Neuroanatomical correlates of behavioural disorders in dementia

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Neurodegenerative diseases are associated with profound changes in social and emotional function. The emergence of increasingly sophisticated methods for measuring brain volume has facilitated correlation of local changes in tissue content with cognitive and behavioural changes in neurodegenerative disease. The current study examined neuroanatomical correlates of behavioural abnormalities, as measured by the Neuropsychiatric Inventory, in 148 patients with dementia using voxel-based morphometry. Of 12 behaviours examined, 4 correlated with tissue loss: apathy, disinhibition, eating disorders and aberrant motor behaviour. Increasing severity across these four behaviours was associated with tissue loss in the ventral portion of the right anterior cingulate cortex (vACC) and adjacent ventromedial superior frontal gyrus (vmSFG), the right ventromedial prefrontal cortex (VMPC) more posteriorly, the right lateral middle frontal gyrus, the right caudate head, the right orbitofrontal cortex and the right anterior insula. In addition, apathy was independently associated with tissue loss in the right vmSFG, disinhibition with tissue loss in the right subgenual cingulate gyrus in the VMPC, and aberrant motor behaviour with tissue loss in the right dorsal ACC and left premotor cortex. These data strongly support the involvement of the right hemisphere in mediating social and emotional behaviour and highlight the importance of distinct regions on the medial wall of the right frontal lobe in regulating different behaviours. Furthermore, the findings underscore the utility of studying patients with dementia for understanding the neuroanatomical basis of social and emotional functions.

Keywords: frontotemporal dementia; neuropsychiatric inventory; voxel-based morphometry; right hemisphere; cingulate

Abbreviations: ACC = anterior cingulate cortex; FTD = frontotemporal dementia; MMSE = Mini-Mental State Examination; NPI = Neuropsychiatric Inventory; OFC = orbitofrontal cortex; ROI = region of interest; SGC = subgenual cingulate gyrus; SPM = statistical parametric mapping; TIV = total intracranial volume; vACC = ventral portion of the right anterior cingulate cortex; VBM = voxel-based morphometry; VMPC = ventromedial prefrontal cortex; vmSFG = ventromedial superior frontal gyrus


Introduction

Disorders of social and emotional functioning are central features of a large number of acquired and developmental disorders ranging from traumatic brain injury and neurodegenerative disease to schizophrenia and autism. New hope for improved treatment of these disorders has arisen over the last few years along with a resurgence of interest in the brain mechanisms underlying social and emotional functions (Dolan, 2002; Blakemore et al., 2004; Ochsner, 2004). Some of the renewed enthusiasm for this area of research has been driven by developments in neuroimaging that allow the study of social and emotional functions in normal subjects, particularly with PET and fMRI (Ochsner, 2004). Additionally, brain injury models have helped to delineate the anatomy of these functions (Harlow, 1868; Eslinger et al., 1984; Adolphs et al., 1996; Hornak et al., 2003).
Neuroanatomy of behaviour disorders

Neurodegenerative dementing disorders offer a valuable opportunity to study the neural underpinnings of social and emotional behaviour, as they are common (Brookmeyer et al., 1998) and affect structures relevant to emotion and social behaviour including the amygdala, anterior temporal neocortex, ventromedial frontal regions, insula and anterior cingulate cortex (ACC) (Boccardi et al., 2002; Hamann et al., 2002; Rosen et al., 2002a). In some types of dementia, disturbed emotional and social behaviour occur early in the course of the disease (Cummings, 1997) and can even define the central diagnostic features of the illness (Neary course of the disease (Cummings, 1997) and can even define the central diagnostic features of the illness (Neary, 1998). An increasing number of studies assessing brain tissue volumes or metabolic function in dementia are demonstrating that regional tissue loss and hypometabolism correlate with specific cognitive and behavioural impairments in ways that are similar to what has been seen with other, more focal types of pathology (Eustache et al., 2000; Gee et al., 2003; Nadeau, 2003).

Previous studies in patients with neurodegenerative disease suggest that dysfunction or atrophy in the right hemisphere is associated with behavioural disturbances including apathy (Ott et al., 1996; Benoit et al., 2002), delusions (Staff et al., 1999; Edelstyn et al., 2001), antisocial behaviour (Mychack et al., 2001), and behavioural dysfunction in general (Miller et al., 1993; Edwards-Lee et al., 1997; Thompson et al., 2003b; Liu et al., 2004; Williams et al., 2005). Specific brain regions have also been implicated in behaviour, in particular the insula and the medial and ventral frontal regions (Craig et al., 1996; Migneco et al., 2001; Tekin et al., 2001; Benoit et al., 2002; Rosen et al., 2002a; Williams et al., 2005). Some of these studies were limited in that they relied upon region of interest (ROI) type analyses, where relationships between behaviour and a priori regions were examined, leaving open the possibility that other unmeasured regions, or smaller portions of the ROIs, had equally strong or stronger relationships with the behaviour. Also, most of the prior studies used small cohorts of patients and examined only a single behaviour. Since dementias are associated with multiple behavioural abnormalities (Cummings, 1997), it has been hard to conclude that the relationship between the behaviour and the region identified were unique. However, a few studies have demonstrated unique relationships between behaviour and volumes or metabolism in selected brain regions measured with ROI analyses (Craig et al., 1996; Sarazin et al., 2003).

Studies of patients with discrete lesions have also examined the neuroanatomical substrates of social and emotional dysfunction, usually focusing on behaviours associated with damage in specific regions. For example, disinhibition has been noted in association with ventromedial prefrontal and orbitofrontal cortex (OFC) injury (Eisinger and Damasio, 1985; Hornak et al., 1996), particularly in the right hemisphere (Tranel et al., 2002). In these studies, patients had a constellation of behavioural abnormalities including dampened and poorly modulated emotions, poor decision-making, disinhibition and lack of insight (Saver and Damasio, 1991; Tranel et al., 2002), suggesting that all these symptoms could have had a common neuroanatomical basis. Lesion studies have also described apathy in the setting of ACC damage as well as other lesion locations (Carota et al., 2002; Kumral et al., 2002). To date, no studies in either dementia or focal lesion cohorts have systematically examined the neuroanatomical correlates of behavioural abnormalities using approaches capable of finding associations in any part of the brain while including multiple, potentially related behaviours in order to identify neuroanatomical relationships unique to each.

The goal of the current study was to identify, in a large cohort of patients with a variety of dementing conditions, the brain regions where grey matter tissue loss correlated with the severity of twelve different behavioural disturbances characteristic of neurological disease and to determine whether unique relationships between individual behaviours and particular brain regions could be discerned. The main hypothesis was that behavioural disturbances would be associated with tissue loss in focal regions in the right hemisphere including the insula and ventral and medial frontal regions. Prior research allowed more specific hypotheses for some behaviours including that disinhibition would be correlated with atrophy in the right ventromedial prefrontal cortex (VMPC; Tranel et al., 2002) and that apathy would be correlated with tissue loss in the right VMPC (Craig et al., 1996; Sarazin et al., 2003) or ACC (Kumral et al., 2002). The analysis was carried out using voxel-based morphometry (VBM), a technique for assessing regional changes in brain tissue content over the entire brain on a voxel-by-voxel basis without the need for a priori ROI (Ashburner and Friston, 2000).

Methods

Subjects

One hundred and forty-eight patients (mean age 64.8 years, standard deviation = 9.4) with dementia were recruited through the University of California San Francisco Memory and Aging Center. Criteria for inclusion were a diagnosis of dementia, the availability of valid Neuropsychiatric Inventory (NPI) data (see below) and a high-quality research MRI scan within 6 months of the NPI assessment. Dementia diagnoses included frontotemporal dementia (FTD) (n = 39), semantic dementia (n = 23), progressive non-fluent aphasia (n = 13), corticobasal degeneration (n = 12), progressive supranuclear palsy (n = 9) and Alzheimer’s disease (n = 52). Patients were diagnosed using published diagnostic criteria (McKhann et al., 1984; Litvan et al., 1996; Neary et al., 1998; Boeve et al., 2003) after a comprehensive evaluation including neurological history and examination, a specialty nursing evaluation that included a behavioural assessment, and neuropsychological testing of memory, executive function, language and mood using a previously described standard protocol (Rosen et al., 2002a; Kramer et al., 2003). The mean Mini-Mental State Examination (MMSE) was 21 (standard deviation = 7.7), and the mean Clinical Dementia Rating (CDR) (Morris, 1997) score was 0.9 (standard deviation = 0.6).
Identification of behavioural abnormalities

The NPI was used for behavioural assessment (Cummings, 1997). The NPI is a validated, caregiver-based behavioural rating system developed for the assessment of dementia that evaluates the presence or absence, severity (rated 1–3, 3 being most severe) and frequency (rated 1–4, 4 being most frequent) of 12 major behavioural disorders, including delusions, hallucinations, aggression/agitation, depression, anxiety, elation/euphoria, apathy, disinhibition, irritability/lability, aberrant motor behaviour, sleep disturbances and eating disorders. An index of severity is created for each behavioural variable by multiplying the frequency and severity scores, creating a frequency by severity product ($F \times S_{\text{prod}}$—see Levy et al., 1996). Data from the NPI were correlated with regional brain tissue loss (see below).

The NPI was always collected by a geriatric specialist nurse trained in its administration who made the judgement about the consistency and reliability of the data. NPI scores from suspect raters were not used. Although informants questioned for the NPI were not screened for cognitive impairment, they were, in general, the same individuals who provided the history used to make the clinical diagnosis of dementia. When caregivers knowledgeable about the patient provide NPI ratings, between-rater reliability across the NPI domains varies between 93.6 and 100%, while test–retest reliability correlations are 0.79 for frequency and 0.86 for severity (Cummings, 1997).

Acquisition and analysis of MRI data

MRI scanning

Structural MR imaging was accomplished using a 1.5-T Magnetom VISION system (Siemens Inc., Iselin, NJ), a standard quadrature head coil and previously described sequences (Rosen et al., 2002a) to obtain (i) scout views of the brain for positioning subsequent MRI slices, (ii) proton density and T2-weighted MRIs and (iii) T1-weighted (MP-RAGE) images of entire brain. MP-RAGE images were used for analysis.

Voxel-based morphometry

VBM is a technique for voxel-wise analysis of local changes in brain tissue content which has been used to study many brain disorders including dementia (Abell et al., 1999; Krams et al., 1999; Ashburner and Friston, 2000; Mummery et al., 2000; Good et al., 2001b; Burton et al., 2002; Rosen et al., 2002a; Boxer et al., 2003; Critchley et al., 2003; Gorno-Tempini et al., 2004; Williams et al., 2005). VBM involves several preprocessing steps before the images are analysed. The VBM preprocessing procedures employed for this study included two recently described procedures developed to optimize spatial normalization and segmentation: (i) creation of a study specific template for normalization made up of the average of all subjects included in the study (Good et al., 2001a) and (ii) optimization of spatial normalization using grey matter images to determine the final normalization parameters (Good et al., 2001b). Preprocessing was implemented as follows. All subject images were first spatially normalized using the Montreal Neurological Institute (MNI) brain provided with statistical parametric mapping (SPM) (linear followed by non-linear $8 \times 8 \times 7$ parameter transform). These images were segmented to create normalized grey, white and cerebrospinal fluid compartments, which were averaged across subjects to create a new averaged whole brain, and grey, white and cerebrospinal fluid images to be used as normalization templates (Good et al., 2001a) and as custom prior probability templates for tissue classification (Testa et al., 2004). The original images were then segmented in native space and the resultant grey matter images were normalized to the study specific grey matter template (same normalization parameters). The parameters obtained from the latter normalization were then applied to the original T1-weighted image, which was segmented again after normalization. Grey matter voxel values were then multiplied by the Jacobian determinants derived from the spatial normalization step in order to preserve the initial volumes (Good et al., 2001b). Finally, the grey matter images were smoothed with a 12 mm full width at half-maximum isotropic Gaussian kernel to reduce error related to intersubject variability in local gyral anatomy and to render the imaging data more normally distributed. Smoothing imaging data with a 12 mm Gaussian filter in the preprocessing stages imposes limits on the analysis such that unique relationships for areas that are <12 mm apart cannot be discerned. The 12 mm kernel used here is one of the more commonly used kernels for VBM and this filter kernel minimizes the risk of false positive findings (Salmond et al., 2002).

All image preprocessing steps and statistical analysis were implemented in the SPM2 software package (www.fil.ion.ucl.ac.uk/spm). For statistical analysis, the image and the NPI $F \times S_{\text{prod}}$ for each participant were entered into a design matrix and the relationships between changes in grey matter content and NPI $F \times S_{\text{prod}}$ were analysed using the general linear model. The significance of each effect of interest was determined using the theory of Gaussian fields. For all analyses, we accepted a threshold of $P < 0.05$, (SPM family-wise error, corrected for multiple comparisons) for statistical significance. Total intracranial volume (TIV) was always used as a covariate.

Statistical analysis was carried out in two steps. First, NPI scores for each of the 12 behaviours were entered into separate ‘covariates only’ design matrices. The relationship between voxel values and the behaviour of interest was examined with a $-1$–$1$ t-contrast, assuming that increasing severity of the behaviour would be associated with decreased tissue content. This allowed identification of those variables that showed significant effects for the purposes of data reduction. For this step, diagnosis was not included in the model, because previous research has shown that some behavioural abnormalities are characteristic of FTD and semantic dementia, while other behaviours are more similar across FTD and semantic dementia and other degenerative diseases (Levy et al., 1996; Bozat et al., 2000; Bathgate et al., 2001; Liu et al., 2004).

Behaviours that showed regions of significant correlation in this first step were entered into a second ‘conditions and covariates’ analysis including diagnostic group (FTD or semantic dementia versus other), age, sex and MMSE as covariates. This design allowed analysis of the average effects for the behavioural disorders identified in the first step and independent contrasts of the individual behaviours. Behavioural effects for each diagnostic group were modelled separately so that covariate-by-condition interactions could be assessed. Figure 1 depicts the final design matrix for the four behaviours ultimately included in the final analysis (see Results section for elaboration). Specific brain–behaviour relationships were tested for these four behaviours using t-contrasts including the average effects across the four behaviours in each group $([-1 -1 -1 -1])$ and $(0 -1 0 -1 0 -1 0)$ with additional zeros for condition and nuisance covariates) and across groups $([-1 -1 -1 -1 -1 -1])$, and unique effects for each behaviour in each group [e.g. $(-1, 0, 0, 0, 0, 0, 0)$ and $(0, -1, 0, 0, 0, 0, 0)$] and across groups [e.g. $(-1, -1, 0, 0, 0, 0, 0)$].
Data were analysed in this latter step at the whole brain level and after the application of a ROI for small volume correction based on a priori hypotheses generated in previous studies (Rosen et al., 2002). The ROI was created from the AAL brain atlas (Tzourio-Mazoyer et al., 2002) and applied to the SPM dataset using WFU-Pickatlas (Maldjian et al., 2003); it included the orbital parts of the superior, middle and inferior frontal gyri, gyrus rectus and olfactory cortex, the medial superior frontal gyrus, the supplementary motor area, the anterior and median cingulate and paracingulate regions, and the insula. Anatomic localization of clusters with significant effects was accomplished by overlaying the t-maps on the study specific template and using the AAL and Brodmann’s atlases that accompany the MRIcro software package (Rorden and Brett, 2000).

Relationships between NPI scores and the other independent variables were examined with Pearson correlation coefficients and linear regression using the SPSS software package (version 10.1 for Windows, SPSS Inc., Chicago, IL). Also, in order to better understand the unique effects contributed by all variables in the regression model and to test for violations of the assumptions of linear regression and multicollinearity, the linear regression performed in SPM was duplicated in SPSS for all peak voxels using raw values from the smoothed grey matter images and the same independent variables entered into the SPM design matrix. The linear form of the relationship of the dependent variable with each independent variable and homoscedasticity of the residuals was examined with scatterplots of the residuals plotted against the independent variables and predicted values with superimposed zero-lines and Lowess curves. Normality of the residuals was inspected with normal q–q plots. Multicollinearity was evaluated with the value inflation factor and comparison of the beta coefficients to the corresponding zero-order correlation coefficients (Cohen et al., 2003).

The study was approved by the UCSF committee on human research. All subjects, or their surrogates provided informed consent before participating.

## Results

### Incidence of behavioural abnormalities and behavioural correlations

Table 1 shows the frequency of each behaviour in the patient group. The most frequent was apathy (62%) and the least frequent was hallucinations (3%). None of the behavioural variables was significantly correlated with MMSE. Age and sex showed a significant correlation with several behaviours (Table 2).

### First step neuroimaging analysis

Of the 12 behaviours examined in the first step of the analysis, 4 showed regions where local decreases in grey matter tissue content were significantly correlated with increased $F \times S_{\text{prod}}$ scores. These were apathy, disinhibition, eating disorders, and aberrant motor behaviours. For the most part, the regions identified were in the right hemisphere, and there appeared to be substantial overlap in the regions associated with each condition. The regions identified included the lateral OFC in all four behaviours, the rostromedial prefrontal cortex including the ventral anterior cingulate cortex (vACC) and the adjacent ventromedial superior frontal gyrus (vmSFG) in apathy and eating disorders, the ACC more dorsally (dACC) in apathy and aberrant motor behaviour, the caudate head/ventral striatum in apathy and eating disorders, the subgenual cingulate gyrus (SGC) in the most medial posterior part of the OFC (or VMPC) and the right temporal pole in disinhibition, and the insula in eating disorders and aberrant motor behaviour. These four behavioural variables were carried forward to the second step analysis.
Second step neuroimaging analysis
(combined analysis using apathy, disinhibition, aberrant motor behaviour and eating disorders)

The only four behaviours showing significant correlations with regional tissue loss were those known to be common in FTD and semantic dementia (Levy et al., 1996; Bozeat et al., 2000; Snowden et al., 2001; Liu et al., 2004). These earlier findings suggested that regions correlated with behaviour in the first analysis could also be regions correlated with diagnosis of FTD or semantic dementia and thus were not specific to behaviour per se. Figure 2 illustrates the distribution of scores for the four behaviours in this study using box plots and shows that the median scores for these behaviours and the maximum scores for these behaviours were indeed higher in FTD and semantic dementia than in the group of patients with non-FTD/semantic dementia diagnoses. Since the goal of the analysis was to identify regions specifically related to behaviour, the effect of diagnostic group (FTD or semantic dementia versus other) was included in the analysis as a condition along with the $F \times S_{\text{prod}}$ scores for apathy, disinhibition, eating disorders and aberrant motor behaviour (with condition by covariate interactions modelled, see Methods) and MMSE, age, sex and TIV as nuisance covariates.

Average effects across all four behaviours

Analysis of the four behaviours as a group revealed a group by behaviour interaction. In the FTD/semantic dementia group, increasing $F \times S_{\text{prod}}$ scores across these four behaviours was correlated with decreasing tissue content in the right frontal lobe, with significant clusters in the vACC, extending anteriorly into the vmSFG, the more posterior VMPC including the SGC, the MFG on the lateral surface, the caudate head, the OFC and the anterior insula (Table 3, Fig. 3A). Limiting the analysis to the ventral/medial frontal and insula ROI bilaterally revealed an additional cluster in the right OFC. No voxels correlated with these behaviours as a group in the non-FTD/semantic dementia diagnostic group.

Regional tissue loss associated with an FTD or semantic dementia diagnosis

In order to understand how the regions correlated with behaviour compared with the regions associated with diagnosis, separate analyses were conducted using diagnostic groups as conditions and MMSE, age, sex and TIV as covariates. These analyses demonstrated that a diagnosis of FTD or semantic dementia in this group was associated, on the average, with
significant tissue loss in the inferior and medial portions of the frontal lobes bilaterally (Fig. 3B). Thus, the regions associated with behaviour in FTD/semantic dementia appeared to be a subset of those associated with a diagnosis of FTD/semantic dementia. When FTD was specifically compared with semantic dementia, FTD showed bilateral frontal atrophy, which was significant at a few locations in the left and right lateral frontal cortex (Fig. 3C). Semantic dementia showed bitemporal atrophy compared with FTD (data not shown).

### Table 3

Regions where $F \times S_{\text{prod}}$ scores for the four behaviours—apathy, disinhibition, eating disorders and aberrant motor behaviour—in the FTD/semantic dementia group were inversely correlated with decreased grey matter tissue content.

<table>
<thead>
<tr>
<th>Anatomical region*</th>
<th>BA†</th>
<th>X, Y, Z‡</th>
<th>Cluster size§</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole brain level, $P &lt; 0.05$, corrected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R vACC/vmSFG</td>
<td>32/10</td>
<td>8, 51, 8</td>
<td>15738</td>
<td>5.33</td>
</tr>
<tr>
<td>R VMPC</td>
<td>11</td>
<td>1, 33, −17</td>
<td></td>
<td>5.04</td>
</tr>
<tr>
<td>R vACC/vmSFG</td>
<td>10/11</td>
<td>10, 50, −7</td>
<td></td>
<td>4.81</td>
</tr>
<tr>
<td>R MFG</td>
<td>45</td>
<td>51, 48, 27</td>
<td>98</td>
<td>5.05</td>
</tr>
<tr>
<td>R caudate head</td>
<td>—</td>
<td>10, 16, −2</td>
<td>1707</td>
<td>4.98</td>
</tr>
<tr>
<td>R OFC</td>
<td>11</td>
<td>20, 9, −20</td>
<td></td>
<td>4.81</td>
</tr>
<tr>
<td>R anterior insula</td>
<td>47</td>
<td>33, 24, −4</td>
<td>11</td>
<td>4.58</td>
</tr>
<tr>
<td>Additional after SVC within ventral/medial frontal and insula ROI, $P &lt; 0.05$, corrected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R OFC</td>
<td>11</td>
<td>28, 35, −16</td>
<td>22</td>
<td>4.06</td>
</tr>
</tbody>
</table>

*Based on the AAL brain, R = right/L = left. OFC = orbitofrontal cortex; ACC = anterior cingulate cortex; MFG = middle frontal gyrus; VMPC = ventromedial prefrontal cortex (posterior, medial orbital frontal region). †BA = Brodmann area. Based on the Brodmann map image provided with MRicro. ‡Coordinate for peak voxel in the cluster. §Cluster size on $P < 0.05$ corrected statistical map. Regions that were within the same cluster are listed consecutively. Peak voxels >12 mm apart within the same cluster were labelled separately.
Unique effects for individual behaviours

Apathy, aberrant motor behaviour and disinhibition showed significant correlations with specific brain regions (Fig. 4, Table 4).

For apathy, a significant effect was detected in FTD/semantic dementia, but not non-FTD/semantic dementia, with behaviour being correlated with tissue loss in the vmSFG, extending back to the cingulate sulcus ($P < 0.05$ corrected, using a ventral/medial frontal and insula ROI for small volume correction—see Methods).

Aberrant motor behaviour showed both a main effect and an interaction. Increasing aberrant motor behaviour was correlated with tissue loss in the right dACC, across the whole dementia group ($P < 0.05$ corrected using the ventral/medial frontal and insula ROI for small volume correction). This region appeared to extend up into the supplementary motor area. In the non-FTD/semantic dementia group, increasing aberrant motor behaviour was correlated with tissue loss in the left premotor cortex ($P < 0.05$ corrected at the whole brain level).

**Table 4 Regions where $F \times S_{prod}$ scores for specific behaviours were uniquely inversely correlated with tissue loss**

<table>
<thead>
<tr>
<th>Anatomical region$^a$ (association)</th>
<th>BA$^b$ X, Y, Z$^c$</th>
<th>Cluster size$^d$</th>
<th>Z-Score</th>
<th>$\beta^e$</th>
<th>Partial correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>R vmSFG (FTD/semantic dementia, apathy)</td>
<td>10 9, 57, 3</td>
<td>96</td>
<td>4.13</td>
<td>FTD/semantic dementia</td>
<td>$-0.554$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-FTD/semantic dementia</td>
<td>$-0.069$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FTD/semantic dementia</td>
<td>$-0.488$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-FTD/semantic dementia</td>
<td>$-0.251$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FTD/semantic dementia</td>
<td>$-0.147$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Non-FTD/semantic dementia</td>
<td>$-0.433$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FTD/semantic dementia</td>
<td>$-0.529$</td>
</tr>
<tr>
<td>R SGC (FTD/semantic dementia, disinhibition)</td>
<td>25 2, 11, −3</td>
<td>19</td>
<td>4.05</td>
<td>FTD/semantic dementia</td>
<td>$-0.004$</td>
</tr>
</tbody>
</table>

$^a$Association = group(s) contributing to the effect at the peak voxel. AMB = aberrant motor behaviour. $^b$Same as in Table 3. $^c$Value is significant at $P < 0.05$ (one-tailed).
Disinhibition showed an interaction, with increasing disinhibition correlating with tissue loss in the SGC in FTD/semantic dementia, but not non-FTD/semantic dementia ($P < 0.05$ using the ventral/medial frontal and insula ROI for small volume correction).

Figure 5 depicts the relationship between adjusted voxel values and behaviour for apathy, disinhibition and aberrant motor behaviour at the peak voxels where these behaviours showed unique effects. Behavioural scores are well distributed for the FTD/semantic dementia group throughout the range of NPI $F \times S_{prod}$ scores. For disinhibition and aberrant motor behaviour, non-FTD/semantic dementia patients tended to cluster in the very low score ranges. For apathy, a substantial number of non-FTD/semantic dementia patients had
evidence of apathy, but only a few had the very high scores seen in FTD/semantic dementia.

Table 4 provides the standardized regression coefficients and partial correlation coefficients for apathy, aberrant motor behaviour and disinhibition at voxels where they showed unique effects. Tests for multicollinearity and violations of the assumptions of linear regression revealed no discernible bias in the estimation of the regression coefficients or their standard errors.

Discussion

The primary goals of this study were to examine the neuroanatomical correlates of behavioural abnormalities in dementia and to identify unique relationships between individual behaviours and particular brain regions that were independent of more general brain–behaviour relationships. Four behaviours: apathy, disinhibition, eating disorders, and aberrant motor behaviour were significantly correlated with tissue loss in several regions in the right frontal lobe. In addition, three of these behaviours: apathy, disinhibition and aberrant motor behaviour were associated with tissue loss in specific brain regions, independent of the effects of the other behaviours. These findings support the results of previous studies indicating that specific behavioural disorders are associated with right frontal dysfunction. In addition, the data indicate that neuronal dysfunction in different regions within the medial frontal cortex has specific implications for social and emotional behaviour that could be elucidated with more directed studies. Furthermore, they provide evidence that specific neuroanatomical–behavioural relationships can be delineated in patients with dementia.

Behavioural dysfunction and the right hemisphere

Behavioural dysfunction was correlated with tissue loss in several cortical regions in the right hemisphere including the vACC and adjacent vmSFG, the VMPC including the SGC, the OFC, the lateral MFG and the anterior insula. The association between behaviour and the right hemisphere supports the results from previous studies by other groups in patients with dementia (Miller et al., 1993; Ott et al., 1996; Edwards-Lee et al., 1997; Staff et al., 1999; Edelstyn et al., 2001; Thompson et al., 2005b) and focal neurological lesions (Tranel et al., 2002).

The specific processes that underlie the specialization of the right hemisphere for regulation of social behaviour are poorly understood. In the case of language, neurophysiological approaches such as fMRI have linked the left hemisphere with basic functions including word processing, lexical semantics and grammatical processing. These studies have helped to further define the role for the left hemisphere in language indicated by lesion studies (Demonet et al., 2005). In contrast, specific links between the right hemisphere and putative functions underlying social and emotional behaviour have not been demonstrated as consistently. For instance, while lesion studies have mostly focused on the role of the right hemisphere in emotional processing (Bowers et al., 1991; Adolphs et al., 1996; Borod et al., 1998; Rosen et al., 2002b), data from physiological studies have suggested that both hemispheres make contributions to emotion (Davidson et al., 1990; Canli, 1999; Wager et al., 2003). Another putatively right hemispheric function suggested by lesion studies is self-awareness, which may be an important component in regulating some social and emotional functions (Craig et al., 1999; Fossati et al., 2003). While the connections between regulation of behaviour and more elemental functions in the right hemisphere are not completely established, the current results add to the growing body of literature indicating that functions mediated by the right hemisphere make unique contributions to the regulation of social and emotional behaviour.

Correlations between specific behaviours and specific regions

Three regions in different parts of the medial frontal cortex had unique associations with specific behaviours. Apathy correlated with tissue loss in the ventral portion of the vmSFG adjacent to the vACC, disinhibition with tissue loss in the SGC, posterior to the region associated with apathy, and aberrant motor behaviour with tissue loss in the dACC and premotor cortex. These findings are largely in agreement with available data from prior studies and suggest unique contributions of each of these regions in regulating behaviour.

Prior studies in patients with neurodegenerative disease have found specific regional associations with behaviour, particularly for apathy. Medial frontal metabolism (Craig et al., 1996; Migneco et al., 2001; Benoit et al., 2002) and plaque burden in the ACC at autopsy (Tekin et al., 2001) have both been correlated with apathy in patients with AD. One study examined the metabolic correlates of emotional and social dysfunction with PET and ROI analysis in a mixed population of patients with frontal lobe pathology including strokes, traumatic brain injury and FTD in about two-thirds of the sample. They found apathy to be correlated with hypometabolism in the right medial BA 10, essentially in the same location as the current analysis (Sarazin et al., 2003). Another group recently demonstrated that the areas of hypometabolism in the medial frontal region associated with apathy in FTD appeared to be anterior to the medial frontal regions associated with disinhibition (Franceschi et al., 2005).

Focal lesion studies are also in close agreement with the current findings. Disinhibition has been associated with lesions to the VMPC (Eslinger and Damasio, 1985; Hornak et al., 1996) and one study based on six patients suggested that the phenomenon was predominantly associated with right-sided VMPC injury (Tranel et al., 2002). Apathy is often considered as part of a larger spectrum of disorders characterized by decreased spontaneous goal directed behaviour that also includes abulia and akinetic mutism (Vijayaraghavan et al., 2002). These disorders are most commonly described
in the setting of medial frontal lesions affecting the ACC or adjacent SFG and may be more common with right hemispheric lesions (Kumral et al., 2002). However, they have been described in the setting of a variety of lesion locations including the basal ganglia and thalamus (Kumral et al., 1999; Carota et al., 2002; Tekin and Cummings, 2002). The current study suggests that although apathy may occur from damage to multiple regions, the vmSFG may have the most specific relationship to apathy and be a critical component in a larger system for motivation and goal directed behaviour that includes subcortical and possibly other cortical structures.

The current results also suggest that atrophy in different regions in the medial frontal cortex results in differing behavioural profiles. The distinction between apathy and disinhibition is particularly interesting because the associated regions are both closely linked to emotional processing and sometimes behave similarly in functional imaging paradigms (Simpson et al., 2001). Prior studies have indicated that the vmSFG region is the most frequently activated region in functional imaging studies involving emotion (Phan et al., 2002) and activity in this region has also been associated with fluctuations in basal peripheral autonomic activity (Critchley et al., 2000; Critchley, 2003), self-reflective thinking (Gusnard et al., 2001), a 'default' state of the brain when specific tasks are not being performed (Raichle et al., 2001) and tracking the expected reward value of particular stimuli (Knutson et al., 2003). In contrast the SGC has shown increased activity with sadness and active depression (Mayberg et al., 1999), and has been implicated in retention of extinction in fear conditioning (Phelps et al., 2004). The SGC region also appears to be at the centre of the VMPC lesions that lead to impaired decision-making based on future consequences, which has been hypothetically linked to the absence of a 'somatic marker' (Bechara et al., 1994). Similar to the vmSFG region, the SGC has been implicated in autonomic function (Devinsky et al., 1995) and tracking of reward value (Rolls, 2000, 2004). While the existing literature on the SGC and vmSFG suggests some overlap in their functional roles, as well as potential distinctions, the fact that these regions are associated with behaviours that appear in many ways so disparate, namely disinhibition and apathy, suggests that further work distinguishing their physiological properties will have important implications for the study of human behavioural regulation.

The analysis of aberrant motor behaviours generated an unexpected but intriguing finding. These behaviours were associated with tissue loss in the dACC. This item on the NPI captures repetitive motor acts such as tapping, pacing, restlessness and frequent rummaging through drawers. These behaviours can be ritualistic, particularly in FTD (Miller et al., 1995; Snowden et al., 2001) and bear a strong resemblance to behaviours seen in obsessive-compulsive disorder (OCD). Functional imaging has linked OCD symptoms to several brain regions including the medial OFC, vACC and dACC (Mataix-Cols et al., 2004). Dorsal ACC is associated with major functional roles in both the cognitive and motor domains that may be relevant to these behavioural abnormalities. In the cognitive domain, dACC has been linked to mediating between responses when conflicting choices are available (van Veen and Carter, 2002). Conceivably, inability to mediate these conflicts may result in repetitive, non-directed behaviour. On the other hand, in the motor domain dACC and the adjacent supplementary motor area participate in planning of complex movements (Picard and Strick, 1996). Notably, the regions of tissue loss associated with aberrant motor behaviour included the dACC and the adjacent supplementary motor area in FTD/semantic dementia as well as premotor cortex in non-FTD/semantic dementia, suggesting that further research might directly investigate the role of motor planning in the development of aberrant motor behaviour.

Unlike the other behaviours included in this analysis, eating behaviours did not uniquely associate with any specific region. From a statistical point of view, this indicates that this behaviour was well correlated with the variance in atrophy common to the other three behaviours. Eating behaviours in FTD are complex and varied, and include carbohydrate craving, overeating with weight gain, obsessions for particular foods and occasionally oral exploration of non-food objects, which may not always coexist in an individual patient (Miller et al., 1995; Ikeda et al., 2002). This variability may have impacted the likelihood of finding unique associations with eating disorders in this analysis.

Neuroanatomical correlates of apathy and disinhibition were only found in our FTD/semantic dementia group, while many of the prior studies that found regional correlates of apathy included patients with AD (Craig et al., 1996; Migneco et al., 2001; Tekin et al., 2001; Benoit et al., 2002). The fact that no relationship was found between tissue loss and some behaviours in the non-FTD/semantic dementia group is probably due to a lack of power. In the case of disinhibition this is understandable because disinhibition was infrequent in the non-FTD/semantic dementia group. Although apathy was the most common behavioural disorder in the non-FTD/semantic dementia group, few of the non-FTD/semantic dementia patients had scores >4, whereas the $F \times S_{prod}$ scores in the FTD/semantic dementia group were well distributed throughout the range of potential scores. Based on the previous work described above, we believe that, at least in the case of apathy, the relationship with vmSFG may be true regardless of dementia subtype.

Methodological issues

VBM has advantages over ROI techniques in allowing analysis of brain–behaviour relationships across the entire brain, but there are some caveats. Some of the regions in the right hemisphere that correlate with the average of all four behaviours may be appearing due to co-atrophy. The VMFC, OFC, insula and ACC (particularly the ventral portion) have all been linked to social and emotional processing through lesion studies (Eslinger and Damasio, 1985; Saver and Damasio, 1991; Calder et al., 2000; Craig, 2003; Hornak et al., 2003;
Vogt et al., 2003) and functional imaging studies (Mayberg, 1994; Phillips et al., 1998; Phan et al., 2002; Knutson et al., 2003; Kringelbach and Rolls, 2003; Phelps et al., 2004). Although the caudate nucleus has a putative role in emotional processing (and hence in social function) as indicated by lesion studies (Kumral et al., 1999) and functional imaging (Lane et al., 1997; Phillips et al., 1998), the precise role of the caudate nucleus in emotional and social processing is still a matter of debate (Milders et al., 2003). The strong interconnections between the caudate and the OFC and ACC (Alexander et al., 1986; Tekin and Cummings, 2002) may have resulted in this region atrophying along with the others, and caudate atrophy may or may not relate to specific behavioural abnormalities. Similarly the dorsolateral frontal cortex also has putative roles in emotion (for instance in regulation—see Ochsner et al., 2002), but this region is traditionally viewed as part of a system for cognitive processing (Alexander et al., 1986; Tekin and Cummings, 2002). Dorsolateral frontal cortex might have appeared in this analysis because of some relationship to the more medial frontal structures, or because of generalized atrophy in the right hemisphere in patients with behavioural dysfunction. More complex implementations of VBM or ROI approaches that directly account for atrophy in different regions of the brain, as well as the inclusion of more explanatory variables, are potentially useful approaches to this problem.

The regional atrophy correlated with each of the individual behaviours is less susceptible to this confound of atrophy because a relatively small set of voxels was identified relating to each behaviour. However, our findings do not imply that these are the only regions relating to these behaviours. Rather, the specific medial frontal regions highlighted may be part of a larger network of regions that must be damaged to cause the behaviour of interest. An excess of damage to one part of the system superimposed on damage to the system as a whole may result in more severe behaviour of a certain type.

The underlying assumptions of VBM have also been the subject of criticism, mainly because VBM cannot comprehensively differentiate changes in tissue content from local misregistration of images (Bookstein, 2001). VBM as currently implemented also assumes simple linear relationships that are qualitatively similar throughout the brain, and thus it may be insensitive to other types of relationships (Davatzikos, 2004). Although the theory behind these criticisms is correct, it has been pointed out that current approaches to VBM attempt to minimize the effects of misregistration through techniques such as tissue-specific normalization templates, and that these caveats appear to have limited applicability to real imaging data (Ashburner and Friston, 2001). Other voxel-based analyses, such as deformation-based morphometry (Studholme et al., 2004; Thompson et al., 2003a) and more elaborate models of possible brain—behaviour relationships (Davatzikos, 2004) can address these issues more directly. Direct comparisons have shown that VBM produces data that is comparable, though not precisely the same as ROI analyses (Good et al., 2002; Testa et al., 2004).

Implications for the neuroscience of behaviour

The current results, along with other recent studies (Galton et al., 2001; Boxer et al., 2003; Gee et al., 2003; Grundman et al., 2003; Kassubek et al., 2004; Williams et al., 2005), indicate that quantitative analysis of tissue loss can reveal important associations between cognitive or behavioural deficits and circumscribed brain regions, even in patients with diffuse disease. Neurodegenerative disorders are ubiquitous, and show injury in regions seldom selectively affected by other disease processes. In addition, the ability to study a changing process in individuals over time behaviourally and with imaging may allow better control for differences across individuals, reducing noise in analyses. Voxel based analyses of patients with dementia can reveal important information about localized neurological functions, particularly those involved in social and emotional behaviour. In the future, voxel-based studies in dementia (including VBM and other approaches) should be combined with ROI studies and traditional focal lesion studies to achieve the most accurate description of these relationships.

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