Neuroimaging biomarkers in genetic frontotemporal dementia : towards a timely diagnosis

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Summary

Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disease characterised by the progressive degeneration of the frontal and temporal lobes, which results in behavioural (behavioural variant FTD; bvFTD) and language (primary progressive aphasia; PPA) disorders. Additionally, FTD patients may develop concurring symptoms of atypical parkinsonism or amyotrophic lateral sclerosis. Patients with FTD are generally younger than patients with different types of dementia, as the typical age of FTD onset is below 65 years. Still, FTD is difficult to diagnose in early stages, as symptoms may vary and overlap with psychiatric disease and/or other dementias.

No effective therapies currently exist to cure FTD or slow disease progression. However, our knowledge of FTD pathophysiology has increased substantially over the past decades, and increasing efforts are currently made to develop *disease modifying treatments*. These treatments aim to inhibit or reverse underlying pathological FTD processes, e.g., protein accumulation, in order to prevent neuronal cell death. A major challenge to developing disease modifying treatments is the presence of atrophy (i.e., irreversible brain damage) at the time of FTD diagnosis, which limits the window of opportunity for treatment. Therefore, reliably diagnosing FTD at an earlier stage (specifically, before atrophy occurs) is crucial for the development of disease modifying treatments.

Approximately 10–30% of all FTD patients have a familial form, which is often caused by mutations in the genes microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), or a repeat expansion in the gene chromosome 9 open reading frame 72 (*C9orf72*). Genetic FTD families offer the unique opportunity to study mutation carriers in a *presymptomatic* stage, where early pathological changes may already occur, but subjects are cognitively healthy. Thus, *biomarkers* may be developed for early detection of FTD, disease progression, and treatment effect evaluation. This dissertation aims to advance the development of *magnetic resonance imaging* (MRI-)based biomarkers for the early detection of FTD.

In **chapter 1**, a general introduction of FTD is given and the goals of the studies within this dissertation are described.

Chapters 2–4 describe studies in which we investigated whether MRI biomarkers for FTD have diagnostic value on the single-subject level to detect FTD-related differences in the presymptomatic disease stage. Traditional group studies have provided insight in the processes that occur in early stages of FTD, and have suggested potential biomarkers for early detection. The translation of these potential biomarkers requires validation in the individual setting, i.e., biomarkers need to be able to make reliable diagnoses in individuals.

Chapter 2 describes the use of MRI measures to classify whether or not a subject is carrier of a pathogenic FTD gene mutation (*MAPT* mutation, *GRN* mutation, or *C9orf72* repeat expansion). The classification was beyond chance level, though not sufficiently accurate for clinical use. The best performing classification models were based on white matter measures.

Next, we followed the same cohort over time in **chapter 3** to study how the *classification score*, i.e., the outcome of the classification model, develops over time in FTD mutation carriers and non-carriers. The classification scores of mutation carriers who remained cognitively healthy during the study and the classification scores of non-carriers did not differ over time. However, some mutation carriers *converted* during the study: they were diagnosed with symptomatic FTD. Compared to the healthy mutation carriers, these converting mutation carriers showed a strong increase in classification score over time. This result confirmed our suspicion that FTD mutation carriers, in terms of MRI changes, remain relatively stable until a couple of years before conversion, after which neuropathological changes progressively develop.

Given the accelerating nature of MRI changes leading up to symptom onset, we wondered whether we could use MRI measures to predict conversion in FTD mutation carriers at a time when they were still healthy. In **chapter 4**, we studied MRI data of FTD mutation carriers who were still healthy after four years of follow-up, and of mutation carriers that had converted to FTD after four years. We found it was possible to predict beyond chance level who would and would not convert to FTD within four years, using diffusion-weighted MRI of the white matter. While this study should be replicated in a larger sample for confirmation, this result offers perspective to include FTD mutation carriers in clinical trials before brain atrophy occurs.

In **chapter 5**, we aimed to advance the combination of *resting-state functional MRI* (rs-fMRI; MRI that measures how brain regions coactivate in functional networks) data between MRI scanners, in order for multicentre data to be collectively analysed. To that end, we applied *FIX* (*FMRIB's ICA-based X-noiseifier*) on multicentre rs-fMRI data from different scanners. FIX is a method to reduce structured noise resulting from hardware and software differences from rs-fMRI data. Nearly all differences in functional connectivity between the centres were reduced to non-significant levels after the application of FIX. The leftover differences were predominantly situated in the visual network and were presumably a consequence of a difference in scan protocol, as one group was scanned with eyes open, while the other group was scanned with eyes closed. Our results demonstrate that FIX reduces structured noise, while physiological differences in functional connectivity are preserved. Therefore, FIX seems a suitable method to harmonise rs-fMRI data from different centres.

Lastly, we studied potential biomarkers for the differentiation between early stages of FTD and Alzheimer's disease. FTD patients have a different pattern of MRI changes in grey matter, white matter, and functional connectivity than patients with Alzheimer's disease. In **chapter 6**, we studied whether such patterns of differences were also apparent in cognitively healthy subjects at genetic risk for these diseases. Although we found differences in white matter diffusion measures of apolipoprotein E ε4 (*APOE4*; risk allele for Alzheimer's disease) carriers compared to non-carriers, these differences were not strong enough to result in a divergent pattern compared to a group of *MAPT* and *GRN* carriers (at genetic risk for FTD). Due to the cross-sectional design of the study, no clinical follow-up was available for these subjects. It is plausible that some mutation carriers were still too young to show MRI changes related to FTD or Alzheimer's disease. Longitudinal research in genetic risk groups is therefore necessary to investigate at which stage patterns of MRI changes start to differ between FTD and Alzheimer's disease.

Chapter 7 describes the conclusions of this dissertation, provides methodological considerations, and presents recommendations for future research. To conclude, we demonstrated that MRI biomarkers can identify presymptomatic FTD mutation carriers at an individual level. We found that these biomarkers are sensitive to an increase in FTD-related MRI changes over time, and can furthermore predict which FTD mutation carriers will convert within four years. Further research in larger samples will have to show whether classification models become more accurate when specifically applied on one type of gene mutation or one clinical FTD variant. This dissertation additionally provides evidence for the hypotheses that the development of MRI changes in the brain accelerates shortly before conversion, and suggests that diffusion-weighted MRI is the most promising measure to detect early changes in genetic FTD. Finally, we showed that the reduction of structured noise facilitates the combination of rs-fMRI data across centres. While our findings require replication in larger samples, this dissertation offers the optimistic prospect that MRI biomarkers may aid early-stage FTD diagnosis.