion in relation to Factor 1

Region	Voxels	Z-score	MNI coordinates *x*	*y*	*z*
Hypoperfusion					
Right middle temporal gyrus (temporal pole)	219	3.11	64	6	–16
Hyperperfusion					
Left medial frontal gyrus (BA 6)	2988	3.21	–4	–28	68
Left precentral gyrus (BA 4)	–	3.12	–32	–30	70
Left medial frontal gyrus (BA 6)	–	3.10	–10	–12	68

BA, Brodmann area; MNI, Montreal Neurological Institute; voxels, number of voxels in each detected region.

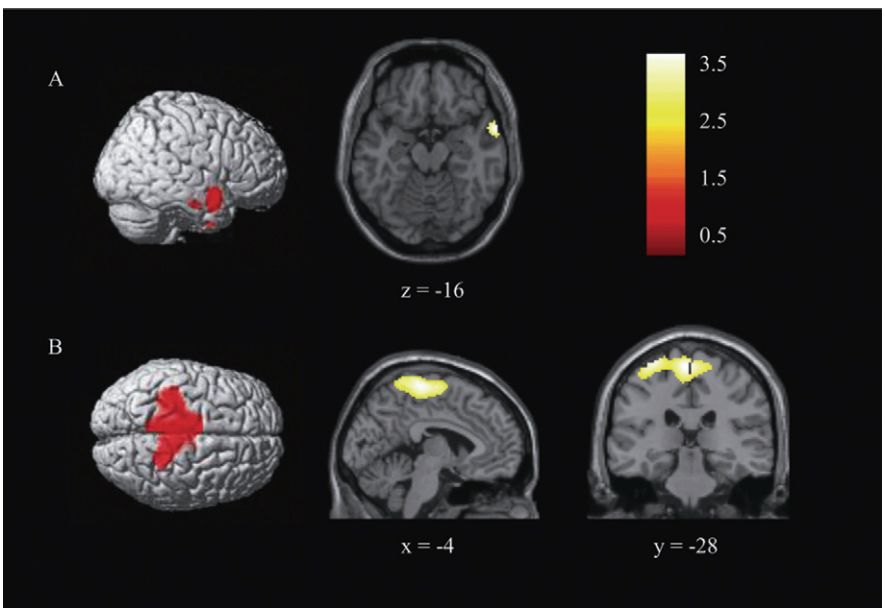

Figure 1 The results of significant (A) hypoperfusion and (B) hyperperfusion related to Factor 1 were superimposed on rendered, axial, sagittal and coronal slices of a standard brain from a single normal subject; *x*, *y* and *z* indicate the sagittal, coronal, and axial slice position in millimetres in the stereotactic space, respectively. The statistical threshold was set at $P < 0.01$ without correction for multiple comparisons. The colour bar reflects the value of the *t* statistic.

in the insula and thalamus. The relationship between the two delusions has never been reported, and thus the neural correlates have never been investigated. In previous studies, the precuneus was involved in discriminating self-relevant information from self-irrelevant information and in retrieving source memories, which are memories when and where the information was obtained.[50–52] Therefore, we thought that failing to discriminate between self-relevant and self-irrelevant information and to retrieve the information source must make the patients hypersensitive to all information. Increased activation in the insula and thalamus was reported in a functional MRI study of psychosis in schizophrenia,[53] and another functional MRI study reported that the activities of the insula are involved in suppression of negative emotions, such as fear and anger.[54] Hyperperfusion in the insula and thalamus in this study probably reflects suppression of emotional unstableness for the delusions.

Delusion of abandonment and delusional jealously were loaded into Factor 3. The relationships of the two delusions are also first reported here. The common phenomenological feature must be thoughts of abandonment. The thought of being abandoned is experienced by aged people, and it has been reported that the thought can be caused by feelings of inferiority as a result of senescence and dependence on the spouse.[55,56] AD patients feel insecurity more strongly and depend on their spouse more than aged people because of their disease; hence, the psychosocial factors are key to the two delusions. These delusions are related to hypoperfusion in the right inferior temporal gyrus and inferior frontal gyrus and hyperperfusion in the left middle frontal gyrus, insula and posterior cingulate gyrus. Previous studies revealed that the right inferolateral temporal region is involved in com-

Table 3 Brain regions showing significant relative hypoperfusion and hyperperfusion in relation to Factor 2

Region	Voxels	Z-score	MNI coordinates *x*	*y*	*z*
Hypoperfusion					
Right precuneus (BA 31)	1093	3.40	4	–74	26
Left precuneus (BA 7)	–	2.66	–14	–72	34
Hyperperfusion					
Left insula	342	2.93	–38	–12	12
Right extra-nuclear	475	2.91	26	–8	20
Right thalamus	–	2.78	24	–26	10
Right frontal sub-gyral	–	2.55	22	–18	36

BA, Brodmann area; MNI, Montreal Neurological Institute; voxels, number of voxels in each detected region.

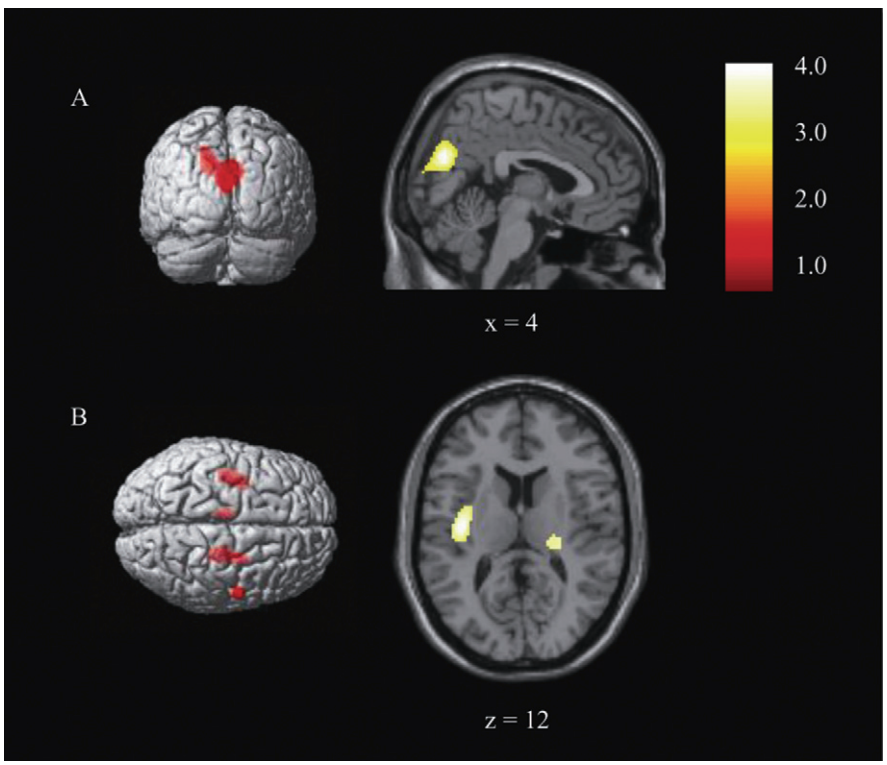

Figure 2 The results of significant (A) hypoperfusion and (B) hyperperfusion related to Factor 2 were superimposed on rendered, sagittal and axial slices of a standard brain from a single normal subject; *x* and *z* indicate the sagittal and axial slice position in millimetres in the stereotactic space, respectively. The statistical threshold was set at $P < 0.01$ without correction for multiple comparisons. The colour bar reflects the value of the *t* statistic.

prehending negative emotion exhibited by facial expression and in reading others' emotional states and feeling empathy.[57,58] Failure to comprehend others' emotional states and feel empathy strains relationships with others, which likely makes patients feel as if they have been abandoned. A previous functional MRI study found that the middle frontal gyrus, insula, and posterior cingulate gyrus, which were observed as hyperperfusion regions in our SPECT study, were activated when a participant was viewing paintings with a theme of rejection.[59] The hyperperfusion in our study must also reflect the state of mind of being abandoned.

In this study, delusion of theft was not loaded into any of the three factors, and the factor loadings for Factors 1 and 2 were negative. A previous factor analysis study of AD also found that delusion of theft differed from delusional misidentification, PBS, and delusion relating to television.[20] Another previous factor analysis study of dementia, including AD, vascular dementia, and dementia with Lewy bodies, revealed that delusion of theft was not associated with PBS, delusion of abandonment, delusion relating to the television or delusion of persecution.[19] Given the results of our study and the two previous factor analysis studies, delusion of theft does not appear to have a relationship with the other types of delusion. However, had we employed different methodologies, it is possible that such a relationship may have been found.

Table 4 Brain regions showing significant relative hypoperfusion and hyperperfusion in relation to Factor 3

Region	Voxels	Z-score	MNI coordinates *x*	*y*	*z*
Hypoperfusion					
Right inferior temporal gyrus (BA 20)	1854	3.94	52	–18	–36
Right inferior frontal gyrus	133	2.78	58	42	–10
Right inferior frontal gyrus	–	2.59	60	34	–2
Right inferior frontal gyrus (BA 10)	–	2.46	54	52	2
Hyperperfusion					
Left middle frontal gyrus	161	3.33	–60	0	44
Left insula	567	3.10	–42	2	8
Left putamen (lentiform nucleus)	–	2.57	–26	–6	–6
Left posterior cingulate gyrus (BA 31)	293	3.02	–16	–44	32

BA, Brodmann area; MNI, Montreal Neurological Institute; voxels, number of voxels in each detected region.

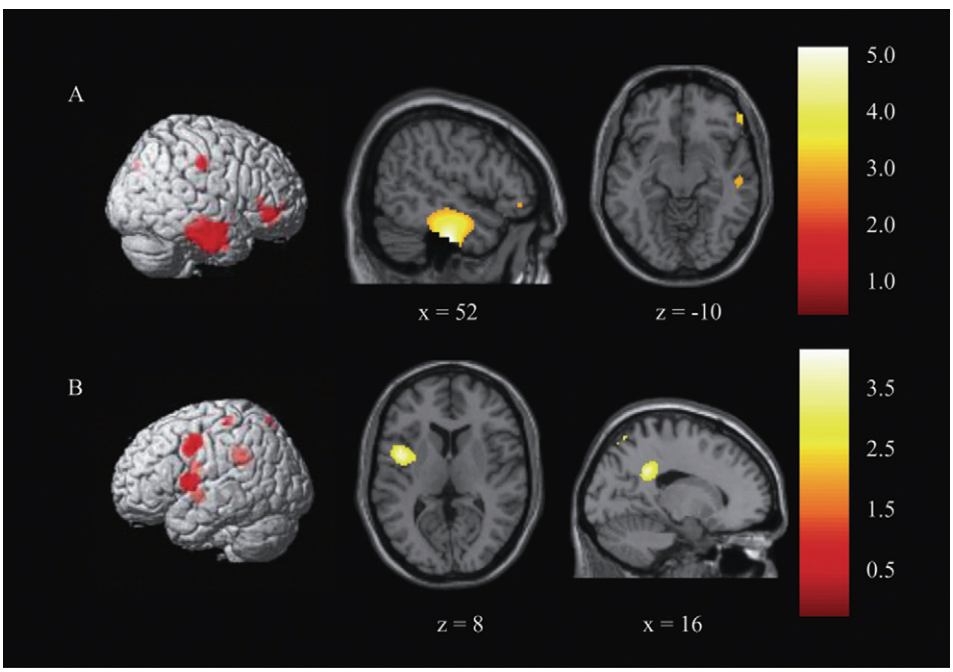

Figure 3 The results of significant (A) hypoperfusion and (B) hyperperfusion related to Factor 3 were superimposed on rendered, sagittal and axial slices of a standard brain from a single normal subject; *x* and *z* indicate the sagittal and axial slice position in millimetres in the stereotactic space, respectively. The statistical threshold was set at $P < 0.01$ without correction for multiple comparisons. The colour bar reflects the value of the *t* statistic.

The delusion of theft in this study was related to hypoperfusion in the bilateral thalami and posterior cingulate gyrus as well as to hyperperfusion in the left inferior frontal regions and anterior cingulate gyrus. The bilateral thalami and left posterior cingulate gyrus have been shown to play important roles in episodic memory in AD.[60,61] A previous study found that delusion of theft in AD was related to hypoperfusion in the right medial posterior parietal region.[22] The authors explained that the right parietal dysfunction brings attention deficit, which declines episodic memory performance, so that delusion of theft develops.[22] This indicates that the delusion of theft is associated with episodic memory impairment, which causes patients to lose their belongings and not to remember where they had left them. Increased rCBF of the left inferior frontal and anterior cingulate gyri have been related to feelings of anxiety.[62] Another study revealed that AD patients with premorbid neurotic personality tend to develop delusion of theft.[63] Hence, patients with delusion of theft are probably constantly alert and anxious that someone will steal from them, and the hyperperfusion relating to delusion of theft found in this study reflects the patients' anxiety.

Several issues in this present study should be taken considered when the findings are generalized, most importantly the small sample size, especially in Study

Table 5 Brain regions showing significant relative hypoperfusion and hyperperfusion in relation to delusion of theft

Region	Voxels	Z-score	MNI coordinates *x*	*y*	*z*
Hypoperfusion					
Left thalamus	521	3.50	–4	–30	2
Right thalamus	–	3.06	2	–26	6
Left posterior cingulate gyrus	177	3.13	–6	–10	38
Hyperperfusion					
Left inferior frontal gyrus (BA 13)	800	3.14	–38	22	8
Left anterior cingulate gyrus	–	2.60	–20	34	20

BA, Brodmann area; MNI, Montreal Neurological Institute; voxels, number of voxels in each detected region.

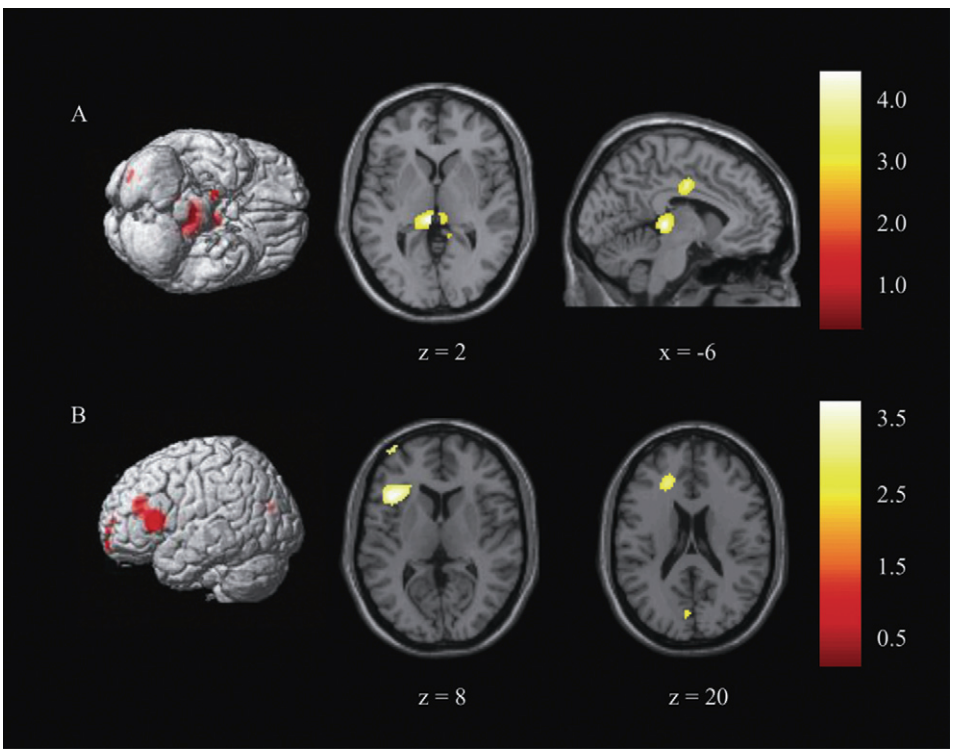

Figure 4 The results of significant (A) hypoperfusion and (B) hyperperfusion related to delusion of theft were superimposed on rendered, axial and sagittal slices of a standard brain from a single normal subject; *x* and *z* indicate the sagittal and axial slice position in millimetres in the stereotactic space, respectively. The statistical threshold was set at $P < 0.01$ without correction for multiple comparisons. The colour bar reflects the value of the *t* statistic.

2. It is difficult to administer ^{123}I-IMP SPECT examinations to patients with BPSD and cognitive impairment because they seldom keep still during the examination due to their symptoms, and sedatives cannot be given to patients before this exam. That is why the sample size for Study 2 is small. Additionally, the patients in this study could not be confirmed as having definite AD. However, most were followed up for several years, and the possibility of other disorders or diseases was ruled out. The results of this study are based on eight delusions, which were evaluated in the NPI. As such, the results might have been different if other evaluation scales, such as the Behavioural Pathology in Alzheimer's Disease Rating Scale or the Behaviour Rating Scale for Dementia, has been used.[64,65]

The present study revealed that delusions in AD are classifiable and can be correlated with rCBF in different regions of the brain. These results should help to develop more effective drugs and therapies for treating delusions in AD.

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