Neural correlates of psychotic symptoms in dementia with Lewy bodies

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The aim of this study was to investigate the association between psychotic symptoms in dementia with Lewy bodies and brain perfusion on single photon emission tomography. Based on factor analysis in 145 patients, psychotic symptoms were classified into five symptom domains (factor 1 to 4-related symptoms and delusions). The relationship between each symptom domain and brain perfusion was assessed in 100 patients with dementia with Lewy bodies, while accounting for the effects of age, sex, dementia severity, parkinsonism and dysphoria. Factor 1 symptoms (Capgras syndrome, phantom boarder, reduplication of person and place and misidentification of person) represented misidentifications, and were significantly related to hypoperfusion in the left hippocampus, insula, ventral striatum and bilateral inferior frontal gyri. Factor 3 symptoms (visual hallucination of person and feeling of presence) represented hallucinations of person and were related to hypoperfusion in the left ventral occipital gyrus and bilateral parietal areas. Delusions of theft and persecution were associated with relative hyperperfusion in the right rostral medial frontal cortex, left medial superior frontal gyrus and bilateral dorsolateral frontal cortices. This study revealed that different psychotic symptoms in dementia with Lewy bodies were associated with distinguishable cerebral networks. Visual hallucinations were related to dysfunction of the parietal and occipital association cortices, misidentifications were related to dysfunction of the limbic-paralimbic structures and delusions were related to dysfunction of the frontal cortices. Our findings provide important insights into the pathophysiological mechanisms underlying psychotic symptoms in dementia with Lewy bodies.

Keywords: dementia with Lewy bodies; hallucination; delusion; delusional misidentification syndrome; cerebral blood flow

Abbreviations: MNI = Montreal Neurological Institute; SPECT = single photon emission computed tomography; SPM = Statistical Parametric Mapping

Introduction

Dementia with Lewy bodies is the second most common neurodegenerative dementia following Alzheimer’s disease (McKeith et al., 2003; Buracchio et al., 2005). Patients with dementia with Lewy bodies typically exhibit psychotic symptoms. Visual hallucinations are the most frequent symptoms and have been identified as one of the core features in the clinical diagnostic criteria of dementia with Lewy bodies (McKeith et al., 1996, 1999). Hallucinations in other modalities and systematized delusions also occur in dementia with Lewy bodies, but are less frequent and are regarded as supportive features. A wide variety of misidentifications, from ‘delusional misidentification syndromes’ e.g. Capgras syndrome, to simple misidentification of a person are also found in dementia with Lewy bodies (Ballard et al., 1999; Hirono and Cummings, 1999). Psychotic symptoms have particular
clinical importance since neuropsychiatric symptoms are more frequent in dementia with Lewy bodies than Alzheimer’s disease, even in the early stages of the disease and they cause a higher degree of caregiver distress (Rici et al., 2009).

Several studies have attempted to determine the neural basis of visual hallucinations in dementia with Lewy bodies (Imamura et al., 1999; O’Brien et al., 2005; Pernecky et al., 2008), but few studies have explored that of delusions or misidentifications. Furthermore, psychotic symptoms in dementia do not occur in isolation. In dementia with Lewy bodies, several types of hallucinations, delusions and misidentifications can be present in a patient (Ballard et al., 1999; Nagahama et al., 2007). In particular, one form of misidentification usually accompanies another; Capgras syndrome sometimes coexists with reduplicative paramnesia (Signer, 1987; Christodoulou, 1991; Weinstein, 1994), and phantom boarder with other misidentifications (Hwang et al., 2003). These observations suggest that such symptoms may be produced by a common underlying pathophysiological alteration. Controlling for a community of interrelated symptoms or confounding effects of other coexisting symptoms is necessary in neuroimaging studies to explore the neural basis of psychotic symptoms.

We recently reported the possible classification of psychotic symptoms in dementia with Lewy bodies using factor analysis, suggesting hallucinations, misidentifications and delusions as independent symptom domains (Nagahama et al., 2007). Based on our previous study, we tried to explore the neural correlates of each psychotic symptom domain in dementia with Lewy bodies patients. In the present study, we combined many psychotic symptoms in dementia with Lewy bodies into a few symptom domains using factor analysis and examined the relationships between regional cerebral blood flow and the presence of each domain symptom, while controlling for the effects of other cognitive, behavioural and psychiatric symptoms.

Subjects and methods

Subjects

First, we examined 145 patients with dementia with Lewy bodies who attended the Memory Clinic, Shiga Medical Centre, between November 2000 and March 2009, to categorize psychotic symptoms. Subjects underwent general physical, neurological and neuropsychological examinations including the Mini-Mental State Examination. All underwent structural neuroimaging and routine laboratory investigations including vitamin B1, B12, and thyroid functions. Parkinsonism was assessed using the motor sign scores derived from the Unified Parkinson’s Disease Rating Scale (Sarmeas et al., 2004). Patients with a history of stroke, significant head trauma, alcohol abuse, major psychiatric illnesses or evidence of other neurological disorders were excluded. Clinical diagnoses were made by agreement between experienced geriatric neurologists (Y.N. and M.M.) according to the consensus criteria for dementia with Lewy bodies (McKeith et al., 1996, 1999). One hundred and thirty six patients with dementia with Lewy bodies fulfilled probable and nine fulfilled possible dementia with Lewy bodies criteria. Patients whose dementia developed 12 months or later after the onset of Parkinson’s disease were excluded from the study.

Patients with an Mini-Mental State Examination score of less than 11, or who showed moderate to severe ischaemic changes on head CT or MRI, were excluded, and finally 100 subjects (92 probable, eight possible dementia with Lewy bodies) were selected for single photon emission computed tomography (SPECT) analysis. Six patients were treated with antiparkinsonian drugs (L-dopa or and dopamine agonist), six with antipsychotics (two with tiapride, two with sulpiride, one with quetiapine and one with haloperidol), and two were treated with antidepressants at their first visit to our hospital. We carefully excluded a possible relationship between these medications and psychotic phenomena by evaluating their detailed clinical history and reducing/Stopping the drugs.

Twenty-one age-matched control subjects without dementia (77.2 ± 4.8 years) were also scanned. They were patients’ spouses and relatives who agreed to the SPECT scan.

Assessment and categorization of psychotic symptoms

Psychotic symptoms were classified based on factor analysis of 145 dementia with Lewy bodies patients. Detailed methods were reported previously (Nagahama et al., 2007). Briefly, a semi-structured interview according to psychoses and dysphoria was conducted by Y.N. and M.M. with patients and their primary caregivers, in order to reveal whether each symptom was present or absent. Then, we subjected 17 psychotic symptoms that occurred in at least five different patients to factor analysis.

The statistical technique of factor analysis is an attempt to reduce the dimensionality of a data set, by grouping of the original variables into so called ‘factors’ in order to simplify interpretation (Krzanowski, 2000). The complete representation of data would (here) require 17 dimensional space, but by calculating linear functions of the original variables that progressively account for maximum amounts of the total variability, the patterns are hopefully compressed into fewer dimensions. This first stage is therefore simply an orthogonal transformation of the original variables. The axes are then rotated so that as many of the coefficients as possible, in the linear functions, are reduced to very small values, leaving the remaining coefficients (loadings) being representative of that factor. In an ideal situation, if virtually all the variability can be compressed into a very few dimensions, interpretation becomes much easier. In the present study, the principal factor procedure was used to extract the initial factors and this was followed by Orthotran/Varimax oblique rotations. The number of factors to be retained was determined by examining the eigenvalues >1.0 and scree plot. Items with factor loadings ≥0.50 were entered into the factor.

This analysis almost replicated and confirmed our previous results (Nagahama et al., 2007) except that the order of factor 3 and 4 was reversed. We obtained a 4-factor solution (Table 1) and correlations between factors were very low. Eigenvalues of factors 1 to 4 were 2.38, 1.70, 1.57 and 1.47, respectively, accounting for 14.0, 10.0, 9.2 and 8.6% of the variance. Factor 1 consisted of misidentification of person, Capgras syndrome, phantom boarder, reduplication of person and reduplication of place. Factor 2 consisted of reduplication of person, the belief that deceased relatives are still alive and the belief that absent relatives are in the house. Factor 3 included hallucination of person and feeling of presence. Factor 4 included hallucination of animals and insects and hallucination of objects. Delusion of theft and delusion of persecution were not loaded into these factors and were considered as an independent category. According to the factor structure, we enrolled 100 dementia with Lewy bodies patients in SPECT...
analysis with at least one symptom in the psychotic symptom domain (factor 1–4 and delusions).

### SPECT imaging

Demographic data of the patients are shown in Table 2. Subjects lay on the scanner bed with their eyes closed, and 740 MBq [99mTc]hexamethyl-propyleneamine oxime (HMPAO) was administered intravenously. Ten minutes after injection, SPECT images were acquired over 20 min using a triple-head SPECT scanner. Subjects lay on the scanner bed with their eyes closed, and 740 MBq [99mTc]hexamethyl-propyleneamine oxime (HMPAO) was administered intravenously. Ten minutes after injection, SPECT images were acquired over 20 min using a triple-head SPECT scanner. After injection, the images were reconstructed with a Ramp back-projection filter. Post-reconstruction attenuation correction was not applied. The reconstruction yielded 1.7 mm × 1.7 mm × 1.7 mm voxels with a 128 × 128 matrix and 80 slices. All subjects and/or caregivers gave informed consent according to the nature of the study and purpose of the SPECT scan.

### Image analysis

SPECT data were analysed with Statistical Parametric Mapping (SPM5, Wellcome Department of Imaging Neuroscience, London, UK). All images were transformed into a standard stereotaxic anatomical space (Mazziotta et al., 1995). The resulting voxel size was 2 mm × 2 mm × 2 mm. The average of spatially normalized scans was calculated and a 20-mm-diameter volume of interest was defined on the bilateral cerebellum. Scan intensity was then normalized by dividing each image by the mean intensity in the cerebellar volumes of interest. The cerebellum was selected as reference region because perfusion/metabolism of the cerebellum was preserved or, at least, less affected than the cerebral cortex in dementia with Lewy bodies (Ishii et al., 1998; Yong et al., 2007). Thereafter, the images were smoothed with a 12 mm Gaussian filter.

Statistical analysis was carried out in two steps. First, group comparison between patients and controls was performed to determine significant hypoperfusion brain areas in dementia with Lewy bodies, treating age as a nuisance covariate. A significant threshold of P < 0.01, corrected for multiple comparisons using the false discovery rate procedure, was applied to minimize the chance of false-positive findings. Extent threshold was set at more than 10 voxels.

Second, the relationship between the psychotic symptom domains (factor 1–4 symptoms and delusions) and regional cerebral blood flow in dementia with Lewy bodies patients was examined with covariate-only design matrices, using the multiple regression model in SPM5. Age, sex, Mini-Mental State Examination, Unified Parkinson’s Disease Rating Scale motor sign score and the presence/absence of dysphoria were entered into the model as nuisance covariates. The specific effects of each psychotic symptom domain were tested using [–1] or [1] t-contrast with additional zeros for the rest of the symptoms and nuisance covariates, assuming that the presence of the symptoms would be uniquely associated with decreased or increased regional cerebral blood flow. Search volumes were restricted a priori to the hypoperfusion areas identified in the first step. Therefore, a statistical threshold of uncorrected P < 0.001 was accepted in this second step analysis and the extent threshold was set at more than 10 voxels. Montreal Neurological Institute (MNI) coordinates (Mazziotta et al., 1995) were used to report brain areas, but descriptions of the anatomical location were also based on visual inspection of the normalized structural MRI and the atlas of Mai (Mai et al., 2008).

### Results

The significant hypoperfusion areas in dementia with Lewy bodies relative to control subjects involved a wide range of bilateral...
frontal, temporal, parietal and occipital cortices (Fig. 1). Bilateral lenticular nuclei and thalamus were also affected.

Factor 1 symptoms, representing misidentifications, were present in 32 dementia with Lewy bodies patients; misidentification of person in 22, Capgras syndrome in 5, reduplication of person in 10, reduplication of place in 5, phantom boarder in 14. Twenty-one patients had ‘delusional misidentification syndromes’ or phantom boarder, and 11 had only misidentification of person. Patients with factor 1 symptoms showed significant hypoperfusion compared with those without factor 1 symptoms in the left hippocampus, insula, the opercular part of the inferior frontal gyrus and ventral striatum/accumbens nucleus (Fig. 2; Table 3). A small hypoperfusion area was also found in the right opercular part of the inferior frontal gyrus. When the threshold was lowered to an uncorrected $P<0.01$ for exploratory purposes, the right ventral striatum (MNI coordinates of $x=8$, $y=10$, $z=-8$), bilateral inferior temporal gyri ($x=-50$, $y=-14$, $z=-38$ and $x=54$, $y=-6$, $z=-38$), right medial frontopolar cortex ($x=4$, $y=64$, $z=-8$) and cingulate gyri ($x=0$, $y=34$, $z=2$ and $x=-12$, $y=-8$, $z=42$) were also uncovered, but the right insula or hippocampal area was not detected. There was no significant hyperperfusion area related to factor 1.

Factor 3 symptoms, representing visual hallucinations of person, were present in 74 dementia with Lewy bodies patients; 68 patients had hallucination of person and 29 had feeling of presence. Patients with factor 3 symptoms showed significant

**Figure 1** Significant hypoperfusion areas in dementia with Lewy bodies compared with the controls. Statistical threshold was set at $P<0.01$ with correction for multiple comparisons.
hypoperfusion compared with those without factor 3 symptoms in bilateral parietal areas (bilateral angular gyri and right supramarginal gyrus) and the left ventral occipital gyrus (Fig. 3; Table 4).

When the threshold was lowered to an uncorrected $P < 0.01$, the right ventral occipital gyrus ($x = 36$, $y = 30$, $z = 36$ and $x = 32$, $y = 24$, $z = 38$), and bilateral posterior cingulate gyri ($x = -10$, $y = -56$, $z = 46$ and $x = 10$, $y = -58$, $z = 50$) were also detected. No significant hyperperfusion area was found related to factor 3.

There was no significant hypoperfusion area related to delusions. Instead, patients with delusions showed significant hyperperfusion compared with those without delusions in the right rostral medial frontal cortex, which centred around the right cingulate sulcus and bilateral middle frontal gyrus, right inferior frontal gyrus, left medial superior frontal gyrus and left middle frontopolar gyrus (Fig. 4 and Table 5).

We found no significant regional cerebral blood flow difference related to factor 2 or factor 4 symptoms.

**Discussion**

We successfully uncovered significant relationships of the regional cerebral blood flow with factor 1 and 3 symptoms and delusions, but not with factor 2 and 4 symptoms. Our failure to obtain significant findings may have been due to the small number of subjects having factor 2 symptoms; however, for factor 4, the reason is uncertain. Visual hallucinations of non-humans might be heterogeneous and different in nature from hallucinations of person. Alternatively, the failure to find correlation between regional cerebral blood flow and factor 2 and 4 symptoms might simply be that there were none; these symptoms may correlate with global deterioration of brain function and not be correlated with focal deficits. Future study is needed to clarify these points.

Because most patients (92%) with factor 3 symptoms had visual hallucinations of person, the effect of factor 3 on regional cerebral blood flow was assumed to be mainly related to visual hallucinations. Hallucinations of person in dementia with Lewy bodies were associated with significant hypoperfusion in the ventral visual stream for face and object recognition (i.e. left ventral occipital
gyrus), and the dorsal stream for spatial location and motion vision (i.e. bilateral parietal cortices). The location of the ventral occipital gyrus closely matched the ‘occipital face area’, which is sensitive to physical aspects of face stimulus and is a critical stage in the face-recognition pathway (Kanwisher and Yovel, 2006). Despite the relative heterogeneity of the previous reports (Imamura et al., 1999; O’Brien et al., 2005), our results support the findings of several previous studies showing that dysfunction of extrastriate visual association areas rather than the primary visual cortex is related to visual hallucination in dementia with Lewy bodies.

Figure 3  Significant hypoperfusion related to the visual hallucinations in dementia with Lewy bodies. The statistical threshold was set at $P < 0.001$ for SPM(Z). The ‘x’ (in millimetres) and ‘y’ indicate the sagittal and coronal slice positions in the stereotactic space, respectively. L = left.

Table 4  Regions that show significant hypoperfusion in relation to hallucinations

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Regions</th>
<th>Voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Angular gyrus, Lt</td>
<td>152</td>
<td>−38</td>
<td>−68</td>
<td>26</td>
<td>3.63</td>
</tr>
<tr>
<td>2</td>
<td>4th occipital gyrus, Lt</td>
<td>138</td>
<td>−32</td>
<td>−76</td>
<td>−10</td>
<td>3.44</td>
</tr>
<tr>
<td>3</td>
<td>Supramarginal gyrus, Rt</td>
<td>70</td>
<td>46</td>
<td>−46</td>
<td>38</td>
<td>3.39</td>
</tr>
<tr>
<td>4</td>
<td>Angular gyrus, Rt</td>
<td>71</td>
<td>34</td>
<td>−72</td>
<td>22</td>
<td>3.37</td>
</tr>
</tbody>
</table>

Voxels = number of voxels in each detected region; (x, y, z) = stereotactic coordinates in the MNI space; Z score = SPM(Z) score; Lt = left; Rt = right.
perceived complex, non-stationary scenarios (Mosimann et al., 2006), similar to hallucinations in patients with temporo-occipital and parieto-occipital lesions (Lance, 1976). Furthermore, Mori et al. (2006) demonstrated that regional cerebral blood flow in ventral occipital regions was increased and visual hallucination was improved in dementia with Lewy bodies after donepezil administration (Mori et al., 2006), and suggested that hypofunction in the visual association areas, which is caused by a lack of cholinergic inputs from the forebrain or brainstem, may be a key to the genesis of visual hallucinations in dementia with Lewy bodies.

Because the ‘misidentification’ factor comprised several different symptoms (including ‘delusional misidentification syndromes’), common regional cerebral blood flow abnormalities among misidentification syndromes may provide the basic underlying pathophysiology. Our findings of significant hypoperfusion associated with misidentifications in limbic (left hippocampus) and paralimbic structures (left insula and bilateral inferior frontal gyri) support and extend earlier suggestions that the ‘delusional misidentification syndromes’ may derive from discordance between emotional accompaniments of sensory and mnemonic images (Signer, 1987; Christodoulou, 1991; Weinstein, 1994; Ellis and Lewis, 2001). Theoretical models of Capgras syndrome proposed that the patient can recognize a face but fails to receive a confirmatory feeling of familiarity, so that the joint information representing face recognition and affective response does not match a stored (and therefore expected) representation of the person (Breen et al., 2000; Ellis and Lewis, 2001). Some researchers argued that the deficit could be explained in terms of intact ventral temporal visual recognition systems, but disrupted connections to the limbic-paralimbic structures, or as impairment of the limbic-paralimbic structures themselves (Hirstein and Ramachandran, 1997; Breen et al., 2000).

Reduplicative paramnesia and Capgras syndrome possess many common features beyond the idea of doubles. In reduplication phenomena, the misidentified person or place is selective and almost always ‘belongs’ to the patient—i.e. the person or place normally has a strong emotional relationship to the patient (Weinstein and Burnham, 1991; Weinstein, 1994). Some researchers (Staton et al., 1982; Fleminger and Burns, 1993) also argued that reduplicative paramnesia is based on a false recollection, in which a patient is unable to integrate a recent observation with past memory stores. To our knowledge, no study has investigated the possible neuropsychiatric mechanism of phantom boarder symptom; however, the bizarre belief that ‘there is someone unfamiliar in the house’ seems to be related to false memories accompanied by strangeness (i.e. feeling of unfamiliarity). Even the misidentification of person goes beyond a simple illusion or naming difficulty and may be a faulty identification based on inaccurately retrieved information and emotional experiences, because it usually involves intimates, such as a spouse, sibling, child or neighbour.

Figure 4 Relative hyperperfusion areas related to delusions in dementia with Lewy bodies. The statistical threshold was set at $P < 0.001$ for SPM{$Z$}. The ‘z’ indicates axial slice position in millimetres in the stereotactic space. L = left.

Table 5 Regions that show significant hyperperfusion in relation to delusions

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Regions</th>
<th>Voxels x</th>
<th>y</th>
<th>z</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rostral medial frontal cortex, Rt</td>
<td>2119</td>
<td>-32</td>
<td>26</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Middle frontal gyrus, Lt</td>
<td>10</td>
<td>46</td>
<td>10</td>
<td>4.04</td>
</tr>
<tr>
<td></td>
<td>Superior frontal gyrus, medial, Lt</td>
<td>-10</td>
<td>38</td>
<td>32</td>
<td>3.46</td>
</tr>
<tr>
<td>2</td>
<td>Middle frontal gyrus, Rt</td>
<td>441</td>
<td>32</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Inferior frontal gyrus, Rt</td>
<td>50</td>
<td>26</td>
<td>24</td>
<td>3.50</td>
</tr>
<tr>
<td>3</td>
<td>Middle frontopolar gyrus, Lt</td>
<td>12</td>
<td>-22</td>
<td>52</td>
<td>2</td>
</tr>
</tbody>
</table>

Voxels = number of voxels in each detected region; (x, y, z) = stereotactic coordinates in the MNI space; Z score = SPM{$Z$} score; L = left; Rt = right.

The hippocampus, insula, frontal operculum and accumbens nucleus are elements of the limbic-paralimbic system. The hippocampus is relevant not only to encoding process of memory but also to recollection of the episode (Cansino et al., 2002; Eldridge et al., 2005; Eichenbaum et al., 2007). Functional imaging studies

(Pernecky et al., 2008) and Parkinson’s disease with dementia (Matsui et al., 2006; Boecker et al., 2007). Dysfunction in both ventral and dorsal streams well matched the clinical characteristics of visual hallucinations in dementia with Lewy bodies because they
revealed that the inferior frontal opercular region was activated when observing the emotional facial expressions of others (right dominant) (Wicker et al., 2003; Jabbi et al., 2007), and in controlling the impact of emotions on cognitive performance (left dominant) (Nelson et al., 2003; Dolcos et al., 2006). Similar inferior frontal regions have been shown to be recruited during affective autobiographical recall (Damasio et al., 2000). The insula forms a key central network in the paralimbic system, which has extensive reciprocal connections to inferior and orbital frontal regions, medial temporal structures such as the hippocampus and amygdala, as well as parietal cortex and medially to the thalamus and basal nuclei (Augustine, 1996). The insular cortex is engaged in tasks that depend on interactions between the extra-personal world and the internal milieu (Mesulam and Mufson, 1982), and disturbance of the insular and temporolimbic system, especially on the left side, is associated with the expression of positive symptoms in schizophrenia (Bogerts, 1997; Crespo-Facorro et al., 2000). The accumbens nucleus is the principal component of the ventral striatum and is most often associated with reward-related behaviour such as emotional learning (Pavlovian conditioning and instrumental conditioning) (Cardinal et al., 2002; Robbins et al., 2008). Human imaging studies demonstrated that the ventral striatum/accumbens was activated with rewarding properties of beautiful faces (Aharon et al., 2001), faces previously presented with a nonthreatening affect (Satterthwaite et al., 2009) and social positive emotion (humour/joy) (Mobsbs et al., 2003; Britton et al., 2006). Thus, we speculated that an impaired memory and emotional function, and their interactions, which were associated with the dysfunction of the limbic-paralimbic systems, might underlie the misidentifications in dementia with Lewy bodies. Our results are also consistent with a previous study showing that Alzheimer’s disease with ‘delusional misidentification syndromes’ had significant hypometabolism in paralimbic (orbitofrontal and cingulate areas bilaterally) and left medial temporal areas compared with Alzheimer’s disease without ‘delusional misidentification syndromes’ (Mentis et al., 1995).

Delusion of theft and persecution were related to relative hyperperfusion in the frontal cortex in dementia with Lewy bodies, which seems in conflict with several reports showing that frontal perfusion is decreased in Alzheimer’s disease patients with delusions (Mega et al., 2000; Staff et al., 2000; Sultzer et al., 2003). The conflicts may be due to differences in patient groups, definition of delusions, clinical state at the time of studies and image analysis techniques. Alzheimer’s disease patients in previous studies were impaired more severely in cognitive function than our subjects (Mega et al., 2000; Staff et al., 2000; Sultzer et al., 2003), and had both persecutory delusions and (delusional) misidentifications (Staff et al., 2000; Sultzer et al., 2003), or hallucinations (Mega et al., 2000). However, the ‘hyperperfusion’ regions in the dementia with Lewy bodies subgroup were not actually hyperactive but rather less hypoperfused, and can be interpreted as dysfunctional areas because these were within significant hypoperfusion regions compared with control subjects. Indeed, direct comparison between the dementia with Lewy bodies subgroup with delusions and control subjects confirmed significant frontal hypoperfusion (online Supplementary Figure). To generate delusions, preserved functions in those frontal areas may be required. When the functions in those regions were severely depressed, like in frontal leucotomy, delusions may no longer emerge. Thus, the frontal cortex in dementia with Lewy bodies with delusions may still operate, but possibly with errors. Several reports have demonstrated that the frontal cortex is relatively hyperactive in relation to positive symptoms of schizophrenia (Liddle et al., 1992; Soyka et al., 2005).

Neuropsychiatric models proposed that people with persecutory delusions preferentially attend to threatening stimuli and recall threatening episodes (i.e. attentional bias), jump to conclusions on the basis of insufficient information, attribute negative events to external causes such as other people or circumstances (i.e. attributional bias), and have difficulty in envisaging other’s intentions, motivations, or state of mind (Blackwood et al., 2001; Bell et al., 2006). Neuroimaging studies pointed to the rostral medial frontal cortex as a key region that plays a crucial role in social cognition (Amadio and Frith, 2006; Gilbert et al., 2007). Social cognitive processes, such as self-reflection, person perception and attribution have been associated with activity extending from the anterior cingulate to the anterior frontal pole, most typically located along the paracingulate sulcus (Harris et al., 2005; Amadio and Frith, 2006), which matches well with the location detected in the present study. Such social inferential processing is based on access to information stored in episodic autobiographical memory, including information about the self, relationships with others and social situations. Bilateral dorsolateral prefrontal areas and the superior medial frontal area, which were also identified here, are known to contribute to episodic memory retrieval (Fletcher and Henson, 2001), and monitor and manipulate information within working memory. Several have shown impaired source monitoring (the ability to distinguish internally from externally generated experiences) in patients with delusions (Brebon et al., 2002; Moritz et al., 2005). Therefore, we speculated that dementia with Lewy bodies patients with delusions preferentially make wrong causal attributions to external people (i.e. other-blaming attributions) based on impaired source monitoring and insufficient information retrieved from episodic memory.

We observed that regional cerebral blood flow differences related to hallucinations and misidentifications were more pronounced in the left hemisphere. Boecker et al. (2007) also reported a left dominant metabolic reduction in occipto-temporo-parietal regions in Parkinson’s disease with visual hallucinations (Boecker et al., 2007); however, our observations may be due to random noise, since hypoperfusion related to hallucinations was found in the bilateral occipital and parietal cortices at the lower statistical threshold of $P < 0.01$. In contrast, greater hypoperfusion in the left compared with right insula and hippocampus related to misidentification was still observed even at a lower threshold. Patients with ‘delusional misidentification syndromes’ usually have lesions in the right and/or bilateral hemispheres, suggesting the right-side dominance of the delusional misidentification syndrome (Devinsky, 2009); however, the very great majority of patients with right hemisphere lesions do not have delusional misidentification syndromes, and many patients that do have bilateral pathology (Weinstein, 1994; Devinsky, 2009). Indeed, our dementia with Lewy bodies group had significant...
Neural basis of psychotic symptoms in dementia with Lewy bodies

A number of mediating factors, such as culture, life experiences, coping styles and temperament, influence the occurrence or content of psychotic phenomena. Nevertheless, our findings provide important insights into the pathophysiological mechanisms underlying psychotic symptoms in dementia with Lewy bodies and may be ultimately informative to develop new therapies for psychotic symptoms in dementia with Lewy bodies.

Supplementary material

Supplementary material is available at Brain online.

References


