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Single-subject classification of presymptomatic frontotemporal dementia mutation carriers using multimodal MRI

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ABSTRACT

Background: Classification models based on magnetic resonance imaging (MRI) may aid early diagnosis of frontotemporal dementia (FTD) but have only been applied in established FTD cases. Detection of FTD patients in earlier disease stages, such as presymptomatic mutation carriers, may further advance early diagnosis and treatment. In this study, we aim to distinguish presymptomatic FTD mutation carriers from controls on an individual level using multimodal MRI-based classification.

Methods: Anatomical MRI, diffusion tensor imaging (DTI) and resting-state functional MRI data were collected in 55 presymptomatic FTD mutation carriers (8 microtubule-associated protein Tau, 35 progranulin, and 12 chromosome 9 open reading frame 72) and 48 familial controls. We calculated grey and white matter density features from anatomical MRI scans, diffusivity features from DTI, and functional connectivity features from resting-state functional MRI. These features were applied in a recently introduced multimodal behavioural variant FTD (bvFTD) classification model, and were subsequently used to train and test unimodal and multimodal carrier-control models. Classification performance was quantified using area under the receiver operator characteristic curves (AUC).

Results: The bvFTD model was not able to separate presymptomatic carriers from controls beyond chance level (AUC = 0.570, p = 0.11). In contrast, one unimodal and several multimodal carrier-control models performed significantly better than chance level. The unimodal model included the radial diffusivity feature and had an AUC of 0.646 (p = 0.021). The best multimodal model combined radial diffusivity and white matter density features (AUC = 0.680, p = 0.005).

Conclusions: FTD mutation carriers can be separated from controls with a modest AUC even before symptom-onset, using a newly created carrier-control classification model, while this was not possible using a recent bvFTD classification model. A multimodal MRI-based classification score may therefore be a useful biomarker to aid earlier FTD diagnosis. The exclusive selection of white matter features in the best performing model suggests that the earliest FTD-related pathological processes occur in white matter.

Abbreviations: 3DT$_1$w, 3-dimensional T$_1$-weighted; AUC, Area under the receiver operating characteristics curve; AxD, Axial diffusivity; *C9orf72*, Chromosome 9 open reading frame 72; DTI, Diffusion tensor imaging; DWI, Diffusion-weighted imaging; FA, Fractional anisotropy; FCor, Full correlations; (bv)FTD, (behavioural variant) Frontotemporal dementia; GM, Grey matter; GMD, Grey matter density; *GRN*, Progranulin; ICA, Independent component analysis; *MAPT*, Microtubule-associated protein Tau; MD, Mean diffusivity; MMSE, Mini-mental state examination; (rs-f)MRI, (resting-state functional) Magnetic resonance imaging; Pcor, Sparse L1-regularised partial correlations; RD, Radial diffusivity; ROC, Receiver operating characteristics; TBSS, Tract-based spatial statistics; WM, White matter; WMD, White matter density

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1. Introduction

Frontotemporal lobar degeneration is a common cause of early-onset dementia with a similar prevalence to Alzheimer's disease in the presenile population (Ratnavalli et al., 2002; Harvey et al., 2003; Rabinovici and Miller, 2010; Seelaar et al., 2011; Rascovsky et al., 2011). Although there are clinical disease criteria for the different clinical variants of frontotemporal dementia (FTD) (Rascovsky et al., 2011; Gorno-Tempini et al., 2011), diagnosis is often complicated and delayed by clinical heterogeneity. This hinders clinicians in providing accurate prognosis, effective disease management and developing new treatments (Mohs et al., 2001; Mendez et al., 2007; Mendez, 2009; Pressman and Miller, 2014).

Multimodal magnetic resonance imaging (MRI) has been suggested as a promising biomarker to improve on diagnostic standards in FTD. In FTD patients, MRI revealed specific patterns of neurodegeneration, involving grey matter (GM) and white matter (WM) atrophy (Whitwell and Jack, 2005; Whitwell et al., 2012; Whitwell et al., 2015; Chao et al., 2007; Rabinovici et al., 2008; Seeley et al., 2009; Frings et al., 2014; Zhang et al., 2011; Pan et al., 2012; Risacher and Saykin, 2013; Möller et al., 2015a; Möller et al., 2015b), differences in diffusion tensor imaging (DTI) measures (Zhang et al., 2011; Möller et al., 2015b; Zhang et al., 2009; Agosta et al., 2012; McMillan et al., 2012; McMillan et al., 2014; Mahoney et al., 2014; Daianu et al., 2016), and differences in functional connectivity (Zhou et al., 2010; Zhou and Seeley, 2014; Farb et al., 2013; Lee et al., 2014; Hafkemeijer et al., 2015; Hafkemeijer et al., 2016).

These patterns have subsequently been utilised on an individual level to create MRI-based classification algorithms that can discriminate between FTD patients and control subjects (McMillan et al., 2014; Davatzikos et al., 2008; Raamana et al., 2014; Koikkalainen et al., 2016; Wang et al., 2016; Meyer et al., 2017; Bron et al., 2017; Bouts et al., 2018). Accurate classification of FTD patients using MRI measures is an important step towards a more substantiated diagnostic standard. However, most classification models are based on established FTD cases, limiting generalisability in patients who are at an earlier disease stage. Still, detection of these early-stage FTD cases is necessary to facilitate precise subject recruitment into clinical trials and potential early treatment with disease-modifying drugs (Huey et al., 2008).

In order to characterise FTD pathophysiology at an earlier stage, presymptomatic carriers of autosomal dominant FTD gene mutations were compared to controls in MRI group analyses (Borroni et al., 2008; Whitwell et al., 2011; Borroni et al., 2012; Rohrer et al., 2013; Premi et al., 2014; Dopper et al., 2014; Rohrer et al., 2015; Lee et al., 2017; Bertrand et al., 2017; Papma et al., 2017; Cash et al., 2018). Carriers of the three most common FTD gene mutations microtubule-associated protein Tau (*MAPT*), progranulin (*GRN*), and chromosome 9 open reading frame 72 (*C9orf72*) show brain alterations on MRI, even well before symptom onset. In these subjects, WM diffusivity changes (Borroni et al., 2008; Dopper et al., 2014; Papma et al., 2017) and functional connectivity changes (Whitwell et al., 2011; Borroni et al., 2012; Premi et al., 2014; Dopper et al., 2014) are often, but not exclusively (Lee et al., 2017; Bertrand et al., 2017; Papma et al., 2017), found in the absence of GM atrophy, suggesting that changes in the functional architecture and WM tracts may precede structural deterioration in the GM (Rohrer et al., 2013). Nonetheless, multi-centre analyses of a large international cohort show GM loss in *MAPT*, *GRN* and *C9orf72* carriers even before conversion (Rohrer et al., 2015; Cash et al., 2018). Although these presymptomatic group differences give insight into the pathophysiological mechanisms of FTD, individual heterogeneity complicates its utility in FTD diagnosis. Therefore, translation from group differences to single-subject classification models is imperative.

The present study brings two research areas together: we combine machine learning with presymptomatic FTD mutation carriers to study individual classification of FTD-pathology at an early stage. Our aim is to distinguish individual presymptomatic FTD mutation carriers from healthy controls using multimodal MRI.

2. Methods

2.1. Design

In order to distinguish presymptomatic FTD mutation carriers from controls, we applied two models. First, we applied a recent behavioural variant FTD (bvFTD)-control classification model (Bouts et al., 2018) to our MRI data to investigate whether the model separates presymptomatic mutation carriers from controls. We shall refer to this model as the “bvFTD model”. In a second analysis, we trained a new classification model on the presymptomatic mutation carriers and controls' data, which we evaluated using cross-validation. We shall refer to this model as the “carrier-control model”. MRI pre-processing, feature selection and classification were performed identically to previous work (Bouts et al., 2018).

2.2. Participants

This retrospective study partially included previously published (Dopper et al., 2014; Papma et al., 2017; Jiskoot et al., 2016) and newly acquired data from the Erasmus Medical Centre and Leiden University Medical Centre. Participants and clinical investigators were blinded to the participants' DNA status. The study was conducted in accordance with regional regulations and the Declaration of Helsinki. The Erasmus Medical Centre and Leiden University Medical Centre local medical ethics committees approved the study, and every participant provided written informed consent.

For the current study, we included 55 presymptomatic FTD mutation carriers (8 *MAPT*, 35 *GRN*, 12 *C9orf72*) and 48 healthy familial controls (6 *MAPT* family, 31 *GRN* family and 11 *C9orf72* family) between May 2010 and March 2016. These subjects were recruited from a cohort of healthy first-degree relatives of FTD patients with either a *MAPT*, *GRN* or *C9orf72* mutation (FTD-Risk Cohort; FTD-RisC) and visited the Erasmus Medical Centre for a one-day assessment in order to ascertain asymptomatic status, collect clinical data, and determine DNA status as described before (Dopper et al., 2014; Papma et al., 2017; Jiskoot et al., 2016). Participants were considered asymptomatic in the absence of (1) behavioural, cognitive, or neuropsychiatric change reported by the participant or knowledgeable informant, (2) cognitive disorders on neuropsychiatric tests, (3) motor neuron disease signs on neurologic examination, and (4) other FTD (Rascovsky et al., 2011; Gorno-Tempini et al., 2011) or amyotrophic lateral sclerosis (Ludolph et al., 2015) criteria. Healthy controls were assumed to have equal FTD risk as the general population. For a more detailed description of the recruitment protocol, see earlier work (Dopper et al., 2014; Papma et al., 2017; Jiskoot et al., 2016). Inclusion criteria for the current study were: age between 40 and 70 years, and availability of a T_1-weighted 3-dimensional MRI ($3DT_1w$) scan, a diffusion-weighted imaging (DWI) dataset, and a resting-state fMRI T_2*-weighted (rs-fMRI) scan. Exclusion criteria were: current or past neurologic or psychiatric disorders, history of drug abuse, large image artefacts, and gross brain pathology other than atrophy.

For details on the sample on which the bvFTD model was trained, please refer to Bouts et al. (2018) (Bouts et al., 2018). In short, 23 bvFTD patients and 35 controls between 40 and 80 years old were included to undergo a clinical assessment and MRI between November 2009 and November 2012. The MRI acquisition protocol was similar to the protocol applied in the current sample of carriers and controls. Image processing steps were identical to processing steps in the current sample.