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White Matter Disease Contributes to Apathy and Disinhibition in Behavioral Variant Frontotemporal Dementia

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Abstract

Objective—To relate changes in fractional anisotropy associated with behavioral variant frontotemporal dementia to measures of apathy and disinhibition.

Background—Apathy and disinhibition are the 2 most common behavioral features of behavioral variant frontotemporal dementia, and these symptoms are associated with accelerated patient decline and caregiver stress. However, little is known about how white matter disease contributes to these symptoms.

Methods—We collected neuropsychiatric data, volumetric magnetic resonance imaging, and diffusion-weighted imaging in 11 patients who met published criteria for behavioral variant frontotemporal dementia and had an autopsy-validated cerebrospinal fluid profile consistent with frontotemporal lobar degeneration. We also collected imaging data on 34 healthy seniors for analyses defining regions of disease in the patients. We calculated and analyzed fractional anisotropy with a white matter tract-specific method. This approach uses anatomically guided data reduction to increase sensitivity, and localizes results within canonically defined tracts. We used nonparametric, cluster-based statistical analysis to relate fractional anisotropy to neuropsychiatric measures of apathy and disinhibition.

Results—The patients with behavioral variant frontotemporal dementia had widespread reductions in fractional anisotropy in anterior portions of frontal and temporal white matter, compared to the controls. Fractional anisotropy correlated with apathy in the left uncinate fasciculus and with disinhibition in the right corona radiata.

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The authors declare no conflicts of interest.

Conclusions—In patients with behavioral variant frontotemporal dementia, apathy and disinhibition are associated with distinct regions of white matter disease. The implicated fiber tracts likely support frontotemporal networks that are involved in goal-directed behavior.

Keywords

diffusion-weighted imaging; frontotemporal dementia; apathy; disinhibition; magnetic resonance imaging

Behavioral variant frontotemporal dementia (bvFTD), the most common presentation of frontotemporal lobar degeneration, is characterized by changes in personality and social conduct and by loss of executive function (Rascovsky et al, 2011). The 2 most common behavioral features of bvFTD are apathy and disinhibition (Massimo et al, 2009; Mourik et al, 2004). These neuropsychiatric symptoms predict accelerated functional decline and earlier mortality for patients and cause high levels of stress to caregivers (Clarke et al, 2010; Massimo et al, 2009; Vilalta-Franch et al, 2013). Notably, apathy has been shown to differentiate bvFTD from other variants of frontotemporal dementia (Liu et al, 2004). The characteristic pattern of gray matter atrophy in bvFTD is widespread bilateral frontal and temporal changes (Whitwell et al, 2011). White matter is also susceptible to pathologic damage in frontotemporal lobar degeneration (Forman et al, 2002; Neumann et al, 2007), but few studies have attempted to characterize the changes in white matter associated with bvFTD.

Although 2 reports have described white matter associations with disinhibition in bvFTD, the studies used very different methods and their results were inconsistent (Borroni et al, 2007; Hornberger et al, 2011). Borroni et al (2007) used a region-of-interest–based approach and reported that fractional anisotropy (FA) in the superior longitudinal fasciculus was related to disinhibition as measured by items from the Frontal Behavioral Inventory. By contrast, Hornberger et al (2011) reported that FA in the uncinate fasciculus, cingulum, and forceps minor was related to disinhibition as measured by items from the Hayling Test. The different methods of analysis and the different measures of disinhibition in these studies could both potentially contribute to the different white matter tracts observed; additional work is needed to resolve these discrepancies.

We are not aware of studies examining white matter associations with apathy in bvFTD.

In the present study, we used a tract-specific analysis technique (Yushkevich et al, 2008) to examine changes in FA associated with bvFTD and to relate these changes to apathy and disinhibition. Tract-specific analysis does not require the user to specify parameters, and therefore maintains consistency and replicability across analyses and users. The technique offers anatomically guided data reduction in 11 major white matter tracts. It increases sensitivity to detect potential differences in white matter integrity by minimizing potential confounds introduced through smoothing and suboptimal registration of diffusion tensor data and by reducing power demands through decreasing the number of comparisons.

We hypothesized that apathy and disinhibition would be associated with distinct regions of white matter disease in bvFTD, and these disruptions would correspond to frontotemporal

networks involved in goal-directed behavior. Specifically, we hypothesized that reduced integrity of white matter fibers connecting ventral frontal and temporal gray matter regions would be involved in the expression of apathy, and that disruption of white matter fibers connecting ventral and dorsal regions of frontal gray matter would be associated with disinhibition.

METHODS

Participants

We recruited 11 patients with bvFTD from the Penn Frontotemporal Degeneration Center at the University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania. We collected neuropsychiatric data, structural magnetic resonance imaging, and diffusion tensor imaging for each patient. All patients met published clinical criteria for bvFTD (Rascovsky et al, 2011) as assessed by a Board-certified neurologist (author M.G.), and all patients had a cerebrospinal fluid profile consistent with frontotemporal lobar degeneration pathology (total tau:β-amyloid ≤ 0.34) as validated in a previous autopsy study (Irwin et al, 2012). The procedure that we used to collect and evaluate the cerebrospinal fluid is described by Irwin et al (2012).

Exclusion criteria were other neurologic conditions such as stroke, head trauma, and hydrocephalus; other causes of dementia; medical conditions associated with cognitive difficulty; primary psychiatric disorders; and contraindications for magnetic resonance imaging. Some patients may have been taking a small dose of a nonsedating antidepressant (eg, sertraline) or a low-potency nonsedating neuroleptic (eg, quetiapine), as needed medically.

We recruited a control group of 34 healthy seniors through flyers and presentations at senior living centers. Inclusion criteria were a minimum age of 50 years and a Mini-Mental State Examination (Folstein et al, 1975) score of ≥28 out of a possible 30. Exclusion criteria were history of a neurologic condition, head trauma, current psychiatric diagnoses, current use of any psychoactive drugs or medications, and contraindications for magnetic resonance imaging. We also collected structural magnetic resonance imaging and diffusion tensor imaging on the controls. We compared the controls and patients in an imaging analysis to define regions of disease in the patients.

The patient and control groups were similar in demographics. The patients' mean age was 60.5 years (standard error of the mean = 2.0) versus 62.8 (1.4) years for the controls; $t(43) = 0.886$, $P = 0.381$. The groups were also similar in sex: The patient group had 7 men and 4 women, and the control group had 18 men and 16 women; $\chi^2 = 0.385$, $P = 0.535$.

We obtained written informed consent from all control participants and patients or patients' caregivers using an informed consent process and study protocol approved by the University of Pennsylvania Institutional Review Board. This protocol included measures to protect participants' privacy and the confidentiality of the research data.

Neuropsychiatric Assessment

We measured our patients' apathetic and disinhibited behaviors using the Neuropsychiatric Inventory (NPI) (Cummings et al, 1994), which evaluates 12 domains of common neuropsychiatric symptoms (Table 1): apathy/indifference, disinhibition, delusions, hallucinations, depression/dysphoria, anxiety, irritability/lability, agitation, euphoria/elation, aberrant motor behavior, sleep/nighttime behavior, and appetite/eating. A caregiver for each patient completed the NPI by rating the frequency of specific abnormal behaviors and rating the overall severity of each domain. The NPI has well-established content validity, concurrent validity, inter-rater reliability, and test-retest reliability (Cummings et al, 1994).

We averaged the frequency of each behavioral item across all items within the same domain to yield a frequency score for the domain. We then multiplied the frequency and severity scores to yield a total frequency-by-severity score for each domain. We examined the correlation of the frequency-by-severity scores for apathy and disinhibition with the scores from each of the other domains.

Neuropsychological Assessment

To get a more complete neuropsychological characterization of our patients, we tested them directly. Within a mean of 3.1 months (standard error of the mean = 1.2) from the time that their caregivers completed the NPI, we gave the patients the Mini-Mental State Examination (Folstein et al, 1975) and the Philadelphia Brief Assessment of Cognition (Libon et al, 2011) (Table 1). The Philadelphia Brief Assessment of Cognition is a collection of tests that rate cognition, behavior, and language. The measures are grouped and scored under 5 subscales with roughly equal weighting: working memory/executive control, lexical retrieval/ language, visuospatial/visuoconstructional ability, verbal/visual episodic memory, and behavior/social comportment.

Imaging Data Acquisition

We acquired all imaging data for each patient during a single structural magnetic resonance imaging session scheduled within a mean of 6.3 months (standard error of the mean = 1.7) from the time that their caregivers completed the NPI. At the time of scanning, the patients had presented symptoms of bvFTD for a mean of 3.3 years (0.7 standard error of the mean). We scheduled the imaging sessions for the controls at their convenience.

The imaging acquisition procedure was identical for patients and controls. We acquired diffusion-weighted images on a Siemens 3.0T Trio scanner (Siemens Medical Solutions, Erlangen, Germany) with an 8-channel coil using a single-shot, spin-echo, diffusion-weighted echo planar imaging sequence (field of view = 245 mm; matrix size = 112 × 112; number of slices = 57; voxel size = 2.2 mm isotropic; repetition time = 6700 msec; echo time = 85 msec; fat saturation). In total, we acquired 31 volumes per participant: 1 without diffusion weighting (b-value = 0 sec/mm^2) and 30 with diffusion weighting (b-value = 1000 sec/mm^2) along 30 noncollinear directions.

During the session, we also obtained a structural T1-weighted 3-dimensional spoiled gradient-echo sequence with a repetition time =1620 msec, echo time = 3 msec, flip angle = 15°, matrix = 192 × 256, slice thickness = 1 mm, and in-plane resolution = 0.9 × 0.9 mm.

We describe the preprocessing of the T1-weighted images and our voxel-wise statistical analysis of gray matter in Supplementary Digital Content 1.

Preprocessing of Diffusion-Weighted Images

We reconstructed diffusion tensor maps from the diffusion-weighted imaging using the Camino software toolkit (http://cmic.cs.ucl.ac.uk/camino/; Cook et al, 2006). After rigid transformation, we aligned tensor images to a healthy aging template through affine and diffeomorphic registration using the Diffusion Tensor Imaging ToolKit (http://dti-tk.sourceforge.net/; Zhang et al, 2007). This is the same template that we used to generate the white matter tract models described below.

Tract-Specific Analysis

For a detailed description of the tract-specific analysis, see Yushkevich et al, 2008. Briefly, 11 white matter tracts have been made available for use with this technique: corpus callosum and bilateral inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, uncinate fasciculus, and corticofugal fibers including the corona radiata. The tracts had been defined from a diffusion tensor imaging template of healthy aging generated from 51 participants (21 men and 30 women, mean age = 70.1 years, standard error of the mean = 0.6 years) from the publicly available IXI database (http://biomedic.doc.ic.ac.uk/brain-development/; Zhang et al, 2010).

We chose the healthy aging template to match the demographic characteristics of our patients and controls, and to model diffusion pathways without severe disease-related alterations. We ran whole-brain tractography on the template using the Fiber Assignment by Continuous Tracking algorithm (Mori et al, 1999) in the Diffusion Tensor Imaging ToolKit, and we used an established region-of-interest–based fiber-tracking protocol to segment the tracts of interest (Wakana et al, 2004). We then converted each tract to a binary volume and modeled by a skeleton and its corresponding boundary using a continuous medial model (Figure 1). For each point in the skeleton, a line segment called a *spoke* connected that point to the closest point on the model's boundary. Spokes were orthogonal to the model's boundary, and no spokes in the model intersected.

For each participant and each tract, we computed maximum FA values from the diffusion tensor image along the spokes of the model and we projected these values onto the corresponding point on the model's surface. We used *t* tests to compare the patients to the controls at each point on the model. Using a *t* value height threshold corresponding to $P < 0.001$, we ran nonparametric, cluster-based statistical analysis with 10,000 permutations. We applied family-wise error correction for multiple comparisons. We report clusters that survived a size threshold equivalent to $P < 0.05$.

We performed regression analyses to relate the neuropsychiatric measures to FA in each tract where we had found clusters with significantly less FA in patients than controls. We

constrained analyses to tracts with FA disruptions so that we could relate apathy and disinhibition severity to white matter degeneration. We ran the regression analyses with the same threshold parameters and number of permutations as the *t* tests, and we identified clusters where frequency-by-severity scores for apathy or disinhibition correlated with FA.

RESULTS

Neuropsychiatric and Neuropsychological Assessments

As shown by the NPI, our patients with bvFTD exhibited apathy and disinhibition (Table 1). To assess the specificity of the apathy and disinhibition, we performed correlation analyses relating frequency-by-severity scores for these domains to each of the other NPI domains. We found a significant correlation only between disinhibition and euphoria ($r[11] = 0.854$, Bonferroni-corrected $P = 0.022$). No other correlations were significant (all P values > 0.2 with Bonferroni correction); notably, apathy did not correlate with disinhibition ($r[11] = -0.079$, $P > 0.2$) or with depression ($r[11] = 0.533$, $P > 0.2$).

These null findings indicate a lack of collinearity between apathy and disinhibition, suggesting that they may have distinct neuroanatomic correlates in our imaging analyses. These findings also provide evidence that apathy in our patients was not likely confounded by depression (Eslinger et al, 2012; Levy et al, 1998).

Neuropsychiatric and Imaging Correlations

Relative to the controls, the patients with bvFTD showed significant FA reductions in the anterior corpus callosum and throughout bilateral uncinate fasciculus, as well as bilateral anterior portions of the inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and corona radiata (Figure 2A). The areas and *P* values of all significant clusters are summarized in Supplementary Table 1 (Supplementary Digital Content 2).

Regression analysis related the frequency-by-severity apathy score to FA in the temporal portion of the left uncinate fasciculus (Figure 2B). Regression analysis also related the frequency-by-severity disinhibition score to FA in the right corona radiata (Figure 2C). No other tracts with FA reductions showed a significant relationship between FA and frequency-by-severity scores for apathy or disinhibition.

DISCUSSION

In 11 patients with bvFTD, we found disruptions of white matter integrity in the corpus callosum and bilateral uncinate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and corona radiata. White matter disease was especially prominent in the anterior portions of the corpus callosum, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and corona radiata. We also found significant disease throughout the bilateral uncinate fasciculus.

These findings are consistent with previous reports of widespread reduction of FA in frontal and temporal white matter in bvFTD (Agosta et al, 2012; Hornberger et al, 2011; Mahoney et al, 2014; Matsuo et al, 2008; Whitwell et al, 2010; Zhang et al., 2009, 2011). Using tract-

specific analysis, we found that our patients replicated a specific bias for disruption of the anterior fibers of the corpus callosum (Agosta et al, 2012; Lillo et al, 2012; Matsuo et al, 2008; Zhang et al, 2009, 2011) and prominent diffusion abnormalities in the uncinate fasciculus in bvFTD (Matsuo et al, 2008).

Brown and Pluck (2000) suggested that frontal and temporal gray matter and white matter structures constitute critical components of a large-scale neural network that is important in regulating goal-directed behavior. From this perspective, orbital and medial regions of the inferior frontal lobe have been shown to contribute to the interpretation of value- and reward-related information (Grossman et al, 2010; Kable and Glimcher, 2007; Kringelbach and Rolls, 2004). Thus, degradation of the white matter projections between orbital and medial regions of the inferior frontal lobe and other areas of the temporal lobe may interfere with motivation and goal-directed behavior. The fibers of the uncinate fasciculus serve as the primary connection between these inferior frontal and anterior temporal regions of gray matter. We found damage in the left uncinate fasciculus to be associated with apathy.

We are unaware of previous studies investigating the relationship between white matter integrity and a specific measure of apathy in bvFTD. In patients with Alzheimer disease, tract-based spatial statistics have associated apathy with FA changes in the bilateral uncinate fasciculus, corpus callosum, right superior longitudinal fasciculus, and left cingulum (Hahn et al, 2013; Smith et al, 2006). These findings further implicate a network of frontal and temporal structures in goal-directed behavior. Two additional studies averaged FA over select regions of interest and found that reduced FA in the anterior cingulum corresponded to apathy in patients with mild cognitive impairment or Alzheimer disease (Kim et al, 2011; Tighe et al, 2012).

In voxel-based morphometry studies of gray matter in patients with bvFTD, apathy has been associated with disease in bilateral medial, orbital, inferior, and dorsolateral frontal areas, as well as bilateral anterior temporal and right caudate regions (Massimo et al, 2009; Zamboni et al, 2008). Similarly, a FDG-PET study showed that apathetic patients with bvFTD had lower brain activity in the orbitofrontal cortex than nonapathetic patients (Peters et al, 2006). In a heterogeneous cohort of patients with dementia, apathy was related to atrophy in ventromedial frontal regions (Rosen et al, 2005).

We report results consistent with previous studies in the gray matter analysis of our own study participants. Supplementary Table 2 (Supplementary Digital Content 3) lists the regions where our patients had gray matter atrophy relative to our controls, and regions where gray matter atrophy correlated with the neuropsychiatric measures of apathy and disinhibition. Supplementary Figure 1 (Supplementary Digital Content 4) maps our patients' regions of gray matter atrophy and illustrates the areas that correlated with apathy and disinhibition. Our findings confirm a characteristic distribution of gray matter disease: widespread bilateral frontal and temporal atrophy. This distribution confirms the representativeness of our sample.

The corona radiata includes white matter fibers that may play a role in linking a functional network involving orbital, dorsolateral, and insular gray matter regions of the frontal lobe as

well as the striatum, during challenges that require inhibitory control (Aron et al, 2003; Liu et al, 2004; Vink et al, 2005). Voxel-based morphometry analyses relate disinhibition to atrophy in these orbitofrontal, dorsolateral, and medial prefrontal gray matter regions, as well as anterior and medial temporal gray matter regions (Hornberger et al, 2011; Liu et al, 2004; Zamboni et al, 2008). Patients with bvFTD have shown impaired performance on complex tests of inhibitory control such as the Hayling test; these patients also had magnetic resonance imaging and FDG-PET evidence of disease in the dorsolateral prefrontal cortex (Kipps et al, 2010).

White matter disease has also been implicated in disordered inhibitory control in patients with bvFTD. In our study, we found an association between disinhibition and loss of white matter integrity in the right corona radiata.

Previous work using region of interest has shown a relationship between FA in the right superior longitudinal fasciculus and certain items of the Frontal Behavioral Inventory addressing disinhibition (Borroni et al, 2007). Although we did not find significantly reduced FA in our patients' right superior longitudinal fasciculus, we did find disinhibition to be related to FA in adjacent white matter fibers of the right corona radiata. Hornberger et al (2011), using tract-based spatial statistics, found that FA in the uncinate fasciculus, cingulum, and forceps minor correlated with disinhibition as measured by the Hayling Test.

Discrepancies such as these may be explained in part by the measures used to assess disinhibition; additional work is needed to resolve these differences. Nevertheless, our observations, along with these other findings, suggest that a large-scale neural network involving dorsolateral, orbital, and insular regions of the frontal lobe contributes to inhibitory control, and that white matter fibers may integrate these regions to facilitate network performance on tasks requiring inhibitory control.

Our correlations of white matter with apathy and disinhibition converge with growing evidence of substantial white matter disease in frontotemporal lobar degeneration. We carefully screened cerebrospinal fluid from our patients in an effort to exclude patients who might have Alzheimer disease pathology (Bian et al, 2008; de Souza et al, 2013; Irwin et al, 2012). This was an important distinction, given that previous diffusion tensor imaging studies have demonstrated that patients with frontotemporal lobar degeneration have substantially worse white matter disease than patients with Alzheimer disease (McMillan et al, 2012). Future studies should address the relative associations of white matter disease with neuropsychiatric correlates in pathologic subtypes of bvFTD because tau and TAR (transactive response) DNA-binding protein 43 proteinopathies also appear to have distinct patterns of white matter disease (McMillan et al, 2013).

Our use of tract-specific analysis in this study combined advantageous characteristics of 3 well-established strategies in diffusion tensor imaging analysis: fiber tractography, voxel-based morphometry, and tract-based spatial statistics.

Several published techniques have extracted centerlines from fiber tractography output, normalized them across participants, and performed statistical inference on diffusion tensor metrics along the centerlines (Corouge et al, 2006; Jones et al, 2005; Maddah et al, 2007).

While this approach is suitable for bundles that have tubular shapes, such as the cingulum, a centerline representation is inappropriate for other shapes, such as corpus callosum.

Voxel-based morphometry allows for more detailed spatial localization. However, white matter structural information is not taken into account during smoothing and analysis (Jones et al, 2005).

Tract-based spatial statistics address this problem by incorporating the geometric features of white matter structures (Smith et al, 2006). However, using the mean FA image in tract-based spatial statistics limits this approach by ignoring orientation information. Thus, adjacent fasciculi with different orientations but similar FA are combined into a single region of skeleton.

Similar to tract-based spatial statistics, tract-specific analysis uses white matter structural information and projects diffusion data onto skeleton-based models. However, tract-specific analysis is structure-specific, with connectivity information from fiber tractography incorporated into structural definitions. This allows for more reliable inference within anatomic structures.

Standard isotropic smoothing in voxel-based morphometry reduces spatial localization equally in all directions. By contrast, the geometric modeling in tract-specific analysis preserves spatial specificity along the more informative directions that follow the surface of the tract model, while reducing spatial specificity along the depth direction (the direction orthogonal to the boundary of the structure). Furthermore, the parametric surface representations in tract-specific analysis allow for surface-based statistical analysis, and robust techniques for the statistical analysis of manifold-based feature maps are well documented in the context of neuroimaging (Yushkevich et al, 2008).

We used a caregiver-based assessment, the NPI, to evaluate the presence and severity of apathy, disinhibition, and other neuropsychiatric symptoms in our patients with bvFTD. The NPI is a well-validated instrument for assessing neuropsychiatric features, but third-party report introduces a substantial confound. Other studies have used a variety of assessment tools to evaluate these features: single-item measures of behavioral features like apathy on the Frontal Behavioral Inventory (Borroni et al, 2007; Farb et al, 2013), multi-item assessments of multiple feature domains such as the NPI (Borroni et al, 2007; Hornberger et al, 2011; Kim et al, 2011; Tighe et al, 2012), and multi-item assessments of specific features such as the Apathy Inventory (Hahn et al, 2013).

The considerable differences among these tests likely contribute to differences in reported neuroanatomic correlations. The development of objective measures of apathy that could determine the features contributing to an apathetic phenotype could allow for more informative and consistent studies of apathy.

Our patients had a correlation between NPI measures of disinhibition and euphoria. This result follows intuitively from previous factor analyses of NPI domains. These analyses grouped disinhibition and euphoria into a common factor (Aalten et al, 2003; Lee et al,

2012). It is possible that disinhibition and euphoria share some common projectional targets within the frontolimbic networks.

Differences in imaging methods are another source of discrepancy between studies. While tract-specific analysis provides manifold-based evaluation of diffusion metrics within 11 major white matter tracts, the technique does not enable many smaller, more challenging regions of white matter to be analyzed. Because diffusion imaging presents challenges in localization, many commonly used region-of-interest- and tractography-based methods provide even less coverage and less specific localization. The advancement of diffusion analysis methods providing whole-brain coverage will allow for more consistent methods in future studies of white matter.

Techniques are also being developed to integrate the evaluation of gray and white matter (Avants et al, 2007, 2010, 2014). These whole-brain techniques are ideally suited to characterizing changes in large functional networks such as the salience network, which has been associated with atrophy patterns in bvFTD as well as affective cognition and behavioral disruptions (Seeley et al, 2007, 2009; Zhou et al, 2010). Future studies using these techniques could provide valuable information about the relative contributions of gray and white matter changes to behavioral impairments in bvFTD.

In summary, using tract-specific analysis, we observed widespread frontal and anterior temporal white matter disease in patients with bvFTD. Damage in the left uncinate fasciculus was associated with apathy, while disruption in fibers of the right corona radiata was related to disinhibition. These novel findings suggest that disease in distinct frontotemporal network structures may contribute to apathy and disinhibition in bvFTD. Specifically, the uncinate fasciculus may support a network of frontal and temporal structures regulating goal-directed behavior, and fibers in the corona radiata may contribute to a frontal network mediating behavioral inhibition.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Glossary

bvFTD	behavioral variant frontotemporal dementia
FA	fractional anisotropy
FDG-PET	fluorodeoxyglucose-positron emission tomography
NPI	Neuropsychiatric Inventory

References

Aalten P, de Vugt ME, Lousberg R, et al. Behavioral problems in dementia: a factor analysis of the neuropsychiatric inventory. Dement Geriatr Cogn Disord. 2003; 15:99–105. [PubMed: 12566599]

Agosta F, Scola E, Canu E, et al. White matter damage in frontotemporal lobar degeneration spectrum. Cereb Cortex. 2012; 22:2705–2714. [PubMed: 21988828]

Aron AR, Schlaghecken F, Fletcher PC, et al. Inhibition of subliminally primed responses is mediated by the caudate and thalamus: evidence from functional MRI and Huntington's disease. Brain. 2003; 126:713–723. [PubMed: 12566291]

Avants BB, Cook PA, Ungar L, et al. Dementia induces correlated reductions in white matter integrity and cortical thickness: a multivariate neuroimaging study with sparse canonical correlation analysis. NeuroImage. 2010; 50:1004–1016. [PubMed: 20083207]

Avants BB, Duda JT, Zhang H, et al. Multivariate normalization with symmetric diffeomorphisms for multivariate studies. Med Image Comput Comput Assist Interv. 2007; 10:359–366. [PubMed: 18051079]

Avants BB, Epstein CL, Grossman M, et al. Symmetric diffeomorphic image registration with cross-correlation: evaluating automated labeling of elderly and neurodegenerative brain. Med Image Anal. 2008; 12:26–41. [PubMed: 17659998]

Avants BB, Libon DJ, Rascovsky K, et al. Sparse canonical correlation analysis relates network-level atrophy to multivariate cognitive measures in a neurodegenerative population. NeuroImage. 2014; 84:698–711. [PubMed: 24096125]

Avants BB, Tustison NJ, Wu J, et al. An open source multivariate framework for n-tissue segmentation with evaluation on public data. Neuroinformatics. 2011; 9:381–400. [PubMed: 21373993]

Bian H, Van Swieten JC, Leight S, et al. CSF biomarkers in frontotemporal lobar degeneration with known pathology. Neurology. 2008; 70:1827–1835. [PubMed: 18458217]

Borroni B, Brambati SM, Agosti C, et al. Evidence of white matter changes on diffusion tensor imaging in frontotemporal dementia. Arch Neurol. 2007; 64:246–251. [PubMed: 17296841]

Brown RG, Pluck G. Negative symptoms: the "pathology" of motivation and goal-directed behaviour. Trends Neurosci. 2000; 23:412–417. [PubMed: 10941190]

Clarke DE, Ko JY, Lyketsos C, et al. Apathy and cognitive and functional decline in community-dwelling older adults: results from the Baltimore ECA longitudinal study. Int Psychogeriatr. 2010; 22:819–829. [PubMed: 20478091]

Cook, PA.; Bai, Y.; Nedjati-Gilani, S., et al. Camino: open-source diffusion-MRI reconstruction and processing. 14th Scientific Meeting of the International Society for Magnetic Resonance in Medicine; Seattle, Washington. 2006. p. 2759

Corouge I, Fletcher PT, Joshi S, et al. Fiber tract-oriented statistics for quantitative diffusion tensor MRI analysis. Med Image Anal. 2006; 10:786–798. [PubMed: 16926104]

Cummings JL, Mega M, Gray K, et al. The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994; 44:2308–2314. [PubMed: 7991117]

de Souza LC, Chupin M, Bertoux M, et al. Is hippocampal volume a good marker to differentiate Alzheimer's disease from frontotemporal dementia? J Alzheimers Dis. 2013; 36:57–66. [PubMed: 23542864]

Eslinger PJ, Moore P, Antani S, et al. Apathy in frontotemporal dementia: behavioral and neuroimaging correlates. Behav Neurol. 2012; 25:127–136. [PubMed: 22425723]

Farb NA, Grady CL, Strother S, et al. Abnormal network connectivity in frontotemporal dementia: evidence for prefrontal isolation. Cortex. 2013; 49:1856–1873. [PubMed: 23092697]

Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]

Forman MS, Zhukareva V, Bergeron C, et al. Signature tau neuropathology in gray and white matter of corticobasal degeneration. Am J Pathol. 2002; 160:2045–2053. [PubMed: 12057909]

Grossman M, Eslinger PJ, Troiani V, et al. The role of ventral medial prefrontal cortex in social decisions: converging evidence from fMRI and frontotemporal lobar degeneration. Neuropsychologia. 2010; 48:3505–3512. [PubMed: 20691197]

Hahn C, Lim HK, Won WY, et al. Apathy and white matter integrity in Alzheimer's disease: a whole brain analysis with tract-based spatial statistics. PLoS One. 2013; 8:e53493. [PubMed: 23301077]

Hornberger M, Geng J, Hodges JR. Convergent grey and white matter evidence of orbitofrontal cortex changes related to disinhibition in behavioural variant frontotemporal dementia. Brain. 2011; 134:2502–2512. [PubMed: 21785117]

Irwin DJ, McMillan CT, Toledo JB, et al. Comparison of cerebrospinal fluid levels of tau and Aβ 1-42 in Alzheimer disease and frontotemporal degeneration using 2 analytical platforms. Arch Neurol. 2012; 69:1018–1025. [PubMed: 22490326]

Jones DK, Symms MR, Cercignani M, et al. The effect of filter size on VBM analyses of DT-MRI data. NeuroImage. 2005; 26:546–554. [PubMed: 15907311]

Jones DK, Travis AR, Eden G, et al. PASTA: pointwise assessment of streamline tractography attributes. Magn Reson Med. 2005; 53:1462–1467. [PubMed: 15906294]

Kable JW, Glimcher PW. The neural correlates of subjective value during intertemporal choice. Nat Neurosci. 2007; 10:1625–1633. [PubMed: 17982449]

Kim JW, Lee DY, Choo IH, et al. Microstructural alteration of the anterior cingulum is associated with apathy in Alzheimer disease. Am J Geriatr Psychiatry. 2011; 19:644–653. [PubMed: 21709610]

Kipps CM, Hodges JR, Hornberger M. Nonprogressive behavioural frontotemporal dementia: recent developments and clinical implications of the "bvFTD phenocopy syndrome". Curr Opin Neurol. 2010; 23:628–632. [PubMed: 20962637]

Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Prog Neurobiol. 2004; 72:341–372. [PubMed: 15157726]

Lee WJ, Tsai CF, Gauthier S, et al. The association between cognitive impairment and neuropsychiatric symptoms in patients with Parkinson's disease dementia. Int Psychogeriatr. 2012; 24:1980–1987. [PubMed: 22835209]

Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. J Neuropsychiatry Clin Neurosci. 1998; 10:314–319. [PubMed: 9706539]

Libon DJ, Rascovsky K, Gross RG, et al. The Philadelphia Brief Assessment of Cognition (PBAC): a validated screening measure for dementia. Clin Neuropsychol. 2011; 25:1314–1330. [PubMed: 22084867]

Lillo P, Mioshi E, Burrell JR, et al. Grey and white matter changes across the amyotrophic lateral sclerosis-frontotemporal dementia continuum. PLoS One. 2012; 7:e43993. [PubMed: 22952843]

Liu W, Miller BL, Kramer JH, et al. Behavioral disorders in the frontal and temporal variants of frontotemporal dementia. Neurology. 2004; 62:742–748. [PubMed: 15007124]

Maddah M, Wells WM 3rd, Warfield SK, et al. Probabilistic clustering and quantitative analysis of white matter fiber tracts. Inf Process Med Imaging. 2007; 20:372–383. [PubMed: 17633714]

Mahoney CJ, Ridgway GR, Malone IB, et al. Profiles of white matter tract pathology in frontotemporal dementia. Hum Brain Mapp. 2014; 35:4163–4179. [PubMed: 24510641]

Massimo L, Powers C, Moore P, et al. Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. Dement Geriatr Cogn Disord. 2009; 27:96–104. [PubMed: 19158440]

Matsuo K, Mizuno T, Yamada K, et al. Cerebral white matter damage in frontotemporal dementia assessed by diffusion tensor tractography. Neuroradiology. 2008; 50:605–611. [PubMed: 18379765]

McMillan CT, Brun C, Siddiqui S, et al. White matter imaging contributes to the multimodal diagnosis of frontotemporal lobar degeneration. Neurology. 2012; 78:1761–1768. [PubMed: 22592372]

McMillan CT, Irwin DJ, Avants BB, et al. White matter imaging helps dissociate tau from TDP-43 in frontotemporal lobar degeneration. J Neurol Neurosurg Psychiatry. 2013; 84:949–955. [PubMed: 23475817]

Mori S, Crain BJ, Chacko VP, et al. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol. 1999; 45:265–269. [PubMed: 9989633]

Mourik JC, Rosso SM, Niermeijer MF, et al. Frontotemporal dementia: behavioral symptoms and caregiver distress. Dement Geriatr Cogn Disord. 2004; 18:299–306. [PubMed: 15305107]

Neumann M, Kwong LK, Truax AC, et al. TDP-43-positive white matter pathology in frontotemporal lobar degeneration with ubiquitin-positive inclusions. J Neuropathol Exp Neurol. 2007; 66:177–183. [PubMed: 17356379]

Peters F, Perani D, Herholz K, et al. Orbitofrontal dysfunction related to both apathy and disinhibition in frontotemporal dementia. Dement Geriatr Cogn Disord. 2006; 21:373–379. [PubMed: 16534207]

Rascovsky K, Hodges JR, Knopman D, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. Brain. 2011; 134:2456–2477. [PubMed: 21810890]

Rosen HJ, Allison SC, Schauer GF, et al. Neuroanatomical correlates of behavioural disorders in dementia. Brain. 2005; 128:2612–2625. [PubMed: 16195246]

Seeley WW, Crawford RK, Zhou J, et al. Neurodegenerative diseases target large-scale human brain networks. Neuron. 2009; 62:42–52. [PubMed: 19376066]

Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. J Neurosci. 2007; 27:2349–2356. [PubMed: 17329432]

Smith SM, Jenkinson M, Johansen-Berg H, et al. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. NeuroImage. 2006; 31:1487–1505. [PubMed: 16624579]

Talairach, J.; Tournoux, P. Co-planar stereotaxic atlas of the human brain. New York, NY: Thieme; 1988.

Tighe SK, Oishi K, Mori S, et al. Diffusion tensor imaging of neuropsychiatric symptoms in mild cognitive impairment and Alzheimer's dementia. J Neuropsychiatry Clin Neurosci. 2012; 24:484–488. [PubMed: 23224456]

Vilalta-Franch J, López-Pousa S, Calvó-Perxas L, et al. Psychosis of Alzheimer disease: prevalence, incidence, persistence, risk factors, and mortality. Am J Geriatr Psychiatry. 2013; 21:1135–1143. [PubMed: 23567368]

Vink M, Kahn RS, Raemaekers M, et al. Function of striatum beyond inhibition and execution of motor responses. Hum Brain Mapp. 2005; 25:336–344. [PubMed: 15852388]

Wakana S, Jiang H, Nagae-Poetscher LM, et al. Fiber tract-based atlas of human white matter anatomy. Radiology. 2004; 230:77–87. [PubMed: 14645885]

Whitwell JL, Avula R, Senjem ML, et al. Gray and white matter water diffusion in the syndromic variants of frontotemporal dementia. Neurology. 2010; 74:1279–1287. [PubMed: 20404309]

Whitwell JL, Jack CR Jr, Parisi JE, et al. Imaging signatures of molecular pathology in behavioral variant frontotemporal dementia. J Mol Neurosci. 2011; 45:372–378. [PubMed: 21556732]

Yushkevich PA, Zhang H, Simon TJ, et al. Structure-specific statistical mapping of white matter tracts. NeuroImage. 2008; 41:448–461. [PubMed: 18407524]

Zamboni G, Huey ED, Krueger F, et al. Apathy and disinhibition in frontotemporal dementia: insights into their neural correlates. Neurology. 2008; 71:736–742. [PubMed: 18765649]

Zhang H, Avants BB, Yushkevich PA, et al. High-dimensional spatial normalization of diffusion tensor images improves the detection of white matter differences: an example study using amyotrophic lateral sclerosis. IEEE Trans Med Imaging. 2007; 26:1585–1597. [PubMed: 18041273]

Zhang Y, Schuff N, Ching C, et al. Joint assessment of structural, perfusion, and diffusion MRI in Alzheimer's disease and frontotemporal dementia. Int J Alzheimers Dis. 2011; 2011:546871. Available at http://dx.doi.org/10.4061/2011/546871. [PubMed: 21760989]

Zhang Y, Schuff N, Du AT, et al. White matter damage in frontotemporal dementia and Alzheimer's disease measured by diffusion MRI. Brain. 2009; 132:2579–2592. [PubMed: 19439421]

Zhang, H.; Yushkevich, PA.; Rueckert, D., et al. A computational white matter atlas for aging with surface-based representation of fasciculi. In: Fischer, B.; Dawant, BM.; Lorenz, C., editors. Biomedical Image Registration: Lecture Notes in Computer Science; Proceedings of the 4th International Workshop; Lübeck, Germany: Springer-Verlag; 2010. p. 83-90.

Zhou J, Greicius MD, Gennatas ED, et al. Divergent network connectivity changes in behavioural variant frontotemporal dementia and Alzheimer's disease. Brain. 2010; 133:1352–1367. [PubMed: 20410145]

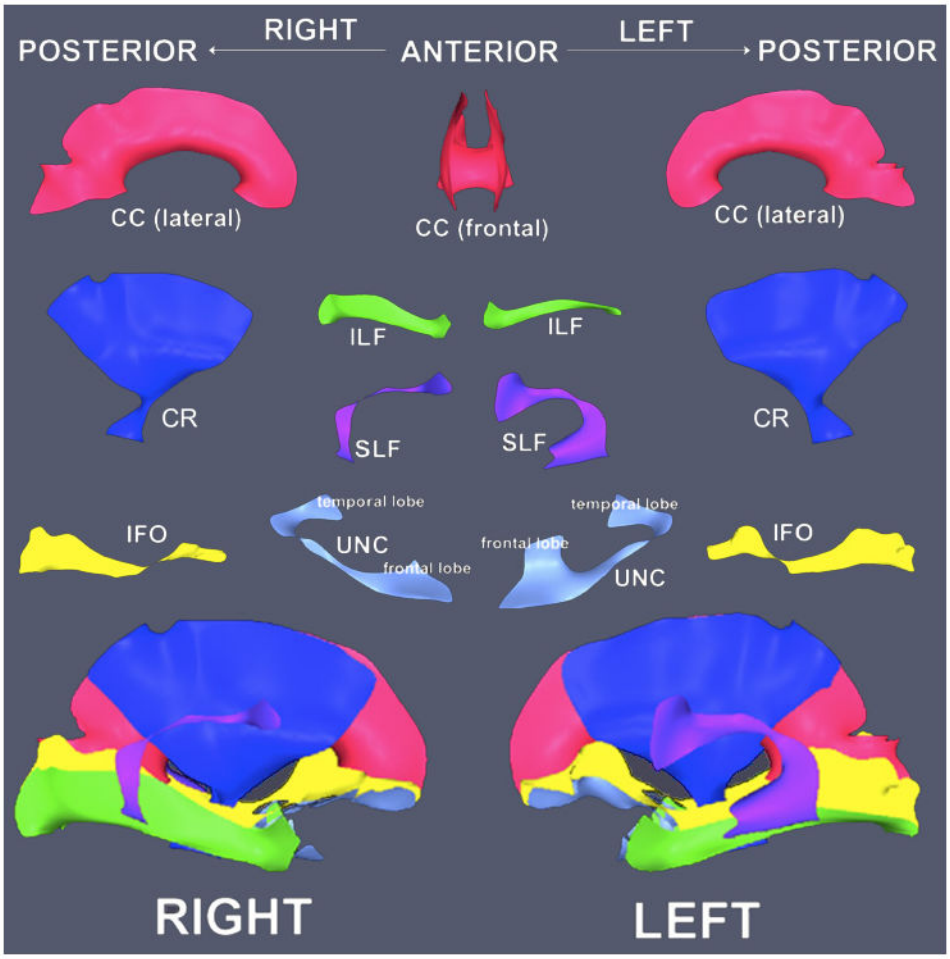

FIGURE 1.

Orientation diagram of white matter tract models based on a template of healthy aging. Upper sections: Each tract model is shown in isolation. The models' arrangement corresponds to the visualizations of our results. The uncinate fasciculus (UNC) models are rotated relative to the anatomic arrangement, to display the surfaces more effectively. Lower section: The tract models are shown assembled in anatomic context. CC = corpus callosum. CR = corona radiata. ILF = inferior longitudinal fasciculus. SLF = superior longitudinal fasciculus. IFO = inferior fronto-occipital fasciculus. UNC = uncinate fasciculus.

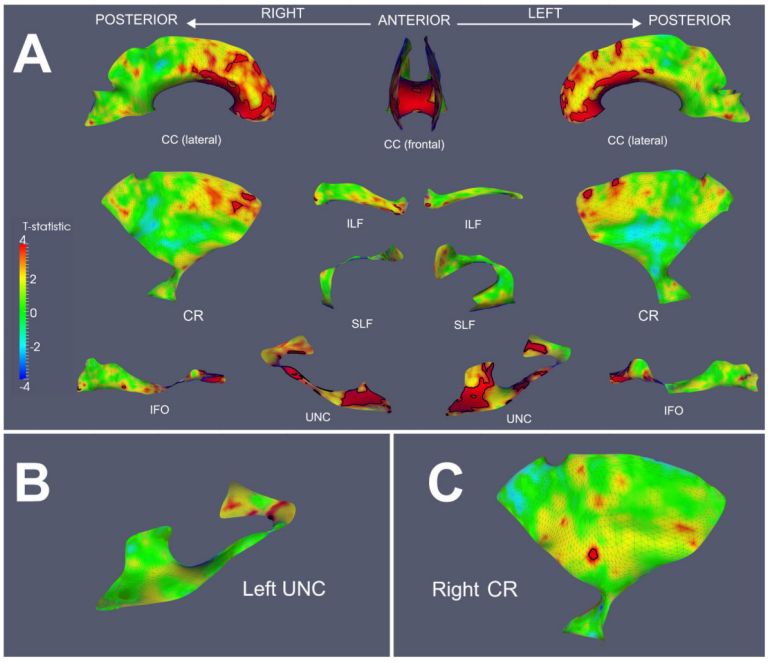

FIGURE 2.

Fractional anisotropy (FA) reductions and correlations with apathy and disinhibition in our 11 patients with behavioral variant frontotemporal dementia (bvFTD). Statistically significant clusters are outlined in black. Panel A: Tract-specific analysis shows areas where FA was significantly lower in the patients with bvFTD than the control group. Panel B: Tract-specific regression analysis in bvFTD correlates FA with the apathy score. Panel C: Tract-specific regression analysis in bvFTD correlates FA with the disinhibition score. CC = corpus callosum. CR = corona radiata. ILF = inferior longitudinal fasciculus. SLF = superior longitudinal fasciculus. IFO = inferior fronto-occipital fasciculus. UNC = uncinate fasciculus.

TABLE 1

Neuropsychological Test Performance in 11 Patients with Behavioral Variant Frontotemporal Dementia

	Mean (Standard Error of the Mean)		
Neuropsychiatric Inventory[1]	**Frequency**	**Severity**	**Frequency-by-Severity**
Apathy/indifference	2.5 (0.5)	1.6 (0.3)	5.2 (1.3)
Disinhibition	2.2 (0.3)	1.6 (0.2)	4.0 (1.1)
Delusions	0.3 (0.3)	0.3 (0.3)	0.5 (0.4)
Hallucinations	0.2 (0.6)	0.2 (0.4)	0.5 (0.5)
Depression/dysphoria	1.0 (0.4)	0.6 (0.3)	1.6 (0.8)
Anxiety	1.8 (0.2)	1.0 (0.2)	2.6 (0.8)
Irritability/lability	2.0 (0.3)	1.3 (0.2)	3.2 (0.8)
Agitation	1.7 (0.2)	1.2 (0.2)	2.6 (0.7)
Euphoria/elation	1.6 (0.3)	0.7 (0.3)	2.2 (0.9)
Aberrant motor behavior	2.7 (0.2)	1.4 (0.3)	4.2 (1.0)
Sleep/nighttime behavior	1.9 (0.4)	0.7 (0.2)	2.2 (0.6)
Appetite/eating	3.1 (0.2)	1.9 (0.2)	6.7 (1.2)
Mini-Mental State Examination[2] (maximum 30)		25.0 (1.4)	
Philadelphia Brief Assessment of Cognition[3]			
Executive scale (maximum 17)*		8.7 (1.1)	
Language scale (maximum 19)*		14.5 (1.3)	
Visual scale (maximum 18)*		15.1 (1.2)	
Memory scale (maximum 21)*		11.9 (2.0)	
Behavioral scale (maximum 18)†		10.9 (1.1)	
Total score (maximum 93)*		60.9 (4.5)	

*Scores for 9 patients.

†Score for 10 patients.

[1]Cummings et al, 1994.

[2]Folstein et al, 1975.

[3]Libon et al, 2011.