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Concurrent white and gray matter degeneration of disease-specific networks in early-stage Alzheimer's disease and behavioral variant frontotemporal dementia

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ABSTRACT

This study investigates regional coherence between white matter (WM) microstructure and gray matter (GM) volume and perfusion measures in Alzheimer's disease (AD) and behavioral variant frontotemporal dementia (bvFTD) using a correlational approach. WM-GM coherence, compared with controls, was stronger between cingulum WM and frontotemporal GM in AD, and temporoparietal GM in bvFTD. In addition, in AD compared with controls, coherence was stronger between inferior fronto-occipital fasciculus WM microstructure and occipital GM perfusion. In this first study assessing regional WM-GM coherence in AD and bvFTD, we show that WM microstructure and GM volume and perfusion measures are coherent, particularly in regions implicated in AD and bvFTD pathology. This indicates concurrent degeneration in disease-specific networks. Our methodology allows for the detection of incipient abnormalities that go undetected in conventional between-group analyses.

1. Introduction

Alzheimer's disease (AD) and behavioral variant frontotemporal dementia (bvFTD) are 2 common types of presenile dementia (onset ≤65 years; Koedam et al., 2010). These diseases are characterized by distinct abnormalities in gray matter (GM) and white matter (WM), as measured with magnetic resonance imaging (MRI; Acosta-Cabronero et al., 2010; Du et al., 2006; Hu et al., 2010; Mahoney et al., 2014; Rabinovici et al., 2007; Zhang et al., 2009). Although regional relationships between GM volume and perfusion have been widely studied in AD and bvFTD (Benedictus et al., 2014; Bron et al., 2014; Dashjamts et al., 2011; Mak et al., 2012; Shimizu et al., 2010; Steketee et al., 2016; Tosun et al., 2012; Wang et al., 2013), it is still largely unclear whether and how WM and GM abnormalities are related. One hypothesis is that WM and GM abnormalities develop in a Wallerian-like degenerative manner, in which GM cell death leads to the degeneration of WM tracts connecting affected GM regions. Another possible mechanism is that WM degeneration occurs independently from GM volume loss and/or hypoperfusion (Amlien and Fjell, 2014). However, because both diseases are characterized by specific WM and GM abnormalities, it is conceivable that these abnormalities do not occur in isolation, but that they co-occur in the context of a common disease process. Regionally concurrent degeneration would then be reflected in regional coherence of abnormalities in WM and GM.

Thus far, relationships between abnormalities in WM microstructure and GM volume have been found to be inconsistent in AD (Agosta et al., 2011; Alves et al., 2012; Lee et al., 2012; Mielke et al., 2012; Wang et al., 2012), whereas in bvFTD WM microstructural abnormalities have been consistently found to exceed GM volume loss (Avants et al., 2010; Mahoney et al., 2014; Whitwell et al., 2010; Zhang et al., 2013). One study looked at the relationship between WM microstructure, GM volume, and GM perfusion in AD and bvFTD (Zhang et al., 2011), and confirmed that WM microstructure is more severely affected in bvFTD than in AD. In addition, they

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confirmed that GM volume loss and WM microstructural abnormalities in bvFTD exceed GM hypoperfusion, whereas in AD, the degree of (micro) structural abnormalities and GM hypoperfusion is similar. However, this study did not assess the spatial relationships between WM microstructure and GM measures. This precludes the demonstration of possible regional relationships between WM and GM abnormalities, which is of particular interest given their disease-specific regional distribution. One study (Lacalle-Aurioles et al., 2016) investigated the regional relationship between WM and GM abnormalities, but limited their investigation to temporoparietal WM-GM relationships in AD, hence leaving whole-brain regional coherence in both AD and bvFTD unexplored. In this study, we aimed to establish whether there is coherence between regional abnormalities of WM microstructure and GM volume and perfusion in AD and in bvFTD. First, we assessed abnormalities of WM microstructure, GM volume, and GM perfusion for each measure separately. Second, we correlated WM measures in affected tracts with volume and perfusion in the GM regions at either end of the tract.

2. Methods

2.1. Participants

Patients were recruited at the Alzheimer Centre Southwest Netherlands and included in the analysis if they were clinically diagnosed with AD (McKhann et al., 2011) or bvFTD (Rascovsky et al., 2011), had an age of 45–70 years, and a mini-mental state examination (MMSE [Folstein et al., 1975]) score of 20 or more. In our memory clinic, it is a common practice to screen for genetic mutations only in case of a positive family history for dementia. In the clinical sample of this study consisting of 9 bvFTD patients, 3 patients were known to have a genetic mutation (2 MAPT, 1 C9orf72).

Patient exclusion criteria were other causes of dementia, other neurological disorders, psychiatric diagnosis, contraindications for MRI, and expected loss to follow up within 1 year.

Healthy age and gender-matched controls with an age between 45 and 70 years, and without psychiatric or neurological history, were recruited from patient peers and through advertisement. Both patients and controls underwent a full neuropsychological assessment evaluating attention and concentration, executive functioning, memory, language, social cognition, and constructive and visuospatial skills and MMSE. The MMSE was assessed in controls after the MRI scan by the researcher.

The study was approved by the local medical ethics committee, and all participants gave written informed consent.

2.2. Image acquisition

Scanning was performed on a 3T Discovery MR750 system (GE Healthcare, Milwaukee, WI, USA).

2.2.1. Diffusion imaging

DTI was acquired with 25 noncollinear directions using a spin echo planar imaging sequence and with full coverage of the supratentorial brain (echo time [TE] set to minimum with range 81.9ms–90.8 ms, repetition time (TR) 7.9 ms, voxel size 1.9 × 1.9 × 2.5 mm^3 with a 240-mm^2 field of view (FOV), array spatial sensitivity encoding technique acceleration factor 2, flip angle 90°, maximum b-value 1000 s/mm^2, 3 nondiffusion-weighted volumes, 59 axial slices per volume, and total acquisition time 3:50 minutes).

2.2.2. Structural imaging

A high-resolution 3-dimensional (3D) inversion recovery fast-spoiled gradient echo T1-weighted (T1w) image was acquired for GM volumetric assessment with TE 3.06 ms, TR 7.90 ms, inversion time 450 ms, isotropic voxel size 1 mm^3 with a 24-mm^2 FOV, array spatial sensitivity encoding technique acceleration factor 2, flip angle 12°, 176 sagittal slices, and total acquisition time 4:41 minutes.

2.2.3. Perfusion imaging

Perfusion images were acquired using whole-brain 3D pseudo-continuous arterial spin labeling (ASL), which is currently the recommended sequence for clinical use (Alsop et al., 2015; interleaved fast spin-echo stack-of-spiral readout of 512 sampling points on 8 spirals, TE 10.5 ms, TR 4632 ms, isotropic voxel size 3.3 mm^3 with a 240-mm^2 FOV, 36 axial slices, number of excitations 3, total acquisition time 4:29 minutes; with background suppression, postlabel delay 1525 ms, and labeling duration 1450 ms). The labeling plane was positioned 9 cm below the anterior commissure-posterior commissure line.

2.3. Demographical analysis

Using SPSS Statistics, version 20.0 (IBM, NY, USA), gender differences across groups were assessed using chi-square tests and age differences using 1-way ANOVA, with Bonferroni correction for multiple comparisons. As MMSE was not normally distributed across groups (Shapiro-Wilk test $p < 0.05$), a nonparametric Kruskal-Wallis test was used to assess differences between groups, with Dunn-Bonferroni correction for multiple comparisons ($p < 0.05$).

2.4. DTI processing and analysis

Data were analyzed using FMRIB Software Library (FSL5, Oxford, UK) (Jenkinson et al., 2012; Smith et al., 2004; Woolrich et al., 2009). Data were corrected for motion and eddy currents using Eddy Correct and then skull-stripped using the brain extraction tool (Smith, 2002). Two analyses were performed. First, tract-based spatial statistics was performed to identify affected WM tracts in AD and bvFTD. Second, tractography was performed to obtain quantitative diffusion metrics per WM tract to correlate WM measures with GM measures.

2.4.1. Tract-based spatial statistics

First, diffusion tensors were reconstructed using DTIFit (Behrens et al., 2003), allowing computation of a fractional anisotropy (FA) image for each participant. Second, using whole-brain tract-based spatial statistics (Smith et al., 2006), WM tracts showing FA abnormalities were identified.

Group differences in FA were tested with Randomise (Winkler et al., 2014), using 5000 nonparametric permutations, threshold-free cluster enhancement (Smith and Nichols, 2009), and multiple comparison correction. Default settings for skeletonized data were applied.

Using the general linear model toolbox, a 1-way ANOVA design with 3 groups (AD ≠ bvFTD ≠ controls) was defined. Six post hoc t contrasts (AD > controls, controls > AD, bvFTD > controls, controls > bvFTD, AD > bvFTD, bvFTD > AD) were constructed.

To identify post hoc t test results within the boundaries of the f test results, common binary masks were created using FSLmaths. First, for the f test and all t tests, a binary mask was created ($p = 0.95$). Second, each t test binary mask was multiplied with the f test binary mask, resulting in a common binary mask for every t test. Last, cluster size (voxels [k] ≥ 50) was extracted from all t test common binary masks using the Cluster tool in FSL.

Using FSLview, results were visualized with the implemented John Hopkins University (JHU) white-matter tractography atlas and the JHU ICBM-DTI-81 white-matter labels. WM tracts showing