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Neuroanatomical correlates of neuropsychiatric symptoms in Alzheimer's disease

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Alzheimer's disease research has largely concentrated on the study of cognitive decline, but the associated behavioural and neuropsychiatric symptoms are of equal importance in the clinical profile of the disease. There is emerging evidence that regional differences in brain atrophy may align with variant disease presentations. The objective of this study was to identify the regions of decreased grey matter (GM) volume which were associated with specific neuropsychiatric behaviours in patients with mild Alzheimer's disease. Voxel-based morphometry was used to correlate GM derived from T_1-weighted MRI images of 31 patients with mild Alzheimer's disease and specific neuropsychiatric symptoms and behaviours measured by the Neuropsychiatric Inventory. Delusions were associated with decreased GM density in the left frontal lobe, in the right frontoparietal cortex and in the left claustrum. Apathy was associated with GM density loss in the anterior cingulate and frontal cortex bilaterally, the head of the left caudate nucleus and in bilateral putamen. Agitation was associated with decreased GM values in the left insula, and in anterior cingulate cortex bilaterally. Neuropsychiatric symptoms of Alzheimer's disease seem to associate with neurodegeneration of specific neural networks supporting personal memory, reality monitoring, processing of reward, interoceptive sensations and subjective emotional experience. The study of neurodegenerative disorders such as Alzheimer's disease using voxel-based morphometry and other imaging modalities may further the understanding of the neural structures that mediate the genesis of abnormal behaviours.

Keywords: delusions; apathy; agitation; dementia; voxel-based morphometry; MRI

Abbreviations: GM = grey matter; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory

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Introduction

The neuropsychiatric symptoms seen in the course of Alzheimer's disease are usually persistent, although with fluctuating intensity, and can be resistant to treatment (Ryu *et al.*, 2005). Such symptoms, particularly when there is a psychotic driver for abnormal behaviour, are linked to higher rates of institutional care and more rapid cognitive decline. An important component of effective intervention to reduce patient and carer distress, therefore, is the appropriate management of abnormal thought content and related behaviours (Yaffe *et al.*, 2002; Cummings, 2003; Perez-Madrinan *et al.*, 2004; Scarmeas *et al.*, 2005). The pathophysiological and psychological mechanisms involved in the development of neuropsychiatric symptoms are still poorly understood.

Initially, syndromes of abnormal thinking and behaviour in the dementias were seen as an inevitable and non-specific consequence of neurodegeneration with global cognitive impairment. The different neuropsychiatric syndromes seen in the course of Alzheimer's disease, however, have stimulated both genetic and neuroanatomical correlative studies in patient groups using different rating scales (Mega *et al.*, 2000; Sweet *et al.*, 2003; Rosen *et al.*, 2005). Discrete regional associations with a range of symptoms have been identified using indices of brain metabolism, blood flow and brain structure. Experimental studies have begun to delineate more specific neurological associations with discrete symptoms or syndromes, and more substantial theoretical accounts have emerged. For example, it is now clear that delusional symptoms are not simply incidental

to multiple cognitive deficits but are likely associated with discrete regional pathologies which often involve the anterior part of the right hemisphere (Sultzer *et al.*, 2003; Shanks and Venneri, 2004). Alzheimer's disease patients with apathy, on the other hand, are more likely to show damage to the medial frontal and anterior cingulate regions (Craig *et al.*, 1996; Migneco *et al.*, 2001; Rosen *et al.*, 2005). Neurofibrillary tangle burden was higher in the left orbitofrontal cortex of Alzheimer's disease patients who had higher agitation scores (Tekin *et al.*, 2001).

These and other regional associations have been inferred either from measures of regional brain dysfunction (brain metabolism or regional blood flow) or gross estimates of structural or neuropathological damage. This study was designed to establish more specific and focal anatomical correlations between regional atrophy and early or emerging neuropsychiatric symptoms, using the method of voxel-based correlation analysis on 3D structural MRI scans of the brains of patients with mild Alzheimer's disease. Improved anatomical definition of structural correlations with specific neuropsychiatric symptoms may be more easily established in patients with mild Alzheimer's disease. At the mild stage of Alzheimer's disease, disorders of experience or behaviour often appear in relative isolation. At a more advanced stage of the disease, the detection of discrete symptom/atrophy associations is less likely when such symptoms occur as part of a cluster of neuropsychiatric disturbances.

Methods

Sample

Thirty one patients with Alzheimer's disease (19 male and 12 female) were recruited from referrals to our old age psychiatry memory clinic. Their mean age was 77.1 years (SD = 8.6, range 56–95) and their mean education was 11.3 years (SD = 3.1, range 9–17). All patients had extensive neuropsychological screening (see Table 1 for their full neuropsychological profile), structural MRI scanning, neuropsychiatric assessment and neurological examination. The patients were selected from a larger group of ~100 patients who had been referred by local general practitioners to an NHS memory clinic. All patients in the study fulfilled the NINCDS-ADRDA criteria for probable Alzheimer's disease of mild severity (McKhann *et al.*, 1984). Selected patients were first referrals with a 6–12 month history of progressive cognitive decline. They were clinically, neuropsychologically and radiologically (MRI) re-examined after at least 6 months and had their clinical diagnosis confirmed. Exclusion criteria included significant symptoms of depression, claustrophobia, radiological evidence of ischemic brain disease, Hachinski Ischaemia score >4, Mini-Mental State Examination (MMSE) score <18/30 and evidence of other degenerative or secondary dementias. Published clinical criteria were used to exclude other potential causes of dementia (Roman *et al.*, 1993; Brun *et al.*, 1994; McKeith *et al.*, 1996) and no patient with a Hachinski scale (Hachinski *et al.*, 1975) score >2 was entered in the study. None of the patients had a premorbid psychiatric history. None of the patients was taking any antipsychotic or psychoactive medication and they had not yet begun cholinesterase inhibitor therapy at the time of investigation. All patients included in the study had widespread atrophy with more prominent neuronal loss in the medial temporal structures (hippocampus and other structures in the hippocampal complex) and no detectable significant ischemic white matter changes with a T_2-weighted MRI scan.

Before entering the study, a brief interview was carried out with each patient and their relative/guardian. Only those patients who were able to give informed consent were enrolled. Ethics approval for the current study was granted by the NHS Trust Regional Ethics Committee.

Neuropsychiatric assessment

Each patient and their caregiver had a semistructured interview with a consultant psychiatrist (M.F.S) who also completed the Neuropsychiatric Inventory (NPI) (Cummings *et al.*, 1994). The NPI is a caregiver-based behavioural rating system developed and validated for the assessment of mental state and behavioural abnormalities in dementia. The NPI records the presence or absence, severity (rated 1–3) and frequency (rated 1–4) of 12 symptom fields. An index of severity is created for each behavioural variable by multiplying the frequency and severity scores. NPI values were then correlated with grey matter (GM) density values extracted from the patients' 3D MRI brain scans.

Structural MRI scanning: acquisition and analysis

Three dimensional T_1-weighted MRI images were acquired on a 1.5 tesla MRI scanner. Voxel dimensions were

Table 1 Mean (and SD) scores of the Alzheimer's disease patients on the neuropsychological tests

Tests	Patients	Cut-off
Mini Mental State Examination	23.30 (2.8)	<27.9
ADAS-Cog	19.80 (5.6)	NA
Confrontation naming	17.58 (1.75)	<19.53
Pyramids and palm trees test	47.73 (3.45)	<49.73
Verbal paired associates	7.81 (2.95)	<8.94
Rey complex figure		
Direct copy	18.42 (9.93)	<20.45
Delayed copy	1.21 (1.70)	<7.11
Semantic fluency	27.50 (9.14)	<42.63
Phonemic fluency	25.57 (10.87)	<29.67
Digit span		
Forward	6.41 (1.21)	<6.29
Backward	4.14 (0.95)	<3.94
Raven's coloured progressive matrices (PM47)	22.45 (5.03)	<28.88
Prose memory		
Immediate recall	4.5 (3.08)	<12.33
Delayed recall (10 min)	3.12 (3.49)	<12.80
Digit cancellation	42.03 (10.6)	<48.55
Stroop test		
Error interference effect	5.48 (8.19)	>0.25
Time interference effect (sec)	47.43 (32.29)	>5.25
Token test	30.00 (2.61)	<30.66
Visuoconstructive apraxia test	12.18 (2.19)	<11.38

Cut-off scores are derived from a local reference sample.
NA = Not available.

$0.937 \times 0.937 \times 1.6$ mm^3. The field of view was 240 mm with a matrix size of $256 \times 256 \times 124$.

A number of pre-processing steps were followed to isolate the GM from the 3D T_1-weighted structural scans before performing the statistical analysis using SPM5 (Wellcome Department of Imaging Neuroscience, UCL, London, UK).

To correct for global differences in brain shape, structural images were warped to standard stereotactic space and segmented to extract GM, white matter and CSF. The GM segments were then modulated to correct for changes in volume induced by non-linear normalization and smoothed using a Gaussian filter set at 12 mm to reduce possible error from between subject variability in local anatomy and render the data more normally distributed. Finally, smoothed GM segments were entered into a voxel-based multiple regression analysis to investigate linear correlations between GM concentration and severity indices for the symptoms assessed by the NPI. Age, number of years of education and MMSE score were also included in the model as covariates for all symptom fields. A measure of executive functions was also included in the model for apathy and agitation, since both of these symptoms have been associated with executive dysfunction (Chen *et al.*, 1998). The *x*, *y*, *z* coordinates of the areas of significant correlation obtained from the analyses were first converted into Talairach coordinates and then identified using the Talairach Daemon Client (http://ric.uthscsa.edu/projects/tdc/).

A T_2-weighted axial scan was also acquired prior to the 3D scan acquisition to better highlight any vascular load and to ensure that all participants included in the 3D structural imaging study had no significant vascular burden.

Results

The frequency of each behavioural abnormality within this group of mild Alzheimer's disease patients is shown in Table 2. Apathy was the most frequent abnormal behaviour (74%) observed in the sample, while hallucinations were rare (3%). The mean frequency and severity scores for each of the symptom fields are also included in the table.

Six of the symptom fields had sufficient variance to be entered in the analysis in this mild Alzheimer's disease sample, and three of these were significantly correlated with cortical atrophy: delusions, agitation and apathy.

The delusional symptoms consisted of misidentifications either of place or of person, and were associated with related confabulations or more persistent delusional memories. Correlation analyses were carried out with demographic and cognitive screening measures. Delusions, agitation and apathy scores were not significantly correlated with the MMSE or ADAS-Cog scores. There were no significant correlations between any of the NPI symptom fields and education, while age was significantly correlated with delusions ($r = 0.43$, $P < 0.05$). Agitation was significantly correlated with delusions ($r = 0.42$, $P < 0.05$) and with apathy ($r = 0.37$, $P < 0.05$). There were no significant correlations between any of the NPI symptoms fields and the scores on the letter fluency test that were used as a measure of executive functions (Table 3).

The voxel-based multiple regression analysis showed that there were significant correlations between GM density values in some cortical and subcortical structures and three of the symptom fields measured with the NPI, i.e. delusions, agitation and apathy.

High delusion scores correlated significantly with low GM density values in the right inferior frontal gyrus and inferior parietal lobule. In the left hemisphere there was significant correlation in the inferior and medial frontal gyri and in the claustrum (Table 4, Fig. 1A and B).

For apathy, high scores correlated significantly with low GM density values in the anterior cingulate cortex, orbitofrontal cortex and regions of the dorsolateral prefrontal cortex in both hemispheres. In addition, there were bilateral subcortical correlations in the putamen and in the head of the left caudate nucleus (Table 4, Fig. 2A and B). High agitation scores were significantly correlated

Table 2 Percentage observed, mean frequency, mean severity and mean composite score for each neuropsychiatric inventory symptom field and total NPI score in the Alzheimer's disease sample

Symptom field	%	Frequency (0–4)	Severity (0–3)	Composite (0–12)
Delusions	16	0.52 (1.23; 0–4)	0.23 (0.56; 0–2)	0.74 (1.93; 0–8)
Hallucinations	3	0.03 (0.18; 0–1)	0.03 (0.18; 0–1)	0.03 (0.18; 0–1)
Agitation	35	0.84 (1.32; 0–4)	0.52 (0.85; 0–3)	1.68 (2.94; 0–12)
Depression	29	0.58 (1.12; 0–3)	0.32 (0.6; 0–2)	0.77 (1.67; 0–6)
Anxiety	48	1.19 (1.42; 0–4)	0.58 (0.67; 0–2)	1.52 (2.13; 0–8)
Elation	6	0.23 (0.88; 0–4)	0.1 (0.4; 0–2)	0.32 (1.28; 0–6)
Apathy	74	2.26 (1.75; 0–4)	0.97 (0.75; 0–2)	3.23 (3.08; 0–8)
Disinhibition	6	0.23 (0.88; 0–4)	0.16 (0.64; 0–3)	0.58 (2.38; 0–12)
Irritability	32	0.81 (1.28; 0–4)	0.48 (0.81; 0–3)	1.29 (2.42; 0–9)
Aberrant motor behaviour	23	0.58 (1.29; 0–4)	0.32 (0.75; 0–3)	1.03 (2.55; 0–9)
Sleep disorders	32	1.0 (1.51; 0–4)	0.42 (0.72; 0–3)	1.29 (2.21; 0–9)
Eating disorders	26	0.87 (1.65; 0–4)	0.42 (0.81; 0–2)	1.65 (3.21; 0–8)
NPI		Frequency (0–48)	Severity (0–36)	Composite (0–144)
Total score		9.14 (14.51; 0–44)	4.55 (7.74; 0–28)	14.38 (26.04; 0–96)

SD and range are given in brackets.

Table 3 Correlations between demographic and cognitive variables and NPI symptom field scores

	Age	Education	MMSE	ADAS-Cog	Delusions	Agitation	Apathy	Letter Fluency
Age	–	−0.37	0.105	−0.111	0.430*	−0.61	−0.075	−0.079
Education	−0.37	–	0.223	−0.232	−0.180	0.047	0.002	0.269
MMSE	0.105	0.223	–	−0.664**	−0.172	−0.160	−0.60	0.260
ADAS−Cog	−0.111	−0.232	−0.664**	–	0.149	0.272	0.348	−0.422*
Delusions	0.430*	−0.180	−0.172	0.149	–	0.420*	0.230	0.041
Agitation	−0.61	0.047	−0.160	0.272	0.420*	–	0.368*	−0.003
Apathy	−0.075	0.002	−0.60	0.348	0.230	0.368*	–	−0.035
Letter fluency	−0.079	0.269	0.260	0.422*	0.041	−0.003	−0.035	–

*Value is significant at $P < 0.05$ (two-tailed). **Value is significant at $P < 0.01$ (two-tailed).

Table 4 Areas of significant correlation between GM density values and delusions; apathy; and agitation

Brain area	Right/Left	Brodmann's area	Talairach Co-ordinates			Z-value at local maximum
			x	*y*	*z*	
Delusions ($P < 0.01$)						
Inferior frontal gyrus	R	45	50	18	12	3.49
Inferior parietal lobule	R	40	34	−50	41	3.04
			42	−52	43	2.79
Inferior frontal gyrus	L	45	−55	22	15	3.14
			−51	26	21	2.88
Medial frontal gyrus	L	11	−8	61	−15	2.86
			−1	56	−15	2.66
Claustrum	L		−38	−2	4	2.75
Apathy ($P < 0.001$)						
Lentiform nucleus (putamen)	R		24	10	1	4.12
Inferior frontal gyrus	R	47	18	20	−21	3.18
Middle frontal gyrus	R	9	28	25	30	3.58
Superior frontal gyrus	R	10	24	47	−1	3.26
Anterior cingulate	R	24	12	−6	37	3.58
Caudate nucleus (head)	L		−12	10	1	3.60
Lentiform nucleus (putamen)	L		−30	0	7	3.60
Inferior frontal gyrus	L	47	−16	18	−19	3.32
		45	−34	29	6	3.58
Middle frontal gyrus	L	9	−30	27	26	3.37
Anterior cingulate	L	24	−14	2	40	3.19
Agitation ($P < 0.001$)						
Anterior cingulate	R	24	12	−2	42	3.49
Insula	L	13	−48	10	1	3.69
Anterior cingulate	L	24	−14	−4	39	3.45

with low GM density in the left insula and bilateral anterior cingulate cortex (Table 4 and Fig. 3).

Discussion

This study has established that some of the neuropsychiatric symptoms seen in early Alzheimer's disease are associated with atrophy of well-defined brain structures. Some of these symptoms, delusions and agitation for example, are frequent in the later stage of the disease, but less common at the mild stage, although one study reported agitation in 47% of their subsample of mild Alzheimer's disease patients (Mega *et al.*, 1996). Significant apathy, on the other hand, is often seen in early presentations of Alzheimer's disease and is sometimes described even before memory deficits become noticeable. This symptom frequency pattern was reflected in this group of early Alzheimer's disease patients.

This study identified those discrete atrophic sites that are most strongly associated with the presence and severity of these symptoms. The association of delusions with atrophy primarily in the right frontoparietal regions supports previous findings from metabolic and regional cerebral blood flow (rCBF) studies (Staff *et al.*, 1999; Sultzer *et al.*, 2003). There was a smaller cluster of significant correlation in the left frontal cortex, but nearly twice as many voxels showed significant association in the right hemisphere than in the left. A left/right asymmetry with relative preservation of the left frontal lobe had already been

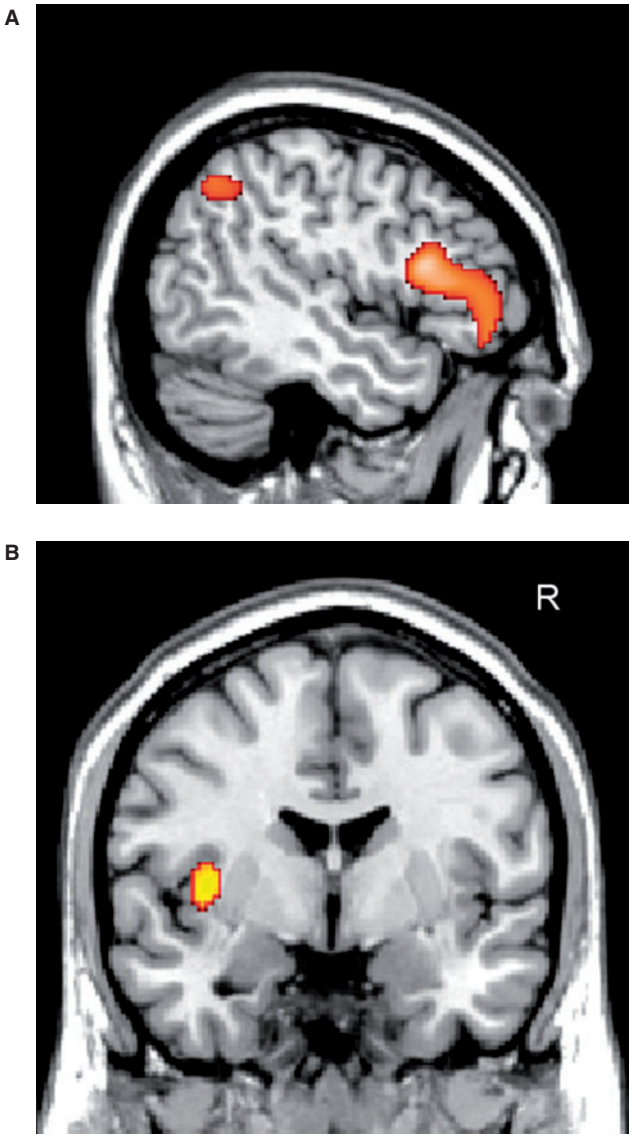

Fig. 1 (**A**) Sagittal view of the right frontal and parietal regions where a significant correlation with the presence and severity of delusions was found. (**B**) Coronal view showing the cluster of significant correlation in the left claustrum. The coronal image is presented in neurological orientation (L/L).

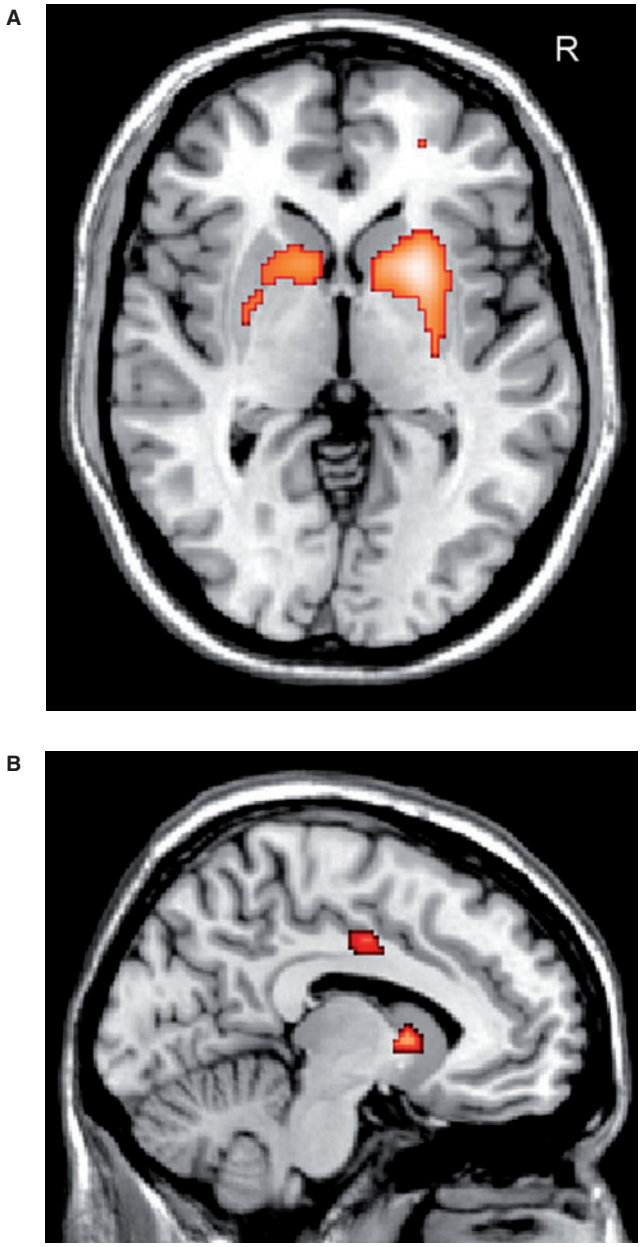

Fig. 2 Areas of significant correlation with the presence and severity of apathy in: (**A**) bilateral striatal structures (axial view) and (**B**) in the left anterior cingulate cortex (sagittal view). The axial image is presented in neurological orientation (L/L).

associated with misidentification delusions in a CT study (Forstl *et al.*, 1991). Right fronto-parietal dysfunction was regularly reported in studies of single cases with a variety of misidentification delusions (Feinberg *et al.*, 1999; Shanks and Venneri, 2002; Abe *et al.*, 2007). It seems, therefore, that an unusually severe impairment of the anterior right hemisphere may appear in a few patients at a relatively early disease stage in association with delusional symptoms. This relatively focal atrophy might either follow from regional variance in Alzheimer's disease neuropathology (reflecting the well-known clinical variance at onset), or perhaps more likely, indicate regional genetic and/or neurodevelopmental susceptibility. This latent variable might then become expressed endophenotypically in the course of neurodegeneration. In either case, damage to the corresponding anatomical network presumably disrupts this region's functional role in aligning mental contents with veridical reality (Shanks and Venneri, 2004). Delusional misidentifications in this sample were associated with content-related confabulations and delusional memories. The region of correlation, especially in the frontal lobe, involves areas which are relevant for personal episodic memory retrieval. There is evidence from behavioural studies that confabulations and delusional memories are strongly correlated with failure of personal episodic

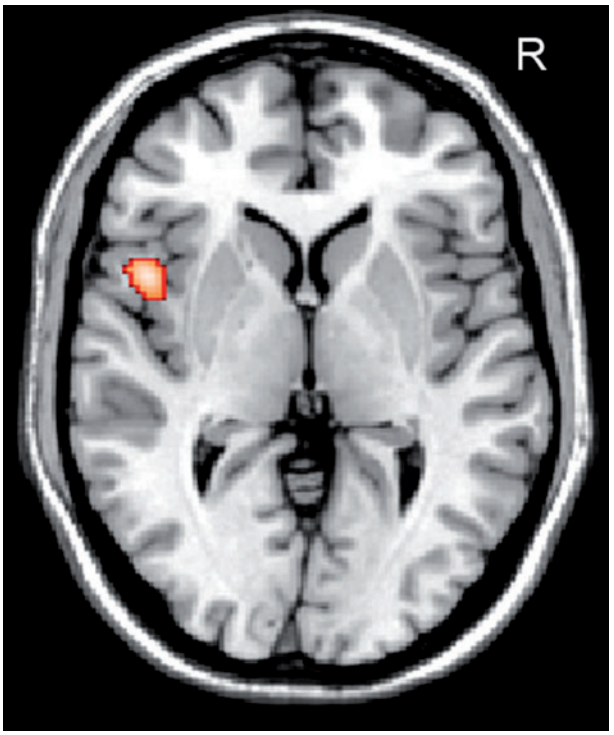

Fig. 3 Areas of significant correlation with the presence and severity of agitation in the left insula (axial view). The image is presented in neurological orientation (L/L).

memory retrieval for late adulthood and recent life periods and relatively preserved personal semantic information (Cooper *et al.*, 2006; Lee *et al.*, 2007). A cluster of significant correlation was also found in the left claustrum. An association between damage to this subcortical structure and delusions has not previously been reported to our knowledge. At first sight, this association seemed difficult to interpret in any theoretical model. The claustrum, however, has unique connectivity, in that the target areas of projections from the cortex overlap only when the cortical areas concerned are themselves interconnected (Pearson *et al.*, 1982). Projections from the claustrum are extensive, mainly ipsilateral but with some neurons projecting contralaterally. Representations in the claustrum, therefore, will be more faithful to a regionally sourced polymodal convergence than to more precise homotopic mapping. The claustrum is well placed to perform higher order, integrative functions and to facilitate rapid transfer of information along its anterio-posterior and ventral-dorsal axes and in this way instantiate multimodal (cognitive, perceptual, motor) syntheses (Crick and Koch, 2005). It follows that damage to this structure might impair the normal synchronization of perceptual and cognitive experiences in Alzheimer's disease patients, contributing to delusional misinterpretation of percepts, memories or mental images.

Apathy was the most frequent symptom in this sample of early Alzheimer's disease patients. This symptom may be an early diagnostic indicator of the disease, and is detectable in a high proportion of patients with mild cognitive impairment (Lyketsos *et al.*, 2002; Palmer *et al.*, 2007). The presence and severity of apathy was significantly correlated with low GM density in subcortical nuclei, the putamen bilaterally and the left caudate nucleus. There were also significant correlations in bilateral anterior cingulate cortex and inferior frontal and orbitofrontal regions of both hemispheres. Atrophy of elements of the limbic circuit, including the cingulate gyrus, together with the more prominent atrophy in mediotemporal structures, is observed early in Alzheimer's disease. Atrophic changes in the periventricular nuclei and the striatum also appear early (Gado *et al.*, 1983; Jack *et al.*, 2005; Shiino *et al.*, 2006). The association of apathy with atrophy in these regions is in accord with the temporal coincidence between the early appearance of this symptom and the first stages of regional neuropathology in Alzheimer's disease (Tekin *et al.*, 2001).

Previous studies using dynamic measures of brain function in Alzheimer's disease patients with apathy have predominantly reported dysfunction in anterior cingulate/medial frontal areas, although one study showed involvement of the medial thalamus (Migneco *et al.*, 2001; Lanctot *et al.*, 2007; Marshall *et al.*, 2007). Neuropathological and structural studies showed involvement of similar cortical regions in apathetic Alzheimer's disease patients (Tekin *et al.*, 2001; Rosen *et al.*, 2005; Marshall *et al.*, 2006; Apostolova *et al.*, 2007). A crucial function of the anterior cingulate cortex relates to the initiation and motivational drivers for goal directed activities, particularly when these are effortful, and damage to this cortical structure would likely, therefore, lead to a degree of behavioural and cognitive inertia (Devinsky *et al.*, 1995; Allman *et al.*, 2001). Apathy has also been linked to dysfunction or atrophy of ventral frontal areas (Rosen *et al.*, 2005; Marshall *et al.*, 2007), and the present finding of an association with an area of atrophy in ventrolateral prefrontal cortex (BA47) may relate to the role of this region in executive functions and social cognition (Blackwood *et al.*, 2000; Wager and Smith, 2003). The other clusters of significant correlation in the present study involved the dorsal striatum predominantly in the left hemisphere. The dorsal portion of the caudate nuclei, particularly the caudate head, is critical for the executive function of a fronto-striatal network. This network, in brief summary, is organized as a feed-forward loop from frontal cortical areas to the caudate nucleus and putamen, which then project to the medial thalamus and back to the prefrontal cortex (Mesulam, 2000). Front-ostriatal mechanisms are important for executive functions including planning, set shifting and strategic thinking, and damage will lead to impairment of these processes as well as a blunting of response to rewarding stimuli. Clearly significant disruption of this network could also contribute to apathy through cognitive, emotional and motivational deficits (Levy and Dubois, 2006). Apathy in a variety of other neuropsychiatric disorders including frontotemporal

dementia, schizophrenia and mood disorders may result from impaired functioning of such frontal-subcortical circuits (Bonelli and Cummings, 2007). In addition, a small number of case studies of patients with caudate lesions report apathy with impaired motivation (Habib and Poncet, 1988; Mendez *et al*., 1989; Trillet *et al*., 1990; Wang, 1991).

Agitation was observed in a third of the patients and the degree of agitation was associated with severity of atrophy in the left insula and in bilateral anterior cingulate cortex. The insula mediates the experience of the basic emotions, and while the right hemisphere is dominant for the regulation of higher social and emotional behaviours like self awareness, there is less evidence for lateralization of basic emotional processes (Davidson and Irwin, 1999). The insula also has a role in body representation, subjective emotional experience, the integration of sensory information and the processing of convergent information to make sensory experience emotionally salient (Damasio, 1996). In this respect, it may have an important role in the experience of pain, as interoceptive sensations are transmitted to the insular cortex. Patients with dementia have difficulty in the identification and expression of somatic symptoms including pain, and insular damage may contribute to replacing normal complaint and help seeking with undirected agitation, and more generally to an exaggerated behavioural response to somatosensory and environmental stimuli. Additional support for a possible role of insular damage in causing agitation comes from studies of epileptic patients where insular seizures can mimic the features, including severe agitation, of temporal lobe epilepsy and nocturnal frontal lobe epilepsy (Ryvlin, 2006; Ryvlin *et al*., 2006). Finally, the insula is the most significantly thickened brain area in meditators, suggesting that training in mental tranquillity may reinforce insular activity as opposed to its suggested impoverishment in states of agitation (Lazar *et al*., 2005).

There were also significant correlations between agitation scores and bilateral atrophy of the anterior cingulate gyrus, a structure which together with damage to orbitofrontal areas had already been associated with agitation in neuropathological studies of Alzheimer's disease (Tekin *et al*., 2001). The present study, while confirming the link between agitation and anterior cingulate atrophy, found no significant correlations between agitation and tissue loss in orbital frontal regions. The neuropathological evidence, however, was of course not contemporary with the appearance of the symptom. Any associations established in that way are likely to be less specific than those observed when the MRI and neuropsychiatric data are collected at the same time (with a one week delay in the present study).

The validity of these results is potentially influenced by the method that was used. Criticisms of the voxel-based morphometry technique include concerns that segmentation inaccuracy may survive the automated processes involved. The method seems reliable, however, when used to identify the neural substrate of specific cognitive deficits using a correlational approach. By treating each individual voxel value in the brain as a continuous variable, a correlation between differences in GM density values and continuous behavioural data can be obtained. The resulting data can better establish associations between brain regions or equivalent damaged structures and related cognitive functions and behaviours (Tyler *et al*., 2005; Venneri *et al*., 2008). These more detailed clinical/pathological correlations would not be feasible using the more traditional region of interest approach, given the *a priori* assumptions about location and extent that the method requires.

The relatively small sample size might also be seen as a limitation and another study included 148 patients with different types and stages of dementia studied with the same methods (Rosen *et al*., 2005). The present study, however, is specific to Alzheimer's disease and focused on the milder level of severity. The investigation of patients only at the earlier stage of the disease might also be seen as a limitation in terms of the full development of neuropsychiatric symptomatology. Previous studies have established that neuropsychiatric symptoms increase in frequency with disease severity (Mega *et al*., 1996). The inclusion of patients at a more advanced stage of Alzheimer's disease would most likely, therefore, have resulted in a wider spectrum of symptom fields observed as well as greater frequency and severity of symptoms. In this mild Alzheimer's disease group, there was no correlation between any of the symptom field scores and the MMSE scores. Significant correlations with disease severity would probably have emerged if patients with a wider range of severity had been included in the sample. On the other hand, identification of discrete anatomical correlations with specific neuropsychiatric symptoms is more likely to be established in Alzheimer's disease patients at the mild stage when disorders of experience or behaviour may appear in relative isolation. At the moderate stage, aggregated effects of disease severity and clustering of neuropsychiatric symptoms would make discriminative correlations of this kind more challenging. Finally, there was no significant correlation between neuropsychiatric symptom scores and letter fluency scores. Executive dysfunction had been associated with agitation and apathy in Alzheimer's disease (Chen *et al*., 1998). The absence of a similar correlation in this sample may follow from the more recent inception of these neuropsychiatric symptoms in these mild patients which may have contributed to the specificity and more focal nature of these anatomical associations.

In conclusion, this study has identified a number of associations between certain foci of GM loss and the presence of different neuropsychiatric symptoms. Discrete regional associations of this kind may be more clearly established in patients with Alzheimer's disease as the disease, while unfolding in a broadly predictable anatomical pattern, can selectively affect discrete brain regions in individual patients with corresponding variation in onset

symptoms. Particularly in the early stages, therefore, the architectonic distribution of neurodegenerative damage and/or predisposing developmental changes may be subtle and limited, allowing more precise correlative analysis than in cases of vascular or traumatic damage. Even so, the evidence obtained from clinicopathological correlation after different pathological processes is remarkably convergent. Correlations of this kind may help to clarify the mechanisms and brain circuits involved in the control of certain social and emotional behaviours, and will guide more rational psychopharmacological and behavioural interventions to alleviate these distressing symptoms.

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