HMPAO SPECT Imaging of Alzheimer's Disease Patients with Similar Content-Specific Autobiographic Delusion: Comparison Using Statistical Parametric Mapping

Roger T. Staff, Annalena Venneri, Howard G. Gemmell, Michael F. Shanks, Simon J. Pestell, and Alison D. Murray

Department of Bio-Medical Physics and Bio-Engineering and Department of Radiology, University of Aberdeen and Aberdeen Royal Infirmary, Aberdeen; Department of Psychology, Kings College, University of Aberdeen, Aberdeen; and Old Age Psychiatry Unit, Royal Cornhill Hospital, Aberdeen, Scotland, United Kingdom

Delusional behavior and thinking are common symptoms in Alzheimer's disease (AD). In the past, these delusions have been considered to be psychotic complications of global neurologic dysfunction. Recently, authors have suggested that content-specific delusions in AD are associated with discrete regional abnormalities of the right hemisphere. **Methods:** This study compared ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) SPECT images of a group of AD patients with a similar autobiographic delusion with a group of AD patients without delusions and a group of AD patients with a range of delusions but without autobiographic content. The reconstructed SPECT data were compared using a statistical parametric mapping technique. **Results:** The autobiographic AD group had a significant area of hypoperfusion in the right frontal lobe when compared with the 2 other groups. The area of hypoperfusion included parts of Brodmann's areas 9 and 10. Region 9 has been identified previously as having a role in episodic memory retrieval. **Conclusion:** This result suggests that autobiographic delusions in AD may have an identifiable neuropsychologic mechanism and that it may be possible to identify an organic cause in some patients using ^{99m}Tc-HMPAO SPECT.

Key Words: SPECT; Alzheimer's disease delusions; statistical parametric mapping

J Nucl Med 2000; 41:1451–1455

It has previously been reported that up to 50% of all Alzheimer's disease (AD) patients have shown delusions and related abnormal behavior at some stage during their illness (*1*). These symptoms can cause distress to both patients and relatives and are often cited as an important reason for the transfer to institutional care (*2*). In the past, these symptoms have been considered to be emergent complications of global neurologic dysfunction.

Received Jul. 14, 1999; revision accepted Jan. 10, 2000.

For correspondence or reprints contact: Roger T. Staff, PhD, Department of Bio-Medical Physics and Bio-Engineering, University of Aberdeen and Aberdeen Royal Infirmary, Foresterhill, Aberdeen, Scotland, AB25 2ZD United Kingdom.

Recently, Binetti et al. (*3*), using CT, have found a significant association between white matter lesions in the right frontal lobe and the presence of delusion. Ponton et al. (*4*) used hexamethyl propyleneamine oxime (HMPAO) SPECT to investigate delusions in AD and found reduced blood flow in the right temporal regions. Mentis et al. (*5*) also investigated delusions in AD using FDG PET and have reported hypometabolism in the cingulate and orbital frontal regions bilaterally and in the left medial temporal area. Collectively, these findings do not point to any discrete brain abnormality to which delusional symptoms can be attributed. A possible criticism of the previous imaging research into delusions in AD is that not all imaging was done while the delusions were present and that patients included in the delusional groups had a wide range of delusional thinking and behavior. Malloy and Richardson (*6*) have suggested that content-specific delusions are distinct and that grouping different delusions together has the potential to produce confounding variables. This suggestion was also made when a group of AD patients with delusions was compared with a group of nondeluded AD patients using HMPAO SPECT (*7*). No distinction was made in the deluded group between patients with different delusions, and all deluded patients were treated as a single group. A large multifocal area of hypoperfusion was seen in the right frontal lobe, and it was proposed that this large multifocal area could be caused by the superposition of smaller lesions from patients with different delusions and that "grouping together significant numbers of patients with similar delusions may result in a clearer pattern."

The aim of this study was to compare AD patients who have a similar content-specific delusion with a group of AD patients who have no clinical history of delusion. A content-specific delusion is a delusion with a consistent theme or subject. This study also compared a group of AD patients who had other types of delusions with those with the content-specific delusion. In each case, the content of the delusion was that the patient had a fixed belief that a

deceased member of the family was still alive. In this work we refer to this group as having a content-specific autobiographic delusion (CSAD) (*8*). The delusional behavior took the form of feeding and talking to photographs of the dead person, reporting to the police that they were missing, and persistently behaving as though the dead person was still alive. In each case, the subject of the delusion was fixed and the behavior was constant without any transient periods of normal behavior.

The comparison between these groups was done using the Statistical Parametric Mapping (SPM) software package (*9*). This package allows SPECT data to be registered and spatially normalized to a standard stereotactic space and then allows a statistical comparison between groups of images on a voxel-to-voxel basis. This approach has been used previously by Staff et al. (*7*) and Patterson et al. (*10*) to establish differences between groups of SPECT images. This approach has the advantage of making no a priori anatomic assumption about the nature of the differences between image groups.

MATERIALS AND METHODS

Patient Group

Forty-five patients meeting the clinical criteria of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association for diagnosis of probable AD (*11*) were included in the study. Alternative diagnoses, such as Lewy body dementia and frontotemporal dementia, were excluded on the basis of criteria set by the appropriate steering committees (*12,13*). Patients with a clinical history that suggested vascular dementia were also excluded. All of these patients underwent a Mini Mental State examination (MMSE) (*14*) to measure the dementia severity. Each of these patients was referred to the nuclear medicine department at Aberdeen Royal Infirmary for a ^{99m}Tc-HMPAO SPECT examination as part of the clinical protocol. Ten of these patients had a fixed CSAD involving a dead relative. A summary of the CSAD group showing time of onset of the delusion and date of death of the subject of the delusion is given in Table 1. All subjects in this group talked about their dead relative as if he or she was alive. Other behavior traits of individuals are also summarized in Table 1. In each case, the patients in this group had shown evidence of normal behavior with respect to the deceased person before the onset of the delusional behavior. Twenty patients had no history of delusions (NHDs). The third group consisted of 15 patients who had a range of delusional beliefs and behaviors, such as a range of paranoia and misidentification syndromes. The patients in this group had a no CSADs (NCSADs) about dead relatives.

No patient in this study had any other medical condition that could be the cause of the dementia, and no patient had a history of previous psychiatric illness, head injury, epilepsy, or transient ischemic attack. All patients were right-handed. No patient was found to have symptoms of depression, other affective disorders, or other behavioral disorders. No consistent response to neuroleptic drug treatment was observed, although in some cases drugs were withdrawn because of unacceptable side effects. All patients in this study have been followed up at regular intervals, and their clinical diagnosis has been confirmed. Table 2 summarizes the distribution of age and sex of each group.

SPECT Imaging

All patients were injected intravenously with 500 MBq ^{99m}Tc-HMPAO in a darkened quiet room with their eyes open. Imaging commenced at least 15 min after injection. The SPECT projection data were collected using a DST-XL dual-head gamma camera (SMV International, Buc, France) fitted with a pair of low-energy, high-resolution, parallel-hole collimators. The radius of rotation was 17 cm. The images were acquired using 128 equally spaced projections with an acquisition time of 20 s per projection. This produced a total imaging time of 22 min. Head motion was restricted with a headrest and a Velcro strap (SMV International). The images were collected into 128 128 × 128 image arrays with a pixel size of 3.4 mm. The projection data were transferred to an UltraSPARC 10 workstation (Sun Microsystems, Inc., Mountain View, CA). The image reconstruction was performed using Link Medical MAPS 10000 nuclear medicine software (Link Medical, Guildford, UK). The reconstruction used a filtered backprojection technique with a Hamming weighted ramp filter with a cutoff at 0.5 cycle/pixel. The reconstructed images were corrected for attenuation using a first-order Chang (*15*) technique with a linear attenuation coefficient of 0.1 per cm.

TABLE 1
Description of Patients in Autobiographic Delusion Group

Patient no.	Sex	Age (y)	Relation	Time between death and delusion	Onset of delusion (mo/y)	Comment
1	F	90	Spouse	6 mo	11/1997	Behaves as if husband is at work; makes supper for him
2	F	77	Mother	23 y	10/1997	Lays place at table for mother
3	F	64	Brother	3 y	4/1997	Calls out and talks to brother
4	M	77	Mother	Several years*	5/1996	Looks for mother, particularly in father's house
5	M	70	Mother	Several years*	7/1997	Wanders looking for mother
6	F	89	Spouse	Several years*	11/1996	Wanders looking for husband; calls taxis for him
7	F	78	Spouse	2 mo	3/1994	Feeds photograph of dead husband; reports him missing to police
8	F	70	Spouse	6 mo	12/1996	Feeds photograph of dead husband
9	F	76	Spouse	6 mo	8/1998	Claims that husband lives next door
10	F	81	Spouse	24 y	10/1998	Describes recent visits that dead spouse has made

*Accurate estimates were not obtained because no close relative of patient was available for consultation.

TABLE 2
Demographic Summary of Groups

Group	CSAD	NHD	NCSAD
n	10	20	15
Sex (M, F)	2, 8	4, 16	7, 8
Age (y)			
Mean ± SD	77.0 ± 5.6	76.7 ± 7.6	80.4 ± 5.1
Range	65–90	66–88	73–91

Statistical Image Analysis

The reconstructed images were then compared using SPM 96 image analysis software (Institute of Neurology, University College London, London. UK). The reconstructed images were first registered onto the coordinate system of Talairach and Tournoux (*16*) using a technique described by Friston et al. (*17*). The registration of the reconstructed SPECT images was done using only linear transformations. This limited form of image normalization has been proposed by Acton and Friston (*18*) because the registration accuracy required is of the same order as the spatial resolution of the SPECT image. The normalized data were then smoothed using a 16-mm Gaussian smooth and compared using an SPM group comparison and proportional scaling. This technique was used to compare the CSAD group with the NHD group and the NCSAD group. SPM uses the general linear model to compare each voxel in each image dataset. The technique produces a statistical map of t values within the imaging volume. This map of t values was then transformed into units of normal distribution, and the threshold was set at levels of significance. This threshold of probability can be described as uncorrected. After the uncorrected threshold has been applied, the resulting clusters of voxels above that threshold were examined in terms of their size, k, and their peak height, u. The significance of each cluster was then estimated using a distributional approximation from the theory of Gaussian fields (*19*). This produced a probability estimate, using a particular uncorrected threshold, of observing a cluster of voxels of size k (or bigger) with a peak height of u (or higher).

RESULTS

Age and Severity

One-way ANOVA comparisons between the CSAD group and the 2 other groups were performed to ascertain whether there is any age difference between the groups. No significant differences were found between the CSAD group and the NHD group ($F_{1,28} = 0.013$, not significant) or the CSAD group and the NCSAD group ($F_{1,23} = 1.725$, not significant). A 1-way ANOVA was also used to compare MMSE scores. No significant differences were found between the MMSE scores when the CSAD group and the NHD group were compared ($F_{1,28} = 2.219$, not significant) and when the CSAD group and the NCSAD group were compared ($F_{1,23} = 2.728$, not significant). The MMSE scores (mean ± SD) were 18.3 ± 3.4, 16.4 ± 4.4, and 20.5 ± 7.0 for the NHD, CSAD, and NCSAD groups, respectively.

SPM

The results for the SPM comparison between the CSAD group and the NHD group testing for areas of hypoperfusion in the CSAD group not present in the NHD group are shown in Figure 1 and Table 3. These results were produced using an uncorrected threshold of $P < 0.001$ and considering only those clusters that have a probability ($P < 0.05$) of being randomly produced. This uncorrected threshold is commonly used in SPM and has been previously applied to SPECT data by Imon et al. (*20*). A comparison testing for hyperperfusion in the CSAD group not present in the NHD group found no clusters of voxels at this significance. Figure 1 also shows the z score for each voxel in this cluster

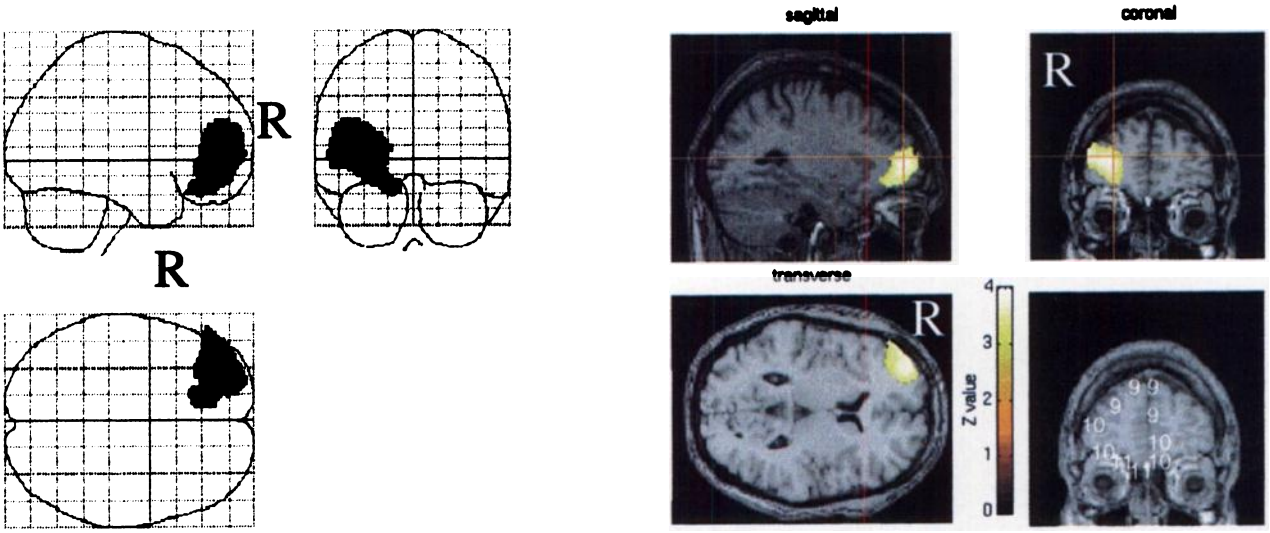

FIGURE 1. HMPAO SPECT images of AD patients with similar CSADs: comparison using SPM. Left: 3-way-glass brain view of area of significant hypoperfusion present in CSAD group compared with NHD group. Right: Sagittal, coronal, and transverse sections of normalized registered MRI brain image with z scores from statistically significant cluster for comparison between CSAD group and NHD group superimposed on them. Positions of slices were −28 mm (sagittal), +52 mm (coronal), and +10 mm (transverse) with reference to stereotactic coordinates of Talairach and Tournoux (*16*). Image in bottom right corner is +52-mm (coronal) slice with approximate position of Brodmann's areas indicated.

TABLE 3
SPM Probability Results

Comparison between groups	Cluster *P* (k, *z*)	Uncorrected *z* max *P*	Position of *z* max (x, y, z mm)
CSAD vs. NHD	0.001 (2230, 4.02)	<0.001	−38, 56, 14
CSAD vs. NCSAD	0.022 (831, 3.91)	<0.001	−22, 62, 4

k = extent or volume of the significant cluster in voxels; *z* = maximum *z* score within that cluster.

superimposed onto a normalized MR image dataset. The results for the SPM comparison between the CSAD group and the NCSAD group testing for areas of hypoperfusion in the CSAD group not present in the NCSAD group are shown in Figure 2 and Table 3. These results were produced using a uncorrected threshold of $P < 0.001$ and considering only those clusters that have a probability ($P < 0.05$) of being randomly produced. A comparison testing for hyperperfusion in the CSAD group not present in the NCSAD group found no clusters of voxels at this significance. Figure 2 also shows the *z* score for each voxel in this cluster superimposed onto a normalized MRI image dataset.

A more familiar way of demonstrating the differences between groups of images is to create a region of interest (ROI) and plot the normalized count density in that group. The cluster shown in Figure 1 was used to create a 3-dimensional ROI. Calculating the mean count density for the CSAD and NHD groups in that ROI normalized to the total brain count gives a count density (mean ± SD) of 100.5 ± 7.0 for the CSAD group and 107.0 ± 4.8 for the NHD group. An unpaired *t* test showed that this difference was significant ($P = 0.001$). A similar comparison between the CSAD and NCSAD groups using an ROI created using the cluster shown in Figure 2 was performed. This produced a count density (mean ± SD) of 98.1 ± 7.6 for the CSAD group and 105.0 ± 3.8 for the NCSAD group. An unpaired *t* test showed that this difference was significant ($P = 0.003$).

DISCUSSION

This study has compared a group of AD patients with a similar autobiographic delusion with a group of AD patients with NHD and a group of AD patients with nonautobiographic delusions. These results show that the group with the autobiographic delusion has a right frontal lobe area of significant hypoperfusion.

The association between cerebral deficits and delusions has been noted previously by several groups using a range of modalities. Binetti et al. (*3*) reported a significant association between frontal white matter lesions and the presence of delusions using CT. Levine and Grek (*21*), in a study using CT, concluded that right cerebral infarcts may be the cause of delusions. A PET study by Mentis et al. (*5*) reported bilateral deficits in the orbital, frontal, and cingulate areas. HMPAO SPECT studies by several authors (*4,7,22*) have found deficits and evidence of right-sided involvement. A clinical study by Förstl et al. (*23*) showed a pronounced degeneration of the right frontal lobe with relative sparing of the left in AD patients with delusions. A recent review by Malloy and Richardson (*6*) highlighted an association between frontal and right-sided lesions and content-specific delusions.

The region of hypoperfusion in the CSAD group includes

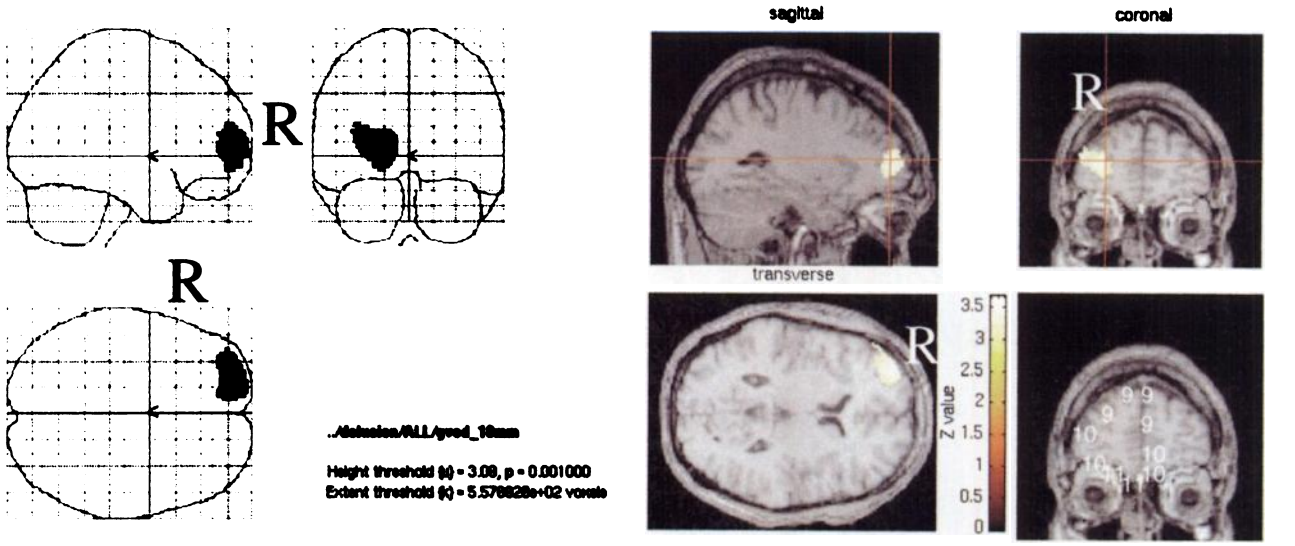

FIGURE 2. HMPAO SPECT images of AD patients with similar CSADs: comparison using SPM. Left: 3-way-glass brain view of area of significant hypoperfusion present in CSAD group compared with group with delusions but no history of autobiographic delusions. Right: Sagittal, coronal, and transverse sections of normalized registered MRI brain image with *z* scores from statistically significant cluster for comparison between CSAD group and group with delusions but no history of autobiographic delusions superimposed on them. Positions of slices were −28 mm (sagittal), +52 mm (coronal), and +10 mm (transverse) with reference to stereotactic coordinates of Talairach and Tournoux (*16*). Image in bottom right corner is +52-mm (coronal) slice with approximate position of Brodmann's areas indicated.

part of Brodmann's area 9, which has been identified as being involved in episodic memory retrieval (*24,25*). Areas in the frontal lobe have also been linked with autobiographic memory by Venneri and Caffarra (*26*). These authors describe a case study in which a patient was suffering from transient autobiographic amnesia. The patient was imaged with and without the amnesia being present. The images showed frontal lobe hypoperfusion when the amnesia was present. A breakdown in episodic memory retrieval may lead to delusional thinking and behavior of this type. This finding suggests that a focal brain dysfunction may be critical in determining the content of the delusion in AD and supports the hypothesis of Malloy and Richardson (*6*) that content-specific delusions in AD are a consequence of discrete regional abnormalities of the right hemisphere.

The use of SPM to analyze groups of reconstructed SPECT data has an advantage over the more conventional ROI approach in that it makes no a priori assumptions about the location and size of any differences between the groups. However, because of the nature of the comparison, assessment of an individual patient is difficult. A possible direction for further work would be to develop ROIs based on territories identified using SPM analysis. These ROIs could be used to determine whether a deficit is present in a region whose dysfunction is known to be associated with a particular symptom. This would support the presence of an organic cause for abnormal beliefs and, in larger series, allow studies of related patient characteristics, natural history, and response to treatment.

The use of a dedicated brain SPECT or PET system would improve image resolution and potentially could identify the exact location of any dysfunction. Alternatively, a functional imaging experiment using either PET or functional MRI to activate episodic memory retrieval, similar to the one described by Fletcher et al. (*24*) using patients with CSADs, could be used. This would further investigate the hypothesis that this type of delusion is associated with the failure of this mechanism in the context of AD.

CONCLUSION

This investigation has used SPM to reveal a localized area of hypoperfusion in the right frontal cortex in patients with a similar content-specific delusion. The strength of SPM is that it requires no a priori assumptions about the location, size, or shape of any regional differences between groups of images. Therefore, SPM is a powerful tool for the analysis of SPECT data in patients with similar clinical features. The identification of an organic cause for such features may assist in the selection of appropriate drug therapy and assist patient management.

ACKNOWLEDGMENT

The authors thank all members of the Department of Nuclear Medicine at Aberdeen Royal Infirmary for their assistance.

REFERENCES

1. Rubin EH. Delusions as part of Alzheimer's disease. *Neuropsychiatry Neuropsychol Behav Neurol.* 1992;5:108–113.
2. Steele SE, Vazquez S, Petracca G, et al. A SPECT study of delusions in Alzheimer's disease. *Neurology.* 1994;44:2055–2059.
3. Binetti G, Padovani A, Magni E, et al. Delusions and dementia: clinical CT correlates. *Acta Neurol Scand.* 1995;91:271–275.
4. Ponton MO, Darcourt J, Miller BL, et al. Psychometric and SPECT studies in Alzheimer's disease with and without delusions. *Neuropsychiatry Neuropsychol Behav Neurol.* 1995;8:264–270.
5. Mentis PF, Weinstein EA, Horwitz B, et al. Abnormal brain glucose metabolism in delusional misidentification syndromes: a positron emission tomography study in Alzheimer's disease. *Biol Psychiatry.* 1995;38:438–449.
6. Malloy PF, Richardson ED. The frontal lobes and content-specific delusions. *J Neuropsychiatry Clin Neurosci.* 1994;6:455–466.
7. Staff RT, Shanks MF, Macintosh L, Pestell SJ, Gemmell HG, Venneri A. Delusions in Alzheimer's disease: SPECT evidence of right hemispherical dysfunction. *Cortex.* 1999;35:549–560.
8. Venneri A, Pestell SJ, Staff RT, Shanks MF. Autobiographical delusions in Alzheimer's disease may reflect episodic memory failure [abstract]. In: *Proceedings of the British Psychological Society XVI Annual Cognitive Section Conference.* Leicester, UK: The British Psychological Society; 1999:41.
9. Friston KJ, Holmes AP, Worsley KJ, Poline JB, Firth CD, Frackowiak RSJ. Statistical parametric maps in functional imaging: a general linear approach. *Hum Brain Mapp.* 1995;26:265–277.
10. Patterson JC, Early TS, Martin A, et al. SPECT image analysis using statistical parametric mapping: comparison of technetium 99m HMPAO and technetium 99m ECD. *J Nucl Med.* 1997;39:1721–1725.
11. McKann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939–944.
12. McKeith IG, Galasko D, Kosaka K. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the consortium on DLB international workshop. *Neurology.* 1996;47:1113–1124.
13. Brun A, Englund B, Gustafson L, et al. Clinical and neuropathological criteria for frontaltemporal dementia. *J Neurol Neurosurg Psychiatry.* 1994;57:416–418.
14. Folstein TE, Folstein SE, McHugh PR. Mini-mental state: a practical method of grading the cognitive state of patients for the clinician. *Psychiatr Res.* 1975;12:189–198.
15. Chang LT. A method for attenuation correction in radionuclide computed tomography. *IEEE Trans Nucl Sci.* 1978;25:638–643.
16. Talairach J, Tournoux P, eds. *Co-Planar Stereotatic Atlas of the Human Brain.* Stuttgart, Germany: Thieme; 1988.
17. Friston KJ, Ashburner J, Firth CD, Poline JB, Heather JD, Frackowiak RSJ. Spatial registration and normalisation of images. *Hum Brain Mapp.* 1995;2:165–189.
18. Acton PD, Friston KJ. Statistical parametric mapping in functional neuroimaging: beyond PET and fMRI activation studies. *Eur J Nucl Med.* 1998;25:663–667.
19. Friston KJ, Worsley KJ, Frackowiak RSJ, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. *Hum Brain Mapp.* 1994;1:214–220.
20. Imon Y, Matsuda H, Ogawa M, Kogure D, Sunohara N. SPECT image analysis using statistical parametric mapping in patients with Parkinson's disease. *J Nucl Med.* 1999;40:1583–1589.
21. Levine DN, Grek A. The anatomic basis of delusions after right cerebral infarction. *Neurology.* 1984;34:577–582.
22. Lebert F, Pasquier M, Steinling M, et al. SPECT data in a case of secondary Capgras delusion. *Psychopathology.* 1994;27:211–214.
23. Förstl H, Burns A, Jacoby R, Levy R. Neuroanatomical correlates of clinical misidentification and misperception in senile dementia of the Alzheimer's type. *J Clin Psychiatry.* 1991;52:268–271.
24. Fletcher PC, Shallice T, Firth CD, Frackowiak RSJ, Dolan RJ. The functional roles of prefrontal cortex in episodic memory. II. Retrieval. *Brain.* 1998;121:1249–1256.
25. Buckner RL, Tulving E. Neuroimaging studies of memory: theory and recent PET results. In: Boller F, Grafman J, eds. *Handbook of Neuropsychology.* Amsterdam, The Netherlands: Elsevier Science; 1995:439–446.
26. Venneri A, Caffarra P. Transient autobiographical amnesia: EEG and single-photon emission CT evidence of an organic etiology. *Neurology.* 1998;50:186–191.