Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioural variant frontotemporal dementia

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Disinhibition is a common behavioural symptom in frontotemporal dementia but its neural correlates are still debated. In the current study, we investigated the grey and white matter neural correlates of disinhibition in a sample of behavioural variant frontotemporal dementia (n = 14) and patients with Alzheimer’s disease (n = 15). We employed an objective (Hayling Test of inhibitory functioning) and subjective/carer-based (Neuropsychiatric Inventory) measure of disinhibition to reveal convergent evidence of disinhibitory behaviour. Mean and overlap-based statistical analyses were conducted to investigate profiles of performance in patients with behavioural variant frontotemporal dementia, Alzheimer’s disease and controls. Hayling Test and Neuropsychiatric Inventory scores were entered as covariates in a grey matter voxel-based morphometry, as well as in a white matter diffusion tensor imaging analysis to determine the underlying grey and white matter correlates. Patients with behavioural variant frontotemporal dementia showed more disinhibition on both behavioural measures in comparison to patients with Alzheimer’s disease and controls. Voxel-based morphometry results revealed that atrophy in orbitofrontal/subgenual, medial prefrontal cortex and anterior temporal lobe areas covaried with total errors score of the Hayling Test. Similarly, the Neuropsychiatric Inventory disinhibition frequency score correlated with atrophy in orbitofrontal cortex and temporal pole brain regions. The orbitofrontal atrophy related to the objective (Hayling Test) and subjective (Neuropsychiatric Inventory) measures of disinhibition was partially overlapping. Diffusion tensor imaging analysis revealed that white matter integrity fractional anisotropy values of the white matter tracts connecting the identified grey matter regions, namely uncinate fasciculus, forceps minor and genu of the corpus callosum, correlated well with the total error score of the Hayling Test. Our results show that a network of orbitofrontal, anterior temporal and mesial frontal brain regions and their connecting white matter tracts are involved in inhibitory functioning. Further, we find convergent evidence for objective and subjective disinhibition measures that the orbitofrontal/subgenual brain region is critical for adapting and maintaining normal behaviour.

Keywords: behavioural variant frontotemporal dementia; disinhibition; orbitofrontal cortex; voxel-based morphometry; diffusion tensor imaging

Abbreviations: FTD = frontotemporal dementia
Introduction

Frontotemporal dementia (FTD) is a common cause of young onset dementia (<65 years) after Alzheimer’s disease (Ratnavalli et al., 2002). Clinical diagnostic criteria have been proposed (Neary et al., 1998), but the differentiation from other dementias remains difficult with standard neuropsychological and imaging tools (Gregory et al., 1997; Torralva et al., 2009). This is particularly true for the behavioural subtype of FTD (behavioural variant FTD), in which patients present with changes in personality (Knabb et al., 2006). Neuroimaging and pathological studies have suggested that the grey matter regions most consistently involved in behavioural variant FTD are mesial/orbitofrontal cortex and anterior insula (Rosen et al., 2002; Davies et al., 2006), which are affected from the very early disease stages (Seeley et al., 2008). More recently, it has also become apparent that the underlying white matter tracts connecting these regions are also affected in behavioural variant FTD (Zhang et al., 2009; Whitwell et al., 2010). Behaviourally, patients with behavioural variant FTD present with a range of symptoms, such as reduced motivation and inhibition with severe implications for management and carer burden (Piguet et al., 2011).

Disinhibition is particularly important in terms of the impact on carers but is difficult to quantify (Mendez et al., 1993; Gregory and Hodges, 1996; Piguet et al., 2009) and its neural basis is still debated (Peters et al., 2006; Zamboni et al., 2008). Behavioural symptoms are typically assessed via carer-based questionnaires, such as the Neuropsychiatric Inventory (Cummings et al., 1994) or the Cambridge Behavioural Inventory (Wedderburn et al., 2008). In one of the earliest studies employing the Neuropsychiatric Inventory, Levy et al. (1996) reported a higher incidence of disinhibition in FTD compared with Alzheimer’s disease and that >70% of patients could be correctly classified on the disinhibition, apathy and depression Neuropsychiatric Inventory scores alone. These findings were corroborated by other studies (Kertesz and Munoz, 1998; Bozat et al., 2000), indicating that disinhibition can be an efficient discriminator of patients with Alzheimer’s disease and patients with FTD, whereas other behavioural symptoms can overlap between the conditions.

Several studies have investigated the neural correlates of disinhibition as measured by carer questionnaires. For example, Peters et al. (2006) showed that the disinhibition score of the Neuropsychiatric Inventory covaried with the PET metabolic activity in posterior orbitofrontal cortex in patients with FTD. They concluded that dysfunction in this region most likely contributed to the disinhibited symptoms. This finding was recently replicated (Krueger et al., 2011) in a large sample of neurodegenerative patients (including behavioural variant FTD) using cortical thickness as a measure of orbitofrontal cortex grey matter integrity. In contrast, another study (Zamboni et al., 2008) using scores of the Frontal Systems Behaviour Scale showed no correlation with orbitofrontal cortex atrophy using voxel-based morphometry analysis, instead the right nucleus accumbens and temporal lobe structures were related to disinhibition on this measure. These discrepant findings highlight the inherent problems of employing subjective (e.g. carer) information alone to establish behavioural symptoms in FTD.

More objective measures of disinhibition have been applied to behavioural variant FTD, notably the Stroop, Go/No-go and Stop Signal tasks. Although impaired on the Stroop test, patients with behavioural variant FTD perform at an equivalent level to patients with Alzheimer’s disease (Pachana et al., 1996; Perry and Hodges, 2000; Collette et al., 2007) emphasizing the multidimensional nature of this task. Go/No-go tasks are potentially more specific. Mendez et al. (2005) contrasted sociopathic versus non-sociopath patients with FTD and found a difference in the performance of the Go/No-go and Alternate Tapping subtests of the Frontal Assessment Battery. Using a short version of a Go/No-go paradigm, Torralva et al. (2009) found a significant difference between behavioural variant FTD and Alzheimer’s disease. In contrast, Collette et al. (2007) found no difference in Go/No-go performance between patients with FTD in contrast to controls or patients with Alzheimer’s disease. Inhibitory performance of patients with FTD has also been explored using a Stop-Signal task (Logan et al., 1984), in which participants are trained to respond as quickly as possible in a reaction time task but on a proportion of trials, a ‘stop signal’ is sounded shortly after the presentation of the usual stimulus, which indicates that the subject has to inhibit its response on that particular trial. The presentation lag of the stop signal is varied across trials and longer delays making it harder to inhibit responses than that for shorter delays. Patients with FTD were only marginally impaired on this task (Dimitrov et al., 2003).

It becomes obvious that these tasks designed to assess inhibitory responses do not reliably distinguish between patients with FTD and other dementias or healthy controls, either because of their lack of specificity (Stroop test) or low sensitivity (Go/No-go). In contrast, the Hayling Test of inhibitory function (Burgess and Shallice, 1997) was specifically developed to assess impulsive and stimulus bound behaviour. The task consists of two parts: part A requires participants to complete a last word of a sentence with a correct word (e.g. ‘He sent the letter without a...’; correct answer: ‘ship’), while in part B participants are asked to complete a new set of sentences, this time with a completely unrelated word (e.g. ‘The captain stayed with the sinking...’; wrong answer: ‘stamp’; possible correct answer: ‘cucumber’). The second part of the Hayling Test, therefore, requires participants to inhibit a prepotent response set up in the first part. Lough et al. (2006) found that patients with behavioural variant FTD were severely impaired on the Hayling Test. A retrospective study on a larger behavioural variant FTD sample further found that performance on the Hayling Test together with reverse Digit Span best discriminated real patients with behavioural variant FTD from the so-called behavioural variant FTD phenocopy cases (Hornberger et al., 2008), despite indistinguishable behavioural presentations. A short version of the Hayling Test was incorporated into the The Institute of Cognitive and Behavioural Neurology (INECO) frontal screening test (Torralva et al., 2009), which appears extremely useful in detecting cognitive dysfunction in behavioural variant FTD, with the Hayling component being a subtest that best discriminated behavioural variant FTD from Alzheimer’s disease. A recent study (Hornberger et al., 2010) corroborated these behavioural findings and established that a combination of orbitofrontal
cortex atrophy (as assessed by visual rating) and inhibition error scores could discriminate > 90% of behavioural variant FTD and patients with Alzheimer’s disease.

The neural correlates of performance in the Hayling Test, which appears sensitive and specific to behavioural variant FTD, have not been explored using automated methods of structural brain analysis, such as voxel-based morphometry or diffusion tensor imaging. Such analysis would not only allow the establishment of grey matter regions associated with objective disinhibition measures in behavioural variant FTD, but also which white matter tracts are associated with the inhibition performance. Finally, the link between objective and subjective disinhibition measures still remains to be established.

This prospective study examined the relationship between performance on the Hayling Test and grey and white matter brain atrophy. We investigated: (i) how atrophy in grey matter areas correlates with the Hayling inhibition performance; and (ii) how white matter changes, as indicated via fractional anisotropy on diffusion tensor imaging, related to inhibitory control. We predicted that orbitofrontal grey matter areas and connecting white matter tracts would be directly correlated with the degree of disinhibition in behavioural variant FTD. To establish a link between objective and subjective measures of disinhibition, we explored the neural correlates of carer-based scores of disinhibition using the Neuropsychiatric Inventory. We hypothesized that if objective and subjective measures tap into the same dysfunction, then similar neural correlates should be identified.

## Patients and methods

### Case selection

Patients were selected from the FRONTIER database (www.ftdrg.org) resulting in a sample of 14 patients with behavioural variant FTD, 15 with Alzheimer’s disease and 18 controls. All patients with behavioural variant FTD met current consensus criteria for FTD (Neary et al., 1998; Rascovsky et al., 2007) with insidious onset, decline in social behaviour and personal conduct, emotional blunting and loss of insight. In light of the recent recognition of the phenocopy syndrome (Hornberger et al., 2008, 2009), only patients with behavioural variant FTD with evidence of clear decline as reported by the caregivers and atrophy on MRI scans were included in the study. All patients with Alzheimer’s disease met NINCDS-ADRDA diagnostic criteria (Mckhann et al., 1984) for probable Alzheimer’s disease. Demographic details are presented in Table 1. Age- and education-matched healthy controls were selected from a healthy volunteer panel or were spouses/carers of patients.

### Behavioural testing

The Hayling Test (Burgess and Shallice, 1997) evaluates inhibition of a prepotent response by employing a sentence completion task. In the first section of the test, consisting of 15 sentences, participants are required to complete a sentence with a word that gives a meaningful sense to the sentence. The second section of the test, again consisting of 15 sentences, requires the participant to complete a sentence with a word that is unconnected to the sentence, which requires inhibiting an automatic response. Errors are recorded for words that do not follow these rules. In addition, the time taken to respond is recorded, which together with the error scores results in an overall score. In the current study, we report the scaled score B, total error score and the overall scaled score of the Hayling Test, which have been shown to be most sensitive to discriminate behavioural variant FTD and Alzheimer’s disease (Hornberger et al., 2010).

As independent measure of behavioural disturbance, we used the Neuropsychiatric Inventory (Cummings et al., 1994). The Neuropsychiatric Inventory screens for a range of symptoms including apathy, agitation, anxiety, irritability, dysphoria, aberrant motor behaviour, disinhibition, delusions, hallucinations and euphoria, which are all scored on a frequency scale of 1 (occasionally, less than once a week) to 4 (very frequently, once or more per day or continuously).

## Table 1  Mean (SD) scores for behavioural variant FTD and controls on demographics and general cognitive tests

<table>
<thead>
<tr>
<th>Demographics, cognitive and behavioural tests</th>
<th>Behavioural variant FTD (n = 14)</th>
<th>Alzheimer’s disease (n = 15)</th>
<th>Controls (n = 18)</th>
<th>F-values</th>
<th>Behavioural variant FTD versus control</th>
<th>Alzheimer’s disease versus control</th>
<th>Behavioural variant FTD versus Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>10/4</td>
<td>11/4</td>
<td>9/9</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Handedness (R/L)</td>
<td>13/0</td>
<td>13/1</td>
<td>18/0</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Education</td>
<td>11.8 (3.4)</td>
<td>13.1 (3.6)</td>
<td>13.6 (2.5)</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mean age at scan (years)</td>
<td>59.3 (7.9)</td>
<td>63.8 (7.7)</td>
<td>64.8 (5.3)</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Length of disease (years)</td>
<td>3.7 (2.6)</td>
<td>2.7 (1.7)</td>
<td>–</td>
<td>NS</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ACE (max. score = 100)</td>
<td>75.6 (11.4)</td>
<td>80.1 (11.4)</td>
<td>95.4 (2.9)</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE (max. score = 30)</td>
<td>24.9 (3.8)</td>
<td>26 (2.8)</td>
<td>29.2 (8)</td>
<td>***</td>
<td>**</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hayling</td>
<td>4.14 (2.3)</td>
<td>4.2 (2)</td>
<td>6 (0)</td>
<td>**</td>
<td>*</td>
<td>*</td>
<td>NS</td>
</tr>
<tr>
<td>Total error score</td>
<td>42 (26.9)</td>
<td>11.9 (10.5)</td>
<td>2.3 (4.2)</td>
<td>***</td>
<td>***</td>
<td>NS</td>
<td>***</td>
</tr>
<tr>
<td>Overall scaled score</td>
<td>2.6 (1.9)</td>
<td>3.9 (2)</td>
<td>6.4 (6)</td>
<td>***</td>
<td>***</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory</td>
<td>1.57 (1.6)</td>
<td>.27 (.46)</td>
<td>–</td>
<td>**</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

F-values indicate significant differences across groups; Tukey post hoc tests compare differences between group pairs. *P < 0.05; **P < 0.01; ***P < 0.001.

ACE = Addenbrooke’s Cognitive Examination; MMSE = Mini-Mental State Examination; NS = non-significant.
We employed the subscore of disinhibition of the Neuropsychiatric Inventory as a carer measure of disinhibition. Patients also underwent general cognitive screening using the Addenbrooke’s Cognitive Examination Revised (Mathuranath et al., 2000; Mioshi et al., 2006) and Mini–Mental State Examination to determine their overall cognitive functioning. Only data from the first clinical presentation of the patients were included in all analyses.

**Behavioural analyses**

Data were analysed using SPSS 17.0 (SPSS Inc.). Parametric demographic (age, education), neuropsychological (Hayling and general cognitive tests) and behavioural (Neuropsychiatric Inventory) data were compared across the three groups (behavioural variant FTD, Alzheimer’s disease and controls) via one-way ANOVAs followed by Tukey post hoc tests. A priori, variables were plotted and checked for normality by distribution by Kolmogorov–Smirnov tests. Variables revealing non-normal distributions were log transformed and the appropriate log values were used in the analyses. Variables showing non-parametric distribution after log transformation were analysed via chi-square, Kruskal–Wallis and Mann–Whitney U tests.

**Imaging acquisition**

All patient and controls underwent the same imaging protocol with whole-brain T₁- and diffusion tensor imaging-weighted images using a 3T Philips MRI scanner with standard quadrature head coil (eight channels). The 3D T₁-weighted sequences were acquired as follows: coronal orientation, matrix 256 × 256, 200 slices, 1 × 1 × 1 mm³ in-plane resolution, slice thickness 1 mm, echo time/repetition time = 2.6/5.8 ms. The diffusion tensor imaging-weighted sequences were acquired as follows: 32 gradient direction diffusion tensor imaging sequence (repetition time/echo time/inversion time: 8400/68/90 ms; b-value = 1000 s/mm²; 55 × 2.5 mm horizontal slices; end resolution: 2.5 × 2.5 × 2.5 mm³; field of view 240 × 240 mm, 96 × 96 matrix; repeated twice). Two diffusion tensor imaging sequences were acquired for each participant, which were in a first step averaged. All scans were then visually checked for field inhomogeneity distortions and corrected for eddy current distortions. The diffusion tensor models were then fitted at each voxel via the FMRIB’s Diffusion toolbox in the FMRIB software library (http://www.fmrib.ox.ac.uk/fsl/fdt/index.html), resulting in maps of three eigenvalues (λ1, λ2, λ3) that allowed calculation of fractional anisotropy maps for each subject.

**Voxel-based morphometry analysis**

Three-dimensional T₁-weighted sequences were analysed with FSL-VBM, a voxel-based morphometry analysis (Ashburner and Friston, 2000; Good et al., 2001), which is part of the FMRIB software library package (http://www.fmrib.ox.ac.uk/fsl/tsvbm/index.html) (Smith et al., 2004). First, tissue segmentation was carried out using FMRIB’s Automatic Segmentation Tool (FAST) (Zhang et al., 2001) from brain extracted images. The resulting grey matter partial volume maps were then aligned to the Montreal Neurological Institute standard space (MN152) using the non-linear registration approach FNIRT (Andersson et al., 2007a, b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The registered partial volume maps were then modulated (to correct for local expansion or contraction) by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (full width half maximum = 8 mm). Finally, a voxel-wise general linear model was applied and permutation-based non-parametric testing was used to form clusters with the threshold-free cluster enhancement method (Smith and Nichols, 2009), tested for significance at P < 0.05, corrected for multiple comparisons by family-wise error correction space.

**Diffusion tensor imaging analysis**

Tract-based Spatial Statistics (Smith et al., 2006) from the FMRIB software library were used to perform a skeleton-based analysis of white matter fractional anisotropy. Fractional anisotropy maps of each individual subject were eddy current corrected and co-registered using non-linear registration FNIRT (Andersson et al., 2007a, b) to the MNI standard space using the FMRIB58 fractional anisotropy template, which is available as part of the FMRIB library software. The template was subsampled at 2 × 2 × 2 mm³ due to the coarse resolution of native diffusion tensor imaging data (i.e. 2.5 × 2.5 × 2.5 mm³). After image registration, fractional anisotropy maps were averaged to produce a group mean fractional anisotropy image. A skeletonization algorithm (Smith et al., 2006) was applied to the group mean fractional anisotropy image to define a group template of the lines of maximum fractional anisotropy, assumed to correspond to centres of white matter tracts. Fractional anisotropy values for each individual subject were then projected onto this group template skeleton. Clusters were tested using permutation-based non-parametric testing as described for the voxel-based morphometry analysis. Clusters reported have significance at P < 0.05, corrected for multiple comparisons across by family-wise error correction space, unless otherwise stated.

**Results**

**Demographics and general cognitive functioning**

Demographics and general cognitive scores are shown in Table 1. Participant groups did not differ in terms of age, education, handedness or sex (all P > 0.1). More importantly, behavioural variant FTD and patients with Alzheimer’s disease did not differ in disease duration (P > 0.1).

**Hayling Test**

The behavioural variant FTD group were impaired on all scores derived from part B of the Hayling Test: scaled score B (P < 0.05); total error score (P < 0.001); overall scaled score (P < 0.001). Patients with Alzheimer’s disease were also significantly impaired on scaled score B and overall score of the Hayling Test in comparison to controls but not on the total error score (P > 0.1). Crucially, however, patients with behavioural variant FTD and Alzheimer’s disease differed on the total error score (P < 0.001) (Fig. 1). A logistic regression using the Enter method and employing only behavioural variant FTD and Alzheimer’s disease, revealed that 75% of the participating patients could be correctly classified into behavioural variant FTD and Alzheimer’s disease on this score alone.
Neuropsychiatric Inventory disinhibition subscore

The average disinhibition frequency score ascribed by carers of patients with behavioural variant FTD (Table 1) was significantly higher than that for patients with Alzheimer's disease ($P < 0.01$).

Voxel-based morphometry group analysis

In a first step of the voxel-based morphometry analysis, we contrasted our participant groups to reveal the pattern of overall brain atrophy. Patients with behavioural variant FTD showed grey matter atrophy in anterior cingulate, orbitofrontal, anterior insula and anterior temporal lobe regions in comparison to controls (Supplementary Table 1 and Fig. 1). The patients with Alzheimer's disease showed a more widespread atrophy pattern (Supplementary Table 1 and Fig. 2), including the hippocampus and posterior cingulate/precuneus brain regions. Comparison of patient groups showed significantly greater atrophy of the orbitofrontal cortex regions in behavioural variant FTD versus Alzheimer's disease (Table 2). The reverse contrast revealed no significant differences after correction for multiple comparisons; however, at $P < 0.001$ uncorrected, the Alzheimer's disease group showed significantly greater atrophy of medial parietal (i.e. precuneus) and lateral occipital cortices (Table 2).

Voxel-based morphometry—correlations with disinhibition

In a second step, we entered the Total Error score of the Hayling Test as a covariate in the design matrix of the voxel-based morphometry analysis. This analysis was conducted on the patients with behavioural variant FTD and with Alzheimer's disease only. As can be seen in Fig. 2 and Table 3, atrophy in three brain regions (ventromedial orbitofrontal/subgenual anterior cingulate, anterior cingulate and temporal pole) was correlated with the Hayling Total Error score at $P < 0.001$ uncorrected. An additional analysis investigated whether the temporal pole findings were due to the semantic nature of the task. We entered, therefore, the patients’ performance in a semantic (naming) task as a covariate in the analysis, which did not change the earlier results.

Similarly, we entered the disinhibition score of the Neuropsychiatric Inventory as a covariate in the voxel-based morphometry analysis, which showed a positive correlation with atrophy in the ventromedial orbitofrontal/subgenual cingulate and temporal pole brain regions (Table 3). Importantly, the atrophy related to both measures partially overlapped for the ventromedial orbitofrontal cortex (Fig. 3).

Diffusion tensor imaging

Analysis of whole brain fractional anisotropy measures across groups replicated the voxel-based morphometry findings. Patients with behavioural variant FTD showed a decrease in fractional anisotropy for mostly frontal and anterior temporal brain regions, while patients with Alzheimer’s disease showed diffuse fractional anisotropy white matter changes for the white matter of the precuneus brain region (Supplementary Table 2).

We investigated fractional anisotropy values of white matter tracts connecting the grey matter regions found to correlate with performance on the Hayling Test. Masks for the following white matter tracts taken from the Johns Hopkins probabilistic white matter tract atlas (Mori et al., 2005) were created: uncinate fasciculus (connecting orbitofrontal and anterior temporal brain regions); cingulum fasciculus (corpus callosum part); and forceps minor fasciculus (connecting medial and lateral prefrontal regions).
Table 2  Voxel-based morphometry results showing regions of significant grey matter intensity decrease for the contrasts of behavioural variant FTD and Alzheimer’s disease patient groups

<table>
<thead>
<tr>
<th>Regions</th>
<th>Hemisphere</th>
<th>MNI coordinates</th>
<th>Number of voxels</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioural variant FTD versus Alzheimer’s disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>Bilateral</td>
<td>−12 16 −22</td>
<td>1204</td>
<td>2.5</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>Left</td>
<td>−46 24 −32</td>
<td>23</td>
<td>1.67</td>
</tr>
<tr>
<td>Alzheimer’s disease versus behavioural variant FTD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precuneus</td>
<td>Bilateral</td>
<td>−2 −90 8</td>
<td>2250</td>
<td>3.03</td>
</tr>
<tr>
<td>Supramarginal gyrus</td>
<td>Left</td>
<td>−48 −42 58</td>
<td>276</td>
<td>3.03</td>
</tr>
<tr>
<td>Lateral occipital cortex</td>
<td>Left</td>
<td>−46 −78 20</td>
<td>219</td>
<td>2.77</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>Left</td>
<td>−28 −6 62</td>
<td>124</td>
<td>2.77</td>
</tr>
</tbody>
</table>

Behavioural variant FTD versus Alzheimer’s disease contrast corrected for multiple comparisons (family-wise error) at P < 0.05; Alzheimer’s disease versus behavioural variant FTD contrast uncorrected at P < 0.001 with at least 100 contiguous voxels.

Table 3  Voxel-based morphometry results showing regions of significant grey matter intensity decrease that covary with disinhibition performance

<table>
<thead>
<tr>
<th>Regions</th>
<th>Hemisphere</th>
<th>MNI coordinates</th>
<th>Number of voxels</th>
<th>T-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayling Test—total error score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal pole</td>
<td>Left</td>
<td>−40 6 −46</td>
<td>1668</td>
<td>3.03</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>Right</td>
<td>32 22 −44</td>
<td>1582</td>
<td>3.03</td>
</tr>
<tr>
<td>Medial prefrontal cortex</td>
<td>Bilateral</td>
<td>2 58 0</td>
<td>371</td>
<td>3.03</td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>Bilateral</td>
<td>−2 24 −18</td>
<td>365</td>
<td>3.03</td>
</tr>
<tr>
<td>Neuropsychiatric Inventory—disinhibition frequency score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal pole</td>
<td>Left</td>
<td>−20 2 −48</td>
<td>228</td>
<td>2.47</td>
</tr>
<tr>
<td>Orbitofrontal cortex</td>
<td>Bilateral</td>
<td>−2 18 −26</td>
<td>74</td>
<td>2.47</td>
</tr>
</tbody>
</table>

All results uncorrected at P < 0.001; only clusters with at least 70 contiguous voxels included.

Figure 3  Overlap of Hayling Test total error score and Neuropsychiatric Inventory (NPI) disinhibition frequency grey matter atrophy in patients with behavioural variant FTD and Alzheimer’s disease. Clusters are overlaid on the MNI standard brain (t > 2.41). Coloured voxels show regions that were significant in the analyses for P < 0.001 uncorrected and a cluster threshold of 70 contiguous voxels.
via the genu of the corpus callosum. Non-parametric permutation tests were run on the fractional anisotropy maps masked for the selected tracts. Fractional anisotropy values were extracted from the tracts at $P < 0.001$, uncorrected and exported into SPSS. Fractional anisotropy and Hayling Total Errors were entered into a linear regression for each tract, separately. Note, only fractional anisotropy values and Hayling Total Errors of the two patient groups (behavioural variant FTD, Alzheimer’s disease) were entered into the linear regression. As can be seen in Fig. 4, the degree of fractional anisotropy decrease was negatively correlated with the inhibition performance on the Hayling task. In particular, fractional anisotropy values of the uncinate fasciculus were highly correlated with Hayling Error scores ($P < 0.001$), as well as fractional anisotropy values for the forceps minor ($P < 0.001$) and cingulum ($P < 0.001$) fasciculi. Similarly, the Neuropsychiatric Inventory disinhibition frequency score showed a statistical trend ($P = 0.07$) for a negative correlation with the fractional anisotropy values of the uncinate fasciculus.

**Discussion**

The principal finding of our study was that ventromedial orbitofrontal, medial frontal and anterior temporal lobe grey matter atrophy is directly related to the degree of disinhibition shown by patients with behavioural variant FTD. In addition, the integrity of white matter tracts connecting these regions appears critical. Atrophy of the ventromedial orbitofrontal/subgenual brain region was related both as an objective measure of inhibitory functioning and a carer-based assessment of disinhibition. These findings have clinical and theoretical implications.

The behavioural data replicated our previous findings (Hornberger et al., 2008, 2010). Patients with behaviour variant FTD showed substantial deficits on the Hayling Test of inhibitory control and were distinguishable from patients with Alzheimer’s disease by the total errors score. Using logistic regression, the total error score could discriminate $\sim 75\%$ of patients on their first assessment. Not surprisingly, carers of patients with behaviour variant FTD reported a significantly greater frequency of disinhibition than caregivers of patients with Alzheimer’s disease on the Neuropsychiatric Inventory. These findings confirm previous reports of a higher incidence of disinhibited behaviour in behaviour variant FTD in comparison to Alzheimer’s disease (Levy et al., 1996; Bozeat et al., 2000). Similar to our previous findings (Hornberger et al., 2010), the Hayling total error score emerged as a sensitive measure to distinguish both groups, with patients with behaviour variant FTD showing on average nearly four times more inhibitory errors on the sentence completion task. The Hayling Test is a simple but
sensitive measure that detects disinhibition in FTD. Other objective disinhibition measures, such as Go/No-go and Stroop tasks have not shown the same level of discrimination of FTD and patients with Alzheimer’s disease (Perry and Hodges, 2000; Collette et al., 2007). Nevertheless, development of a test of disinhibition, equivalent in some way to the Hayling, but based upon non-verbal stimuli, might be even better as it would allow the inclusion of aphasic patients with FTD.

Both patients with behavioural variant FTD and Alzheimer’s disease showed the classic pattern of grey matter brain atrophy commonly reported (Seeley, 2008; Whitwell et al., 2009); in behavioural variant FTD, medial frontal/ anterior cingulate, orbitofrontal, anterior insula and temporal lobe atrophy was present. In contrast, patients with Alzheimer’s disease showed atrophy of medial temporal, including parahippocampal and hippocampal areas, as well as involvement of posterior cingulate/precuneus brain regions. A direct comparison revealed that patients with behavioural variant FTD could be discriminated from patients with Alzheimer’s disease on orbitofrontal atrophy, whereas regional atrophy of the precuneus was indicative of an Alzheimer’s disease presentation. Our findings corroborate previous results, highlighting the differential atrophy in typical Alzheimer’s disease and behavioural variant FTD, with Alzheimer’s disease showing more parietal (Rusinek et al., 1991; Jones et al., 2006) and FTD more frontal atrophy (Rosen et al., 2002; Seeley, 2008), while both patient groups can show temporal atrophy (Whitwell and Jack, 2005; Whitwell et al., 2009). It is clear that ventromedial frontal and medial parietal regions are key for differential diagnosis of these dementias (Womack et al., 2011).

More importantly, the differential atrophy mapped onto the clinical symptoms. The degree of ventromedial orbitofrontal/subgenual cingulate atrophy covaried with the level of disinhibition. In particular, the Hayling Error scores correlated with the ventromedial orbitofrontal cortex/subgenual brain regions as well as anterior temporal and medial frontal grey matter atrophy. Crucially, the disinhibition scores on the Neuropsychiatric Inventory also correlated with the ventromedial orbitofrontal cortex region. Thus, we have convergent evidence from both an objective measure (i.e. the Hayling Test) and a carer-based assessment (i.e. Neuropsychiatric Inventory) that this region is critical for the genesis of disinhibited behaviour.

Interestingly, as mentioned above, atrophy in two other brain regions covaried with the disinhibition error score of the Hayling Test, the anterior temporal pole and the medial frontal/ anterior cingulate cortex. Importantly, the medial frontal/ anterior cingulate region was not evident in the analysis with the carer disinhibition information. The correlation with the grey matter atrophy of the anterior temporal pole may reflect the verbal nature of the Hayling task. The anterior temporal pole has been shown to be critically involved in semantic processing (e.g. Patterson et al., 2007; Lambon Ralph et al., 2010). It should not be surprising that patients with atrophy in this region would perform poorly on the Hayling task, which requires patients to understand the sentence fragments for successful completion. Nevertheless, inclusion of a semantic naming covariate in the Hayling Test analysis did not change the initial results. Further, the carer evaluation of disinhibited behaviour also showed a correlation with the left temporal pole, though not overlapping and more medial to the Hayling atrophy correlates. It is currently not clear why the carer-based assessment should be related to temporal pole degeneration. One possibility, which should be explored in the future, is that atrophy in this region might reflect more verbal disinhibition (e.g. inappropriate comments) instead of a purely behavioural disinhibition (e.g. perseverative behaviour). It is also possible that temporal pole pathology has a role in the genesis of behavioural disinhibition as overlapping symptoms are reported by caregivers of patients with behavioural variant FTD and semantic dementia (Bozeat et al., 2000) that are typically attributed to accompanying frontal pathology. This notion is further supported by findings in monkeys with temporal pole lesions and patients with Klüver–Bucy syndrome, which involves mainly the temporal pole, who show grossly abnormal social behaviours (for review see Olson et al., 2007). Further, Zahn et al. (2009) have shown that combined temporal pole and orbitofrontal cortex atrophy is associated with disinhibited social behaviour, as indicated on the Neuropsychiatric Inventory, which corroborates with our findings. The interaction of the orbitofrontal cortex with temporal regions via the uncinate fasciculus might be crucial in maintaining normal behaviour and in particular inhibitory performance (see also Green et al., 2010 for related findings).

The atrophy in the medial frontal/ anterior cingulate region is more difficult to explain. This frontal region is important for Theory of Mind processing (Eslinger, 1998; Gregory et al., 2002) and perspective taking (Kripps et al., 2009; Shamay-Tsoory et al., 2009). Other studies report the importance of this region in cognitive control (Kerns et al., 2004). It is not clear which of those functions might have affected the performance on the Hayling Test, but cognitive control appears the most plausible candidate, as previous studies have found that this region is implicated in error detection and correction on Go/No-go tasks (Hester et al., 2009). Future investigations are needed to identify the overlap of inhibition and cognitive control processes to address this finding. Importantly, findings from the diffusion tensor imaging analysis revealed that integrity of the white matter tracts connecting orbitofrontal cortex with temporal pole and medial frontal brain regions also correlated with the Hayling performance, suggesting that a network of regions is involved in the performance of this task.

On a theoretical level, our findings further establish the ventromedial orbitofrontal cortex region as crucial in maintaining normal behaviour and adapting responses to changed contingencies in the environment. Classically, orbitofrontal cortex damage has been attributed with drastic changes in behaviour, as most famously described in the case of Phineas Gage (Harlow, 1868). Gage showed disinhibition as indicated by inflexible and perseverative behaviour as well as risky decision making after a tamping iron traversed his orbitofrontal cortex. Such behavioural changes have also been observed in monkeys with ventromedial orbitofrontal cortex lesions (Mishkin, 1964; Izquierdo et al., 2004; Kringelbach and Rolls, 2004), who fail or are slow to adapt their responses when the cue–outcome associations in tasks are changed. Thus, the intactness of the ventromedial orbitofrontal cortex appears crucial for flexible behaviour and adapting the response to a changed environment. Rahman et al. (1999) showed that...
patients with FTD are impaired on the reversal stages of a visual discrimination task, i.e. they fail to adapt their behaviour when the contingencies changed, while they perform normally when the contingencies are maintained. Rahman et al. (1999) concluded that the known ventromedial damage in FTD likely contributed to these deficits, although volumetric neuroimaging data were not available in the eight patients tested. They further concluded that the results are consistent with current theories that damage to this cortical region results in the inability to reform stimulus-reinforcement associations when contingencies change. Our findings are concordant. The Hayling Test requires that participants change their response contingencies from part A to part B of the test. The results further suggest that disinhibited behaviour in behavioural variant FTD may be based on a failure to adapt behaviour flexibly, although there may be a number of different and interrelated processes that contribute to this disinhibited behaviour (Murray et al., 2007). Along with the ventromedial orbitofrontal cortex, other prefrontal brain regions also have been implicated in inhibitory functioning, in particular the lateral orbitofrontal cortex/right inferior frontal cortex (for a review see Aron, 2007). The inferior frontal cortex is consistently activated in functional neuroimaging studies of inhibitor functioning in healthy young participants (Garavan et al., 1999; Konishi et al., 1999; Rubia et al., 2003) and also affects stop-signal performance in stroke patients with right inferior frontal cortex lesions (Aron et al., 2003). The same region, however, is conspicuously absent in any atrophy disinhibition correlations in neurodegenerative diseases. One potential reason might be that most functional neuroimaging tasks employ stop-signal tasks, while patient studies often use Go/No-go type task, like the Hayling Test. Recent evidence suggests that stop-signal task performance, which relies on response completion inhibition, can be dissociated from Go/No-go task performance, which is dependent on response selection inhibition (Eagle et al., 2008). These two related but separable processes might, therefore, rely on different neural substrates (e.g. inferior frontal cortex versus orbitofrontal cortex). Another potential reason for an absence of inferior frontal cortex atrophy being correlated with disinhibition performance could be that the inferior frontal cortex is not as affected in behavioural variant FTD as the ventromedial orbitofrontal cortex and thus there might still be a relation but below the statistical threshold.

On a clinical level, it becomes obvious that the ventromedial orbitofrontal cortex region is crucial for the maintenance of intact behaviour. As previous studies have shown (Peters et al., 2006; Hornberger et al., 2010), atrophy in this region is related to behavioural deficits in FTD. A prior study established that a simple visual magnetic resonance rating of the orbitofrontal cortex, in conjunction with the Hayling Test, could discriminate behavioural variant FTD and patients with Alzheimer’s disease in > 90% of instances (Hornberger et al., 2010). In the present study, ~75% of patients with behavioural variant FTD and with Alzheimer’s disease could be distinguished on the basis of their behavioural scores alone. This becomes particularly relevant in the light of recent findings of impaired episodic memory in patients with behavioural variant FTD that can be of a similar magnitude to that seen in patients with Alzheimer’s disease (Hornberger et al., 2010; Pennington et al., 2011). The differentiation is further complicated by the fact that patients with Alzheimer’s disease can present with prominent dysexecutive symptoms (Gleichgerrcht et al., 2010; Dickerson and Wolk, 2011). Measures of disinhibition emerge as a powerful diagnostic tool, that target the function of a brain region specifically impaired in behavioural variant FTD. The caregivers of patients with behavioural variant FTD report high level of stress and burden in excess of that reported for patients with Alzheimer’s disease (Mioshi et al., 2009). Attempts to understand the cognitive and neural basis of disinhibition, one of the leading symptoms in behavioural variant FTD, is clearly of considerable practical importance.

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**Supplementary material**

Supplementary material is available at Brain online.

**References**


