

# Neuroanatomical profiles of personality change in frontotemporal lobar degeneration

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## Background

The neurobiological basis of personality is poorly understood. Frontotemporal lobar degeneration (FTLD) frequently presents with complex behavioural changes, and therefore potentially provides a disease model in which to investigate brain substrates of personality.

## Aims

To assess neuroanatomical correlates of personality change in a cohort of individuals with FTLD using voxel-based morphometry (VBM).

## Method

Thirty consecutive individuals fulfilling consensus criteria for FTLD were assessed. Each participant's carer completed a Big Five Inventory (BFI) questionnaire on five key personality traits; for each trait, a change score was derived based on current compared with estimated premorbid characteristics. All participants underwent volumetric brain magnetic resonance imaging. A VBM analysis was implemented regressing change score for each trait against regional grey matter volume across the FTLD group.

## Results

The FTLD group showed a significant decline in extraversion, agreeableness, conscientiousness and openness and an increase in neuroticism. Change in particular personality traits was associated with overlapping profiles of grey matter loss in more anterior cortical areas and relative preservation of grey matter in more posterior areas; the most robust neuroanatomical correlate was identified for reduced conscientiousness in the region of the posterior superior temporal gyrus.

## Conclusions

Quantitative measures of personality change in FTLD can be correlated with changes in regional grey matter. The neuroanatomical profiles for particular personality traits overlap brain circuits previously implicated in aspects of social cognition and suggest that dysfunction at the level of distributed cortical networks underpins personality change in FTLD.

## Declaration of interest

None.

Personality, defined broadly as a dynamic and organised set of characteristics that uniquely influences an individual's cognition, motivation and behaviour,<sup>1</sup> is a complex and challenging concept. Even the definition and quantification of personality traits is problematic. The 'five factor' model of personality has met with wide acceptance due to its robustness across ages, genders and cultures.<sup>2,3</sup> According to this model, personality results from the stable balance of five key traits, extraversion, agreeableness, conscientiousness, neuroticism and openness to new experiences, often called the 'big five'.<sup>4</sup> However, although this model suggests a framework for the study of personality, the neurobiological basis of personality remains poorly understood. Personality traits are likely to be mediated by distributed brain networks<sup>5,6</sup> and commonly implicated areas include prefrontal, anterior cingulate and orbitofrontal cortices.<sup>7,8</sup> These areas are likely to play a key role in the cognition of interpersonal and other social behaviours.<sup>9</sup>

Frontotemporal lobar degeneration (FTLD) is an important cause of young-onset dementia that frequently manifests with progressive behavioural abnormalities and social dysfunction, as recognised in consensus diagnostic criteria. As acknowledged in current definitions,<sup>10</sup> behavioural characteristics and their modulation in social contexts powerfully influence the maintenance of personality, implying that significant or persistent behavioural abnormalities may alter personality structure. Although much work in FTLD has focused on particular aspects of disturbed behaviour, there is evidence that more pervasive changes in personality are indeed a hallmark of diseases in the FTLD spectrum.<sup>11,12</sup> From a neurobiological perspective, FTLD therefore presents an opportunity to assess the critical brain substrates that maintain a stable personality structure. Studies in healthy individuals have revealed neuroanatomical substrates overlapping with brain regions that are selectively damaged in

FTLD.<sup>6,13–15</sup> Whereas behavioural change has been linked with structural brain damage in Alzheimer's disease and FTLD,<sup>16,17</sup> particularly the subgroup with right temporal lobe atrophy,<sup>18,19</sup> studies assessing personality change per se are fewer. Agreeableness in FTLD has been correlated with changes in the volume of orbitofrontal cortex,<sup>20</sup> whereas traits clustered according to properties such as affiliation and agency have been shown to correlate with patterns of distributed atrophy across a range of neurodegenerative diseases.<sup>12</sup> However, little information is available concerning the cerebral correlates of longitudinal change in particular personality traits in neurodegenerative disease. From a clinical perspective, it has been shown that profiles of personality change can distinguish neurodegenerative diseases; analysis of personality change might potentially provide tools for early diagnosis of particular neurodegenerative diseases, and FTLD in particular.<sup>21</sup>

Here we investigated cerebral correlates of longitudinal change in key personality traits in FTLD (as measured on a validated caregiver questionnaire) using voxel-based morphometry (VBM). We hypothesised that change in particular personality traits in FTLD would correlate with distinct profiles of brain atrophy and these profiles would overlap frontotemporal networks previously implicated in social cognition.

## Method

### Participants

Thirty individuals (mean age 64.6 years (s.d. = 8.5); 21 males) attending the tertiary cognitive disorders clinic at the National Hospital for Neurology and Neurosurgery with clinical diagnoses representing each of the major canonical syndromic subgroups

of FTLD (10 with behavioural variant frontotemporal dementia, 10 with semantic dementia and 10 with progressive non-fluent aphasia) according to current consensus criteria<sup>10,22</sup> participated in the study. The diagnosis in each individual was supported by detailed neuropsychological assessment. Depression and anxiety symptoms exhibited by the participant cohort were indexed using the Neuropsychiatric Inventory (NPI).<sup>23</sup> Executive function was assessed using Part B of the Trail Making Test<sup>24</sup> and the task-switching component of the Trail Making subsection of the Delis–Kaplan Executive Functions System.<sup>25</sup> Clinical and demographic details of all participants are summarised in Table 1. The mean age of the progressive non-fluent aphasia subgroup was significantly older ( $P < 0.05$ ) than the behavioural variant frontotemporal dementia subgroup; syndromic subgroups did not differ in gender distribution, mean Mini-Mental State Examination (MMSE)<sup>26</sup> score or disease duration. The mean NPI depression score was 1.6 (s.d. = 2.5) and mean anxiety score was 1.5 (s.d. = 2.4) (maximum score 12) for the combined FTLD cohort; in a subgroup analysis the mean anxiety score in the behavioural variant frontotemporal dementia subgroup (mean 3.6 (s.d. = 3.2)) was significantly higher ( $P = 0.01$ ) than for other subgroups. Two-thirds of participants ( $n = 20$ ) scored below the tenth centile on tests of executive function.

The study was conducted in accord with the Declaration of Helsinki and ethics approval was obtained from the Joint Research Ethics Committees of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

### Assessment of personality change

The Big Five Inventory (BFI), a 44-point personality assessment tool, was completed by a caregiver respondent for each participant.<sup>27</sup> Caregivers have been shown to be a reliable source of longitudinal personality questionnaire information in dementia.<sup>28,29</sup> For the purposes of this study, the caregiver respondent was a first-degree relative with excellent personal knowledge of the participant over at least a 10-year period. The respondent was asked to rate each personality trait based on their

knowledge of the participant currently and 10 years previously (i.e. before the clinical onset of disease: see disease duration data in Table 1). The BFI is structured to allow independent analysis of the traits of agreeableness, conscientiousness, extraversion, neuroticism and openness to new ideas. Patient data were validated in comparison with non-self-respondent data for a group of 10 neurologically healthy individuals age matched to the FTLD group. Examples of questions for each trait from the BFI are provided in the Appendix. All answers were scored on a linear scale, from 'disagree strongly' to 'agree strongly'. A previously developed scoring syntax<sup>27</sup> was used to derive a numerical score for each trait, and a change score (the difference between current and premorbid scores for that trait) was computed for each participant. Changes in personality scores were assessed statistically for the entire FTLD group and for each syndromic subgroup using analysis of variance methods implemented in STATA version 8.0 for Windows XP.

### MRI acquisition

Each participant had brain magnetic resonance imaging (MRI) on a 1.5 Tesla GE Signa scanner (General Electric, Milwaukee, Wisconsin, USA) using a standard quadrature head coil. The  $T_1$ -weighted volumetric images were obtained with a 24 cm field of view and  $256 \times 256$  matrix to provide 124 contiguous 1.5 mm thick slices in the coronal plane (echo time (TE) = 5 ms, repetition time (TR) = 512 ms, inversion time (TI) = 5650 ms).

### Image analysis

Voxel-based morphometry of brain images was performed using the DARTEL toolbox of SPM5 ([www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) running under Matlab 7.0 (Mathworks, Sherborn, Massachusetts, USA). An optimised VBM protocol was used.<sup>30</sup> Normalisation, segmentation, modulation and smoothing of grey and white matter images were performed using default parameter settings. In order to adjust for individual differences in global grey matter volume, total intracranial volume was calculated for each

**Table 1** Characteristics of participants with frontotemporal lobar degeneration (FTLD) and controls

	Behavioural variant frontotemporal dementia subgroup ( $n = 10$ )	Semantic dementia subgroup ( $n = 10$ )	Progressive non-fluent aphasia subgroup ( $n = 10$ )	FTLD group ( $n = 30$ )	Control group ( $n = 10$ )
Age, years: mean (s.d.)	60.4 (7.7)	63.8 (9.5)	69.5 (6.3)	64.6 (8.5)	65.2 (6.3)
Gender, male:female	8:2	4:6	9:1	21:9	3:7
Total intracranial volume, mm <sup>3</sup> : mean (s.d.)	1763 (169)	1725 (226)	1763 (128)	1750 (174)	1622 (144)
Mini-Mental State Examination score (maximum score 30), mean (s.d.)	26 (4.0)	22.7 (4.1)	23.8 (4.4)	24.2 (4.3)	29.9 (0.3)
Disease duration, years: mean (s.d.)	5.7 (1.9)	5.4 (1.7)	5.7 (1.7)	5.6 (1.7)	–
Neuropsychiatric Inventory, depression: mean (s.d.)					
Patient score (maximum score 12)	1.3 (2.0)	2.4 (3.5)	1.0 (1.5)	1.6 (2.5)	–
Caregiver distress (maximum score 5)	1.3 (1.9)	1.9 (1.6)	1.3 (1.9)	1.5 (1.8)	–
Neuropsychiatric Inventory, anxiety: mean (s.d.)					
Patient score (maximum score 12)	3.6 (3.2)*	0.7 (0.7)	0.3 (0.7)	1.5 (2.4)	–
Caregiver distress (maximum score 5)	2.3 (2.0)	0.9 (1.2)	0.8 (1.7)	1.3 (1.8)	–
Executive function <sup>a</sup>					
< 1st centile	7	3	3	13	0
< 10th centile	1	2	4	7	1
10–25th centile	1	2	1	4	0
> 25th centile	1	3	2	6	9

a. Tests of executive function comprised part B of the Trail Making Test part B or the Task-switching component of Trail making subsection of the Delis–Kaplan Executive Function System.  
\* $P = 0.01$  behavioural variant frontotemporal dementia subgroup v. other subgroups.

participant (Table 1) by summing grey matter, white matter and cerebrospinal fluid volumes following segmentation of all three tissue classes. Linear regression models were used to examine regional grey matter volumes correlated with the BFI change score for each trait ( $\beta_1 = BFI_{now} - BFI_{10years}$ ). Voxel intensity (grey matter volume),  $V$ , was modelled as a function of the BFI change score across the group, including participants age, gender and total intracranial volume (TIV) as nuisance covariates:

$$V = \beta_1 FTL D + \beta_2 age + \beta_3 gender + \beta_4 TIV + \mu + \varepsilon$$

(where  $\mu$  is a constant and  $\varepsilon$  is error). Personality traits were analysed both in a common design matrix including all five trait scores (in order to assess brain correlates of each trait independently of other traits) and also in separate design matrices for each individual trait (a trait-specific design). Separate design matrices were constructed for the combined FTL D group and for each syndromic subgroup. To protect against voxel drop-out because of marked regional atrophy in particular participants, we implemented a customised explicit brain mask using a specified ‘consensus’ voxel threshold intensity criterion:<sup>31</sup> using this consensus mask, a voxel was included in the analysis if grey matter intensity at that voxel was  $>0.1$  in  $>70\%$  of the participants (rather than in all participants, as with the default statistical parametric map mask).

Statistical parametric maps of regional grey matter volume correlating with score on each trait were examined at a threshold of  $P < 0.001$  uncorrected and at a threshold of  $P < 0.05$  after voxel-wise false discovery rate correction over the whole brain. A cluster extent threshold of 50 voxels was applied when reporting significant brain regions. Maps were displayed as overlays on a study-specific template, created by warping all native space

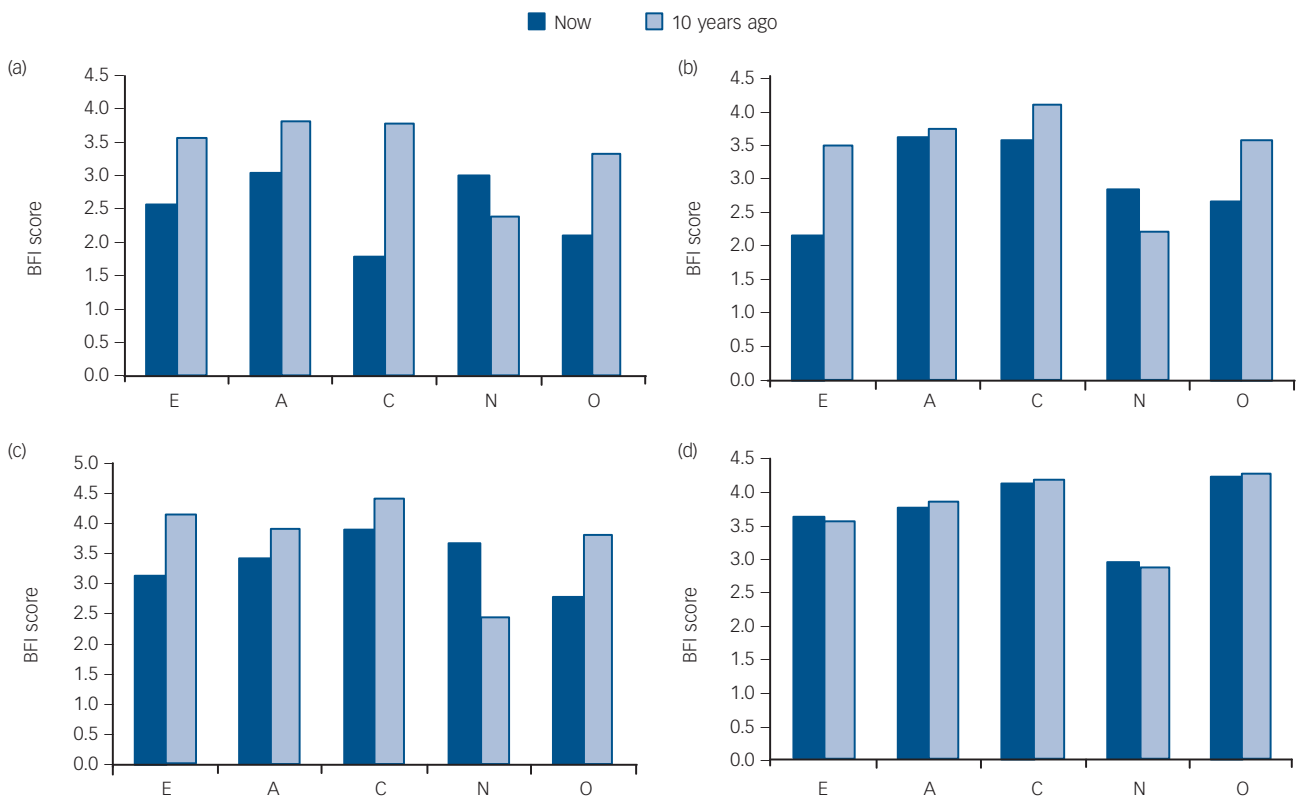
whole-brain images to the final DARTEL template and calculating the average of the warped brain images. In order to assess any grey matter correlates of personality change in relation to the overall distribution of disease-related brain damage, we derived a map of FTL D-related brain atrophy in a separate VBM subanalysis comparing magnetic resonance images from the FTL D group with images (obtained using the same scanner and acquisition parameters) from a group of 20 healthy age- and gender-matched controls (mean age 65.2 years (s.d.=7.3); 8 females; total intracranial volume 1620 ml (s.d. = 152)).

## Results

### Personality data

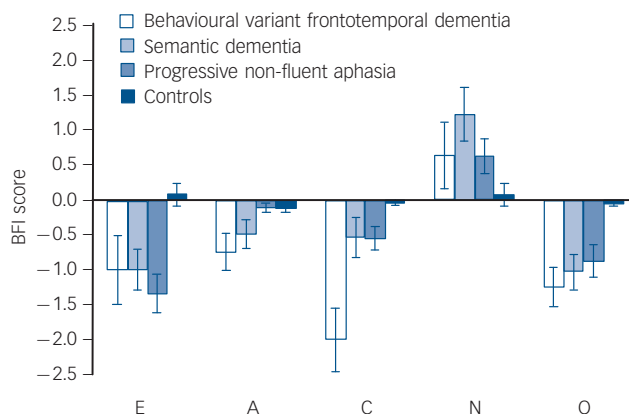
The participants with FTL D when considered as a single group showed significant change in each personality trait when current were compared with estimated premorbid characteristics. There was a decrease in mean scores for agreeableness ( $-0.45$  (s.d.=0.66)), conscientiousness ( $-1.03$  (s.d.=1.21)), extraversion ( $-1.11$  (s.d.=1.14)) and openness to new ideas ( $-1.05$  (s.d.=0.8)), and a mean increase in neuroticism score ( $+0.83$  (s.d.=1.2)) (all  $P < 0.001$ ). The healthy control group showed no significant changes between current trait score and score 10 years previously.

The FTL D subgroups showed broadly similar patterns of personality change. Raw BFI data for FTL D subgroups and controls are presented in Fig.1, and change scores are shown in Fig. 2. The behavioural variant frontotemporal dementia subgroup showed a statistically significant ( $P < 0.05$ ) decrease in mean scores for agreeableness (0.74 (s.d.=0.84)), conscientiousness (2.0 (s.d.=1.44)) and openness (1.24 (s.d.=0.87)) and a non-significant trend towards decreased extraversion (1.0



**Fig. 1** Personality trait scores in participants with frontotemporal lobar degeneration (present and premorbid) and controls.

(a) Behavioural variant frontotemporal dementia subgroup; (b) progressive non-fluent aphasia subgroup; (c) semantic dementia subgroup; (d) control group. BFI, Big Five Inventory; E, extraversion; A, agreeableness; C, conscientiousness; N, neuroticism; O, openness.



**Fig. 2** Personality change data in participants with fronto-temporal lobar degeneration and controls.

BFI, Big Five Inventory; E, extraversion; A, agreeableness; C, conscientiousness; N, neuroticism; O, openness.

(s.d. = 1.58) ( $P = 0.08$ ). The semantic dementia subgroup showed a significant decrease in mean scores for agreeableness (0.49 (s.d. = 0.66)), extraversion (1.0 (s.d. = 0.93)) and openness (1.03 (s.d. = 0.81)) and a trend towards decreased conscientiousness (0.53 (s.d. = 0.89)) ( $P = 0.09$ ); this subgroup also showed an increase in mean score for neuroticism (+1.2 (s.d. = 1.22)). The progressive non-fluent aphasia subgroup showed a significant decrease in mean scores for extraversion (0.34 (s.d. = 0.87)), conscientiousness (0.55 (s.d. = 0.54)) and openness (0.88 (s.d. = 0.74)) and a significant increase in mean score for neuroticism (+0.63 (s.d. = 0.79)). Comparing subgroups, change in conscientiousness score differed significantly ( $P < 0.01$ ) between the behavioural variant frontotemporal dementia subgroup and both language (semantic dementia and progressive non-fluent aphasia) subgroups. Change scores for other traits did not differ significantly between subgroups.

**VBM data**

Correlations between grey matter and personality change were investigated over the entire FTLD group and for each syndromic

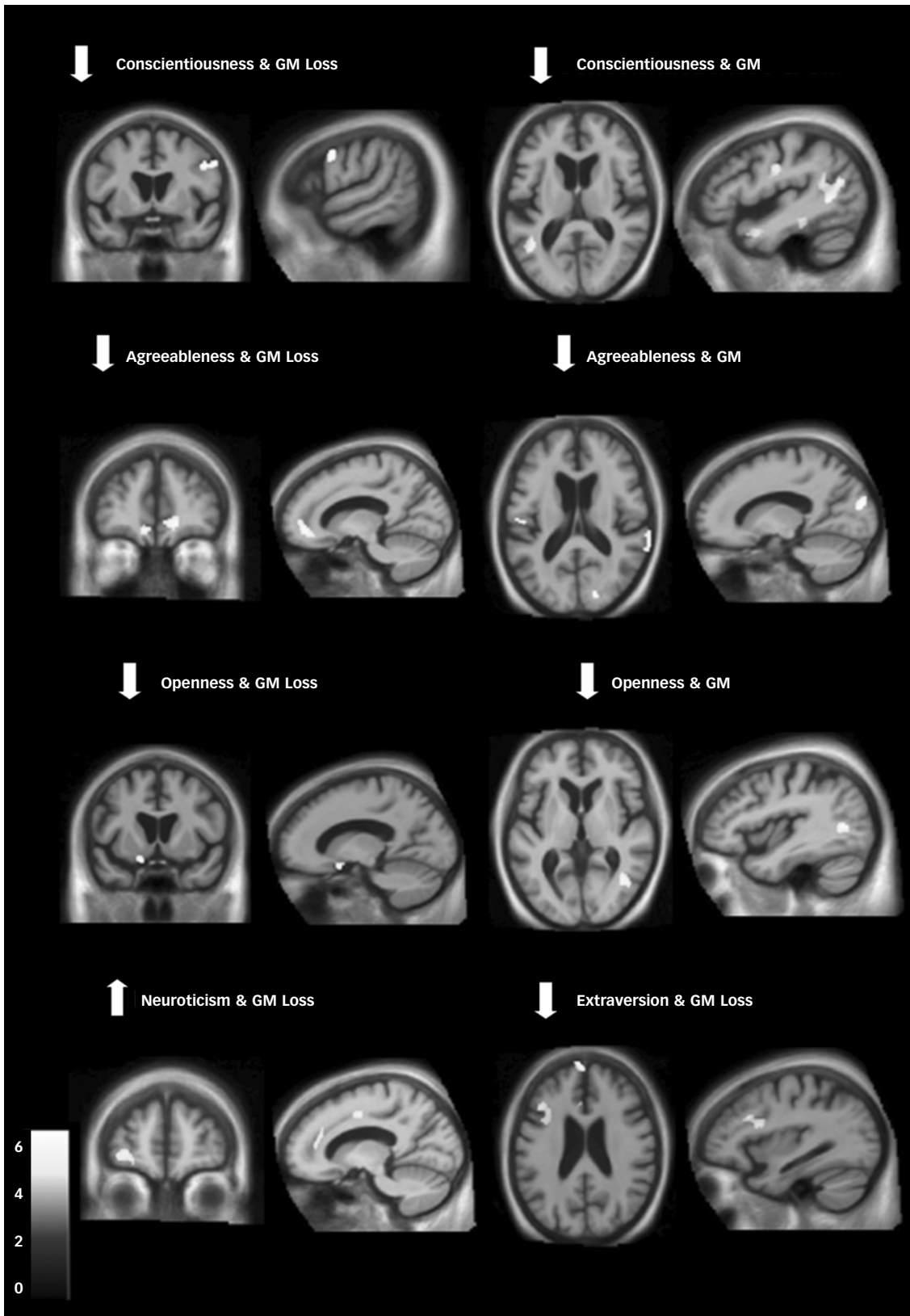
subgroup. Here we report cortical areas where trait change scores were associated with grey matter loss and areas where change scores were inversely associated with grey matter volume. The separate contrast between the FTLD group and a healthy control group (thresholded at  $P < 0.05$  after false discovery rate correction over the whole brain volume) revealed a typical profile of extensive disease-related atrophy involving frontal, temporal and parietal lobes bilaterally. These regions of disease-related grey matter loss included the areas identified as correlates of personality change in FTLD, allowing us to conclude that any inverse association between regional grey matter and personality change in these areas signifies relative preservation of grey matter (rather than an absolute increase in local grey matter).

For the combined FTLD group, VBM correlates of personality change are presented in Table 2 and Fig. 3 (a colour version of Fig. 3 can be found online (Fig. DS1)). Reduced conscientiousness was associated with grey matter loss in right premotor cortex ( $P < 0.001$  uncorrected) and associated with relative preservation of grey matter in left posterior superior temporal sulcus and superior temporal gyrus ( $P < 0.05$  false discovery rate corrected over the whole brain volume when analysed in a trait-specific design;  $P < 0.001$  uncorrected after covarying for other personality traits), left middle, inferior temporal and fusiform gyri and left central sulcus (all  $P < 0.001$  uncorrected). Less robust cerebral correlates (all  $P < 0.001$  uncorrected) of personality change were identified for other traits, analysed both in a combined design and separately for each trait. Reduced agreeableness was associated with grey matter loss in bilateral orbitofrontal cortices and left fronto-opercular cortex and associated with relative grey matter preservation in bilateral posterior superior temporal gyrus, right cuneus and left postcentral gyrus. Reduced extraversion was associated with grey matter loss in left medial prefrontal cortex, left dorsolateral prefrontal cortex, left premotor cortex and left anterior cingulate cortex; no areas of relative grey matter preservation correlated with reduced extraversion were identified. Reduced openness was associated with grey matter loss in left medial orbitofrontal cortices and associated with relative grey matter preservation in the region of the right temporo-occipital junction. Increased neuroticism was associated with grey matter loss in left lateral and medial orbitofrontal cortex and bilateral anterior cingulate cortex; no areas of relative grey matter preservation correlated with increased neuroticism were identified.

**Table 2** Summary of voxel-based morphometry regional grey matter correlates of personality change in the frontotemporal lobar degeneration group<sup>a</sup>

Trait	Reduced grey matter		Relatively preserved grey matter	
	Left hemisphere	Right hemisphere	Left hemisphere	Right hemisphere
Conscientiousness		Premotor	Posterior superior temporal Inferior temporal/ fusiform Central sulcus Anterior superior temporal	
Agreeableness	Orbitofrontal Fronto-opercular	Orbitofrontal	Posterior superior temporal Postcentral gyrus	Posterior superior temporal Cuneus
Openness	Medial orbitofrontal			Temporo-occipital junction
Neuroticism	Lateral orbitofrontal Anterior cingulate Medial orbitofrontal	Anterior cingulate		
Extraversion	Dorsolateral prefrontal Medial prefrontal Premotor Anterior cingulate			

a. Empty cells indicate no grey matter correlates were identified at the voxel-wise ( $P < 0.001$  uncorrected) and cluster extent (50 voxel) thresholds used.



**Fig. 3** Voxel-based morphometry correlates of personality change in frontotemporal lobar degeneration (FTLD). See Fig. DS1 for a colour version of this figure. For each personality trait, panels show statistical parametric maps of associated grey matter loss (GM loss) or relative grey matter preservation (GM). Maps have been rendered on the mean  $T_1$ -weighted normalised brain image for the FTLD group; the left hemisphere is presented on the left. For display purposes, maps are thresholded at  $P < 0.001$  uncorrected for all results.  $T$ -scores of grey matter change are coded as indicated on the colour bar (lower left).  $T$ -scores of grey matter change are coded as indicated on the grayscale bar (lower left).

In the separate VBM analyses for each syndromic subgroup, grey matter correlates of personality change were similar to that of the combined FTLT group: no additional or syndrome-specific grey matter correlates were identified.

## Discussion

Here we have demonstrated profiles of personality change and their neuroanatomical associations in FTLT. Participants with FTLT exhibited widespread alterations in personality compared with healthy age-matched controls: disease onset was associated with significant decline in the traits of extraversion, agreeableness, conscientiousness and openness, but an increase in neuroticism. Our findings corroborate previous studies of personality alteration in FTLT<sup>11,12</sup> and further underline that personality change is a cardinal symptom of diseases in the FTLT spectrum. Previous work focusing on measurement of personality change in Alzheimer's disease has shown a qualitatively similar although less marked profile of personality alteration, with increased neuroticism and decreased conscientiousness, openness and extraversion.<sup>32</sup> Although some evidence suggests that the trait of agreeableness is largely stable,<sup>33</sup> other work has reported a modest decline.<sup>34</sup> Little quantitative information is available concerning personality alterations in other neurodegenerative diseases. In one study, participants with Parkinson's disease had a profile of personality change similar to Alzheimer's disease, with a slight emphasis on decreased extraversion.<sup>35</sup>

### Neuroanatomical substrates for personality traits

The most robust neuroanatomical correlate of personality change identified here was the association of decreased conscientiousness with relative grey matter preservation in the region of the left superior temporal sulcus and superior temporal gyrus. This region has previously been linked to a diverse range of cognitive (including social behavioural) functions.<sup>36–38</sup> A recent large VBM study of brain structure and the BFI in healthy adults<sup>39</sup> showed a profile of regional volume change similar to the profile we observed in the FTLT group in our study: conscientiousness was positively associated with brain volume in prefrontal (and superior parietal) cortex but negatively associated with volume in other areas including fusiform and paracentral cortices. Superior temporal cortex has been implicated in the pathogenesis of personality disorders and sociopathy.<sup>40,41</sup> As lack of concern for others' well-being and with the consequences of one's own behaviour are prominent features of sociopathy, it is unsurprising that those scoring highly on scales of sociopathy should have correspondingly reduced scores for the trait of conscientiousness.<sup>42</sup> This line of evidence suggests that temporal lobe cortices may have an important role in regulating conscientiousness. In the present study, a number of additional cortical areas were identified as correlates of reduced conscientiousness, including regions previously implicated in analysis of social signals, programming of social behaviours and representation of others' emotional states.<sup>43–46</sup>

The cerebral correlates of change in other personality traits in our study implicated distributed frontal, temporal and parietal lobe areas. Our findings are consistent with previous evidence concerning the brain substrates of particular traits. Reduced agreeableness had a correlate in orbitofrontal cortex bilaterally, as demonstrated previously in FTLT.<sup>20</sup> Reduced extraversion had a correlate in medial and dorsolateral prefrontal cortex, consistent with previous structural and functional imaging evidence in healthy populations<sup>5,47–49</sup> and in neurodegenerative disease.<sup>12</sup> Increased neuroticism had a correlate in anterior

cingulate cortex, which has previously been implicated in conflict monitoring and avoidance,<sup>50,51</sup> and in the pathogenesis of obsessive-compulsive disorder, a condition with high levels of neuroticism.<sup>52</sup>

A broad neuroanatomical pattern that emerges from this study is the association of personality change with grey matter loss in more anterior and dorsal cortical areas and relative preservation of grey matter in more posterior and ventral areas. These findings suggest that personality change in FTLT results from dysfunction within a distributed network of cortical areas; besides the effects of disease-related brain damage per se, personality alterations may arise from the abnormal interaction of more severely damaged with less severely damaged cortex. The concept of neural network dysfunction in the pathogenesis of FTLT and other neurodegenerative diseases has gained currency,<sup>53</sup> and network dysfunction is likely to be particularly relevant to complex behavioural symptoms. Frontomedial cortices (orbitofrontal cortex, prefrontal cortex) and their connections (in particular, superior temporal gyrus and sulcus) have been linked to mentalising and other social cognitive skills and behaviours in previous structural and functional imaging studies in both healthy and clinical populations.<sup>54–59</sup>

A multidimensional neural construct such as personality is unlikely to bear any simple unitary relation to macro-anatomical parameters such as regional brain volume. Evidence from healthy participants<sup>39</sup> supports the present clinical findings, demonstrating that anatomical correlates of personality traits are both distributed and bidirectional: a particular trait associates with increased brain volume in some regions and reduced volume in others. Although our understanding of the neural mechanisms that sustain personality remains too rudimentary to specify how these volume changes are related, one plausible hypothesis is that personality traits represent the net output of a balance of competing processes. For example, from a social cognition perspective, traits such as agreeableness or neuroticism might reflect an altered interaction between self (inwardly directed) and mentalising (externally directed) perspective-taking processes.<sup>60,61</sup> We do not of course suggest that any single such simple dichotomy will capture the richness of human personality structure or its erosion by disease, although we speculate that 'reduced conscientiousness' might require (in addition to diminished regard for the consequences of one's behaviour) preserved understanding of one's own selfish interests. Furthermore, in the present study, the cortical areas implicated in particular personality alterations showed substantial overlap. This suggests that regional anatomical specificity for particular traits should be regarded as relative rather than absolute: any neuroanatomical specificity for personality change in FTLT is likely to emerge as a profile of brain damage distributed among areas in one or more cerebral networks that mediate personality.

### Directions for future work

This study has several methodological limitations. In particular, change in personality was based on retrospective indices, and neuroanatomical correlation was performed at a single time point. A further important limitation of this study is that diagnoses were clinical, without neuropathological correlation: this leaves open the possibility that at least a proportion of participants in this series had a histopathological substrate outside the FTLT spectrum. Moreover, detailed correlation with neuropathological data will ultimately be required in order to define the neurobiological basis for personality change in FTLT. These limitations notwithstanding, the findings provide initial evidence that the clinical signal of personality alteration in FTLT may be associated with signature

patterns of structural brain damage. From a neurobiological perspective, FTL D presents a unique 'experiment of nature' that allows identification of brain substrates critical for maintenance of stable personality traits. Important issues for future work will include the corroboration of these findings using prospectively acquired personality indices and longitudinal measures of brain atrophy (including measures of earliest clinical change in genetic mutation carriers), and evaluation of altered personality in FTL D in relation both to other neurodegenerative diseases and to different pathological subtypes within the heterogeneous FTL D spectrum.

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First received 4 Oct 2010, final revision 8 Dec 2010, accepted 15 Dec 2010

## Funding

This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. The Dementia Research Centre is an Alzheimer's Research Trust Co-ordinating Centre. This work was also funded by the Medical Research Council UK. C.J.M. is supported by an MRC programme grant. J.D.R. was supported by a Wellcome Trust Research Training Fellowship and R.O. by a Royal College of Physicians/Dunhill Medical Trust Research Fellowship. M.N.R. is an NIHR senior investigator. J.D.W. is supported by a Wellcome Trust Senior Clinical Fellowship.

## Acknowledgements

We are grateful to the individuals who participated.

## Appendix

### Examples of questions used to assess personality traits in the Big Five Inventory

Extraversion (contrasts talkativeness or assertiveness with taciturnity or passivity): Is he/she talkative? Is he/she reserved?

Agreeableness (contrasts helpfulness or altruism with hostility or selfishness): Is he/she helpful with others? Does he/she easily find fault with others?

Conscientiousness (contrasts organisation or attention to detail with negligence or carelessness): Is he/she a reliable worker? Does he/she tend to be disorganised?

Neuroticism (features of nervousness or temperamentality): Can he/she be moody? Does he/she remain calm in intense situations?

Openness to new ideas (contrasts creativity with narrow-mindedness): Is he/she sophisticated with art or music? Does he/she prefer to work in a routine?

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