Neuroimaging biomarkers in genetic frontotemporal dementia : towards a timely diagnosis

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Chapter 1

General introduction

Background

Frontotemporal dementia (FTD) is a common and devastating form of dementia that often occurs in the presenile population, i.e., aged under 65 years (Ratnavalli et al., 2002; Harvey et al., 2003; Hogan et al., 2016). It was first described in 1892 by Arnold Pick in a patient with aphasia and asymmetric temporal lobe atrophy (Pick, 1892). Today, FTD represents a diverse spectrum of clinical syndromes. The disease is typically characterised by progressive degeneration of the frontal and temporal lobes, leading to behavioural disorders and language deficits (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). However, FTD patients may additionally develop symptoms of amyotrophic lateral sclerosis (ALS; Lomen-Hoerth et al., 2002), corticobasal syndrome (CBS), or progressive supranuclear palsy (PSP; Josephs et al., 2006). Moreover, considerable clinical overlap exists with other dementias and psychiatric disorders (Krudop et al., 2015). For example, Alzheimer's disease (AD) patients may exhibit behavioural symptoms (Johnson et al., 1999), whereas FTD patients may present with memory deficits (Graham et al., 2005). As such, clinical diagnosis is challenging, especially in the initial stages of the disease.

Early-stage and accurate diagnosis is important for establishing a prognosis and organising patient care. Furthermore, early-stage diagnosis is crucial for the development and application of disease modifying treatments. Most dementia treatments aim to reverse the neuropathological pathways that lead up to neuronal cell death, for example through inhibition of pathological proteins' accumulation (Cummings et al., 2018). The ability to diagnose patients before they develop marked cerebral atrophy is therefore essential to increase the window of opportunity to test these potential treatments. This dissertation aims to establish neuroimaging biomarkers that are sensitive to early-stage FTD.

Frontotemporal dementia heterogeneity

FTD is a many-faced disease. There are multiple distinct clinical FTD syndromes, and several types of underlying neuropathological substrates. Furthermore, FTD has symptomatic overlap with psychiatric diseases and different dementia types. To illustrate FTD heterogeneity, **Figure 1.1** shows a simplification of the relationships between the clinical FTD syndromes, the underlying pathology, and genetics.

Clinical heterogeneity

The most common FTD manifestation is behavioural variant FTD (bvFTD), which accounts for 50–80% of all FTD cases (Johnson et al., 2005; Seelaar et al., 2008; Hogan et al., 2016). Typically, bvFTD patients show signs of disinhibition, apathy, loss of empathy, compulsive behaviour, dietary changes, and/or executive dysfunction. On magnetic resonance imaging (MRI), bvFTD is characterised by frontal and/or anterior temporal atrophy (Rascovsky et al., 2011).

The other main FTD manifestation is primary progressive aphasia (PPA), which can be subdivided into three variants: non-fluent variant PPA (nfvPPA), semantic variant PPA (svPPA), and logopenic variant PPA (lvPPA). The non-fluent variant is characterised by agrammatism, apraxia of speech, and, in later stages, mutism. However, nfvPPA patients usually have spared single-word comprehension and object knowledge. In these patients, brain atrophy is predominantly seen in the left posterior fronto-insula on MRI (Gorno-Tempini et al., 2011; Spinelli et al., 2017). Patients with svPPA typically have impaired confrontation naming, single-word comprehension, object knowledge, and surface dyslexia or dysgraphia. Repetition and speech production in terms of

grammar and motor speech are usually spared. These patients show bilateral atrophy of the ventral and lateral parts of the anterior temporal lobes on MRI, though the left side is usually more strongly afflicted (Gorno-Tempini et al., 2011). The logopenic variant is the most recently described PPA variant, and is characterised by impaired single-word retrieval, sentence repetition deficits, and phonologic errors. However, single-word comprehension, object knowledge, and motor speech are preserved. Patients with lvPPA usually show brain atrophy in left temporo-parietal junction areas, such as the posterior temporal, supramarginal, and angular gyri (Gorno-Tempini et al., 2011; Spinelli et al., 2017).

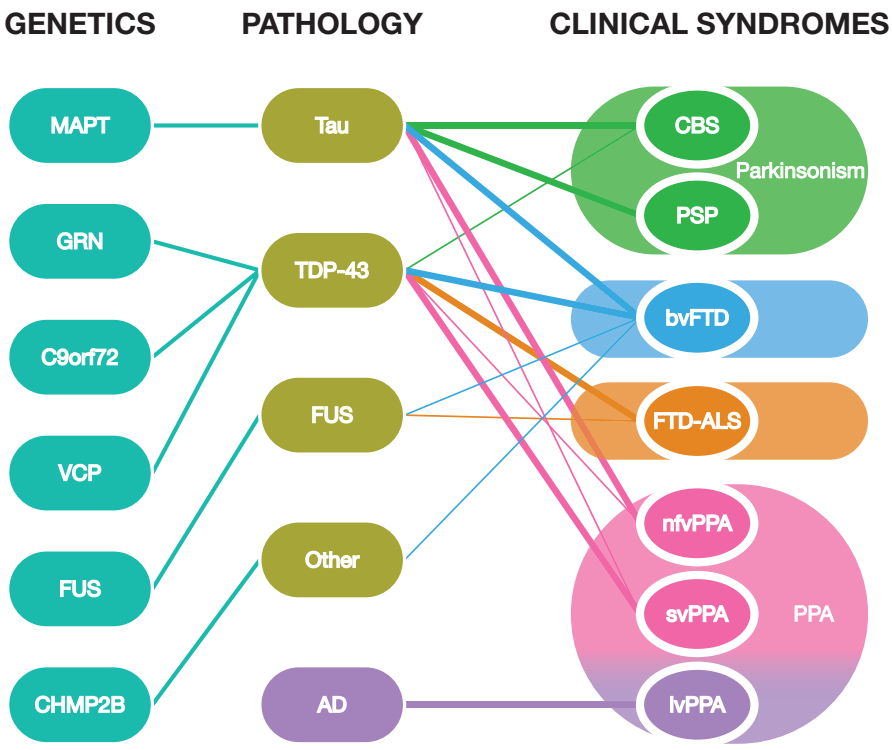

Figure 1.1 Heterogeneity in frontotemporal dementia.
This diagram features the complex relationships between the clinical FTD syndromes, the underlying pathology, and genetic causes. Thicker lines denote stronger relationships, e.g., svPPA patients usually have TDP-43 pathology, although patients may also show tau pathology (Josephs et al., 2011).
Genetics: *MAPT*, microtubule-associated protein tau; *GRN*, progranulin; *C9orf72*, chromosome 9 open reading frame 72; *VCP*, valosin-containing protein; *FUS*, fused in sarcoma gene; *CHMP2B*, charged multivesicular body protein 2b.
Pathology: TDP-43, transactive response DNA binding protein 43 kDa; FUS, fused in sarcoma protein; AD, Alzheimer's disease pathology.
Clinical syndromes: CBS, corticobasal syndrome; PSP, progressive supranuclear palsy; FTD, frontotemporal dementia; bvFTD, behavioural variant FTD; FTD-ALS, FTD with amyotrophic lateral sclerosis; PPA, primary progressive aphasia; nfvPPA, non-fluent variant PPA; svPPA, semantic variant PPA; lvPPA, logopenic variant PPA.
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In addition to cognitive disorders, some FTD patients develop atypical parkinsonian syndromes, such as CBS or PSP, while others develop ALS. Conversely, patients with CBS, PSP, and ALS may develop behavioural or language dysfunction (Kertesz et al., 2005). Clinically, CBS is characterised by unilateral rigidity, apraxia, myoclonus, and the alien hand phenomenon (Armstrong et al., 2013). PSP patients typically develop vertical gaze palsy, falls, axial rigidity, and pseudobulbar palsy (Boxer et al., 2017). ALS is a motor neuron disease characterised by progressive loss of upper and/or lower motor neurons, resulting in muscle weakness, fasciculations, and eventually immobility, dysphagia, and respiratory complications (Brooks et al., 2000).

Neuropathological heterogeneity

Underlying these clinical syndromes are three groups of neuropathological substrates, named after the protein inclusions found at autopsy: tau, transactive response DNA binding protein 43 kDa (TDP-43), and RNA binding protein fused in sarcoma (FUS). Together, tau, TDP-43, and FUS constitute the neuropathological umbrella term frontotemporal lobar degeneration (FTLD). As shown in **Figure 1.1**, FTLD pathologies generally have multiple associated clinical syndromes, and vice versa, though some clinicopathological associations are stronger than others. Therefore, determining which pathology underlies a certain clinical syndrome remains challenging (Josephs et al., 2011). Interestingly, lvPPA is usually caused by AD pathology, even though its clinical syndrome may be similar to nfvPPA and svPPA (Chare et al., 2014). This dissertation will primarily focus on the clinical FTD syndromes with FTLD pathology, i.e., bvFTD, nfvPPA, and svPPA.

Genetic heterogeneity

Around 25–50% of FTD patients have a positive family history for dementia or a related disorder, such as ALS or parkinsonism. Moreover, 10–30% of FTD patients have an autosomal dominant inheritance (Seelaar et al., 2008; Rohrer et al., 2009; Benussi et al., 2015). Several gene mutations have been identified that are associated with monogenic FTD. Most commonly, genetic FTD patients have a mutation in the microtubule-associated protein tau (*MAPT*) or progranulin (*GRN*) genes, or a chromosome 9 open reading frame 72 (*C9orf72*) repeat expansion. Other, more infrequently affected genes include valosin-containing protein (*VCP*), charged multivesicular body protein 2B (*CHMP2B*), and fused in sarcoma (*FUS*; Benussi et al., 2015). These gene mutations have an autosomal dominant inheritance pattern and are all highly penetrant. Therefore, roughly 50% of subjects from genetic FTD families will eventually develop FTD. Though pathogenic FTD mutations each lead to a specific FTLD pathology, patients with the same mutation may develop different clinical FTD syndromes (Benussi et al., 2015).

The significance of a timely diagnosis

Currently, there are no United States Food and Drug Administration (FDA-)approved therapies for FTD. In fact, most pharmacological treatments for FTD involve off-label use of psychotropic medication for symptomatic relief (Pressman & Miller, 2014). Recently, advances in the understanding of FTLD pathophysiology have led to increased efforts to develop disease modifying treatments. These treatments aim to inhibit, or reverse, underlying neuropathological processes to prevent neuronal cell death. For example, disease modifying treatments may aim to inhibit tau protein aggregation, stabilise microtubules, or increase progranulin levels. A comprehensive review of past and current clinical trials until 2019 involving the FTLD spectrum has been published recently (Logroscino et al., 2019). Due to their working mechanism, disease modifying treatments

have an optimal potential in early FTD disease stages, before atrophy occurs. However, inclusion criteria for clinical trials typically include FTD diagnosis based on the relevant diagnostic criteria (Gorno-Tempini et al., 2011; Rascovsky et al., 2011), in which brain atrophy on MRI is included as diagnostic criterion. FTD patients included in clinical trials therefore often have marked atrophy, reducing the potential benefit of treatments that aim to prevent cell death. The insensitivity of current diagnostic criteria to early disease stages therefore hinders the efforts to develop disease modifying treatments.

Diagnostic delay, calculated as the time between symptom onset and diagnosis, has been estimated between three and six years for bvFTD, around three years for nfvPPA, and around five years for svPPA (Hodges et al., 2003; Pasquier et al., 2004; Roberson et al., 2005). Given that the mean survival from symptom onset is estimated at roughly eight years for bvFTD, nfvPPA, and svPPA (Kansal et al., 2016), this diagnostic delay significantly shortens the window of opportunity for FTD disease modifying treatments. Multiple factors contribute to this delay. Most importantly, neuropsychological symptoms in early stages are not specific for FTD, and may be misinterpreted as manifestations of psychiatric disease (Pijnenburg et al., 2004), especially when the patient is relatively young. FTD patients are typically younger than patients with other types of dementia; the mean age of symptom onset is roughly 58 years for bvFTD, 64 years for nfvPPA, and 60 years for svPPA (Kansal et al., 2016). In other patients, symptoms may overlap with AD (Graham et al., 2005). Consequently, diagnosis may be delayed by one or two years even after patients are first referred to a neurologist or memory clinic (Pijnenburg et al., 2004). Diagnostic delay is also partly caused by patient delay. For example, bvFTD patients typically lack disease insight and can be reluctant to seek professional help (Neary et al., 1998; Pijnenburg et al., 2004).

In order to improve clinical trial efficacy through timely diagnosis, biomarkers are necessary that are sensitive to early-stage FTD-related pathological changes. Additionally, differential diagnostic biomarkers could power clinical trials through trial stratification (e.g., based on clinical FTD variant or underlying pathology), and disease progression biomarkers could facilitate more accurate evaluation of disease modifying treatments' effects.

MRI biomarkers in genetic frontotemporal dementia

Due to the autosomal dominant inheritance and high penetrance of pathogenic FTD mutations, genetic FTD families provide an ideal population to study the pathological mechanisms that underlie FTD in early stages of the disease, and to develop biomarkers for early FTD detection. Specifically, it is possible to follow mutation carriers from such families over time, while they are still in the 'presymptomatic' stage, i.e., before symptom onset.

In recent years, presymptomatic FTD mutation carriers of *MAPT*, *GRN*, and *C9orf72* repeat expansion have been increasingly investigated to find early changes with potential MRI-based (Borroni et al., 2008; Miyoshi et al., 2010; Whitwell et al., 2011a; Dopper et al., 2014; Rohrer et al., 2015; Lee et al., 2017; Papma et al., 2017; Bertrand et al., 2018; Cash et al., 2018; Jiskoot et al., 2018a, 2019; Panman et al., 2019), cognitive (Dopper et al., 2014; Rohrer et al., 2015; Jiskoot et al., 2016, 2018b; Papma et al., 2017; Bertrand et al., 2018), fluid (Meeter et al., 2016a, 2016b, 2018a, 2018b; Lehmer et al., 2017; Galimberti et al., 2018), and positron emission tomography (PET; Miyoshi et al., 2010; Jacova et al., 2013) biomarkers. Notably, application of MRI-based biomarkers in the clinic seems viable due to the non-invasive nature and ready availability of MRI. MRI-based biomarker candidates include grey matter and white matter structure, as well as functional connectivity. Grey matter structure can be analysed using voxel-based morphometry on structural MRI scans (Good et al., 2001; Douaud et al., 2007). White matter structure is usually tested using

diffusion tensor imaging (DTI), which measures the diffusion of water inside the brain (Smith et al., 2006). The directionality of water diffusion is often used as a proxy for white matter integrity, although this interpretation remains controversial (Wheeler-Kingshott & Cercignani, 2009). Functional connectivity is calculated from resting-state functional MRI (rs-fMRI), and sheds light on how different brain regions coactivate as distinct functional networks (Beckmann & Smith, 2004). Below, we briefly outline the reported presymptomatic changes in grey matter structure, white matter diffusion, and functional connectivity in the three most common pathogenic FTD mutations.

Microtubule-associated protein tau

Presymptomatic atrophy in *MAPT* mutation carriers is located in the temporal pole and hippocampus (Panman et al., 2019). In the white matter, presymptomatic *MAPT* mutation carriers predominantly show cross-sectional DTI abnormalities in the uncinate fasciculus (Dopper et al., 2014; Jiskoot et al., 2018a). These abnormalities increase over time in the uncinate fasciculus, and expand to the left anterior thalamic radiation and left inferior fronto-occipital fasciculus (Panman et al., 2019). Functional connectivity with the default mode network, a functional brain network involved in emotional processing, self-reference, and memory (Raichle, 2015), is decreased in the lateral temporal lobe and medial prefrontal cortex in presymptomatic *MAPT* mutation carriers, and is increased in the medial parietal lobe (Whitwell et al., 2011a).

Progranulin

Presymptomatic *GRN* mutation carriers do not typically show presymptomatic atrophy (Borroni et al., 2008; Dopper et al., 2014; Cash et al., 2018; Panman et al., 2019). White matter DTI abnormalities occur in the uncinate fasciculus, inferior fronto-occipital fasciculus (Borroni et al., 2008), the splenium, and in the anterior and posterior internal capsule (Jiskoot et al., 2018a). Functional connectivity is reduced in presymptomatic *GRN* mutation carriers in the default mode network and in the salience network, which is involved in emotional processing (Dopper et al., 2014).

Chromosome 9 open reading frame 72 repeat expansion

Presymptomatic differences in *C9orf72* repeat expansion carriers are more abundant and present at an earlier stage. Grey matter atrophy predominantly occurs in the thalamus, cerebellum, and insula, but also extends to other frontotemporal regions (Rohrer et al., 2015; Lee et al., 2017; Papma et al., 2017; Bertrand et al., 2018; Cash et al., 2018; Panman et al., 2019). White matter DTI abnormalities also include widespread areas, such as the corpus callosum, anterior thalamic radiation, corticospinal tract, and the superior and inferior longitudinal fasciculi (Lee et al., 2017; Papma et al., 2017; Bertrand et al., 2018; Jiskoot et al., 2018a; Panman et al., 2019). Functional connectivity is reduced in the salience network and the default mode network (Lee et al., 2017).

Clinical translation of biomarkers using machine learning

The group differences described above show that MRI-based biomarkers may be promising for the early detection of FTD. However, the clinical translation towards a diagnostic tool requires that biomarkers have discriminative value on the individual level, not merely on group-level. To harness the full potential of biomarkers on the individual level, artificial intelligence, or more specifically machine learning, can be applied. In machine learning, labelled data is used to train

a classifier to distinguish between groups, for instance between FTD patients and controls. Once the classifier is trained, it can be used to classify new subjects whose group label is unknown. An important characteristic is that classifiers can be trained on multiple inputs to increase performance by combining complementary information (Schouten et al., 2016). While machine learning allows for many different inputs, classifiers typically generate a single score per subject, allowing for a straightforward clinical implementation in the diagnostic work-up. Recently, MRI-based classifiers have been used to study the classification of FTD patients and controls. Classifiers based on grey matter volume (Raamana et al., 2014; Klöppel et al., 2015; Koikkalainen et al., 2016; Bron et al., 2017; Canu et al., 2017; Meyer et al., 2017; Bouts et al., 2018), white matter diffusion (Bron et al., 2017; Canu et al., 2017; Bouts et al., 2018), and functional connectivity (Canu et al., 2017; Bouts et al., 2018) perform well in the classification of FTD patients and controls. However, these classification studies were performed in patients with symptomatic FTD, and it is unknown whether these results generalise to earlier FTD disease stages. The accurate classification of early-stage FTD patients or presymptomatic FTD mutation carriers could facilitate early inclusion into clinical trials with disease modifying treatments, but is currently lacking.

Aims and outline of this dissertation

Based on group differences between FTD mutation carriers and non-carriers, MRI-based biomarkers in genetic FTD show promise for early FTD detection, which may in turn facilitate clinical trial efficiency. The main goal of this dissertation is to further the translation of potential MRI-based biomarkers for FTD towards clinical application by applying them in a single-subject classification setting analogous to a diagnostic test.

In **chapter 2**, we study MRI-based classification in a cross-sectional sample of presymptomatic FTD mutation carriers and non-carriers. To assess whether a classification model based on full-blown FTD generalises to the presymptomatic disease stage, we use a bvFTD classification model (Bouts et al., 2018) to classify presymptomatic FTD mutation carriers and non-carriers. Furthermore, we comprehensively evaluate the classification performance for different MRI features by training and testing unimodal and multimodal (i.e., based on multiple MRI features) carrier-control classification models.

In **chapter 3**, our aim is to evaluate the sensitivity of MRI-based classification to FTD-related changes over time. We apply the same bvFTD classification model on longitudinal data of FTD mutation carriers and non-carriers to obtain classification scores on multiple time points. We test whether longitudinal patterns differ between non-carriers, mutation carriers that remain presymptomatic within our study's follow-up time, and mutation carriers that 'convert' to FTD (i.e., develop FTD symptoms) during follow-up.

Chapter 4 describes the use of MRI-based classification to predict which FTD mutation carriers will convert to FTD within the timespan of four years, and which mutation carriers will remain presymptomatic. We aim to evaluate the prognostic value of MRI-based biomarkers to predict symptom onset in genetic FTD, since an accurate prognostic test for symptom onset could facilitate early inclusion of FTD mutation carriers into clinical trials.

The prevalence of FTD mutation carriers is relatively low. The combination of existing MRI data across centres would facilitate the pooling of subjects into larger cohorts, as well as unique study contrasts with rare groups. However, combining data from different scanners is problematic due to hardware, software, and environmental differences. In **chapter 5**, we aim to facilitate the

combination of existing rs-fMRI data from different centres through the reduction of structured noise. We apply a new noise removal method on rs-fMRI data of two groups of healthy controls from different sites to reduce scan site bias.

Another important step to develop MRI measures into specific biomarkers is to establish whether MRI changes in presymptomatic FTD mutation carriers are unique for this group, or whether they also exist in subjects at risk for different dementias, such as AD. In **chapter 6**, we jointly analyse *MAPT/GRN* mutation carriers vs. non-carriers, and apolipoprotein E ε4 (*APOE4*; the most important risk gene for AD) carriers vs. non-carriers to investigate whether early changes in risk mutation carriers of FTD and AD follow different patterns.

To conclude, we summarise and discuss the main findings of this dissertation in **chapter 7** and provide methodological considerations as well as recommendations for future research.