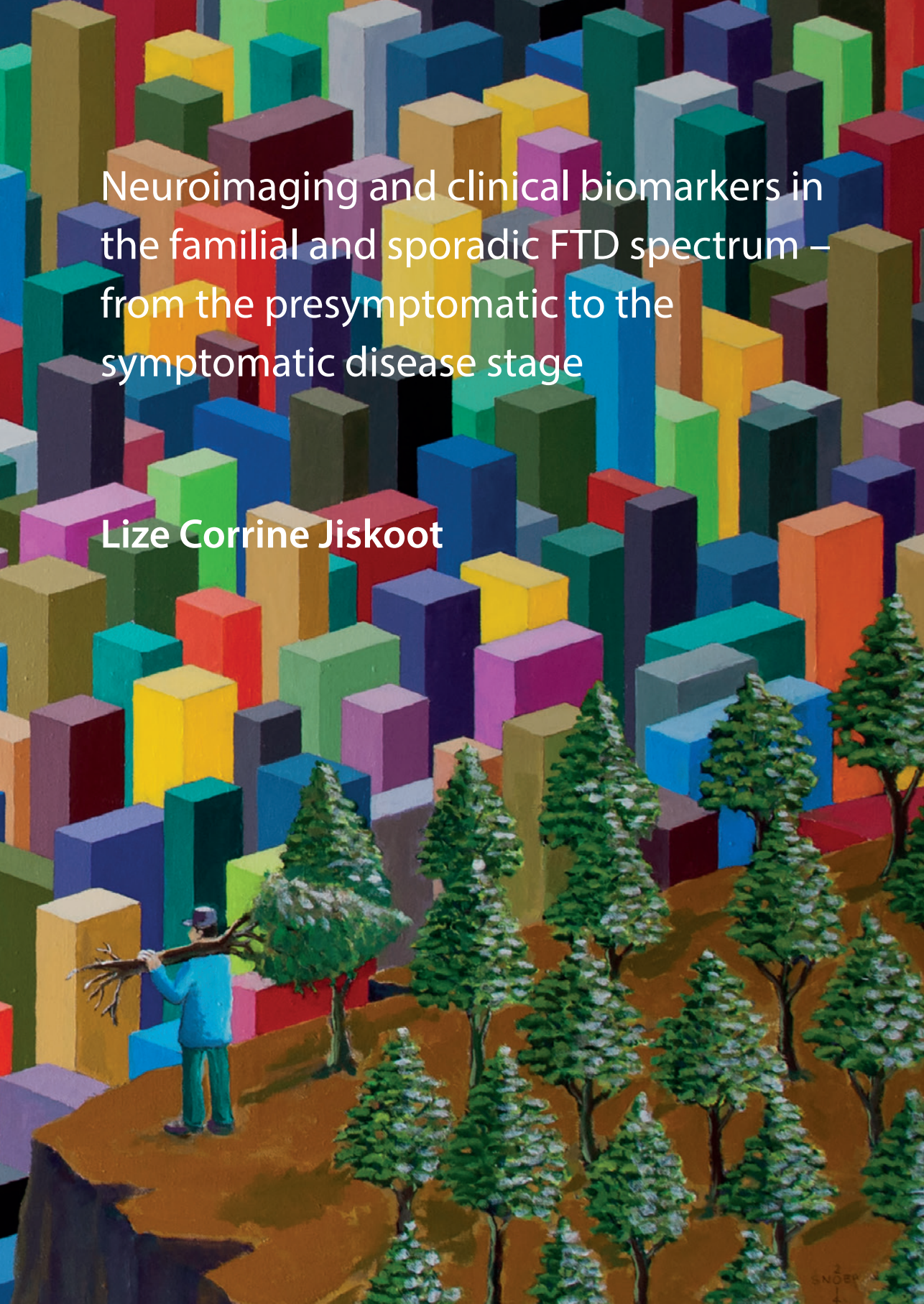
Neuroimaging and clinical biomarkers in the familial and sporadic FTD spectrum – from the presymptomatic to the symptomatic disease stage

Lize Corrine Jiskoot



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Neuroimaging and Clinical Biomarkers in the Familial and Sporadic FTD Spectrum – from the Presymptomatic to the Symptomatic Disease Stage

Neuroimaging en klinische biomarkers in het familiaire en sporadische FTD spectrum **–** van de presymptomatische tot de symptomatische ziektefase

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"Eerst moet de inhoud er zijn, dan zoek ik de vorm die er het best bij past.
Esthetiek zonder inhoud is leeg."

— Michel Snoep —

In dit proefschrift zijn diverse werken opgenomen van kunstenaar Michel Snoep (1959). Deze van oorsprong Schiedamse beeldend kunstenaar overleed in 2016 aan de gevolgen van een erfelijke vorm van FTD, de ziekte die niet alleen zijn moeder trof, maar ook zijn twee broers. Michel was een veelzijdig kunstenaar met een omvangrijk oeuvre. Het maakte schilderijen, linoleumsneden, foto's, tekeningen maar ook objecten, aquarellen en installaties. Terugkerende onderwerpen in zijn werk zijn boten, bruggen, water, vogels, bomen, vliegtuigen en steden. De impact van FTD op zijn leven wordt eveneens symbolisch weergegeven, zoals zichtbaar op de voorzijde van dit proefschrift. Michel Snoep studeerde aan de Willem de Kooning Academie in Rotterdam en was als docent twintig jaar verbonden aan de Koninklijke Academie van Beeldende Kunsten te Den Haag. De laatste tien jaar van zijn leven woonde hij met zijn gezin op Goeree-Overflakkee.

Contents

Chapter 1

General introduction

First described by Arnold Pick, a Czech psychiatrist, in 1892, frontotemporal dementia (FTD) is the second most common presenile dementia after Alzheimer's disease (AD), with symptom onset usually before the age of 65 [1-2]. FTD accounts for approximately 10% of all dementia cases, but prevalence (0.01-4.6 per 1000 persons) and incidence (0.0-0.3 per 1000 persons/year) estimates are highly variable due to changing concept and nomenclature over the years, clinical and pathological heterogeneity, and large overlap with other types of dementia and psychiatric disorders, making clinical diagnosis challenging [3-4]. FTD is equally common in males and females [3-5]. Mean survival from diagnosis lies between 3-12 years, and causes of death often include pneumonia, circulatory system failure, and cachexia [4]. The term frontotemporal lobar degeneration (FTLD) commonly refers to an overarching term for the clinicopathological complex, including the neuropathological substrates causing degeneration of the frontal and/or temporal lobes, and the clinical phenotypes describing changes in behaviour, language, executive function and motor symptoms [4,6]. The most frequent forms of familial FTD include mutations in progranulin (*GRN*), microtubule associated protein tau (*MAPT*) and a repeat expansion in the chromosome 9 open reading frame 72 (*C9orf72*) (Figure 1.1).

Clinical syndromes

The two main clinical manifestations of FTD – behavioural variant FTD (bvFTD) and primary progressive aphasia (PPA) – are distinguished by their early and predominant symptoms of either behavioural or language deterioration [4,7-8]. PPA can be further divided into three subtypes: 1) semantic variant PPA (svPPA), 2) non-fluent variant PPA (nfvPPA), and 3) logopenic variant PPA (lvPPA) [8]. There is considerable clinical and neuropathological overlap of FTLD with atypical parkinsonism in the form of corticobasal degeneration and -syndrome (CBD/CBS) and progressive supranuclear palsy (PSP), and concomitant motor neuron disease (FTD-MND) and amyotrophic lateral sclerosis (ALS) [4,9] (Figure 1.1).

bvFTD

bvFTD is the most common clinical phenotype, representing about 50% of all cases of FTD [10]. Clinical criteria have been revised over the years, but the most recent criteria define three levels of diagnostic certainty and six behavioural and cognitive clusters of symptoms [7] [Box 1.1]. As stated by these criteria, bvFTD is characterized by early decline of social behaviour and personal conduct, as a result of disinhibition, apathy, loss of empathy and sympathy, perseverative and/or stereotyped behaviour, and hyperorality or dietary changes [4,7].

About 75% of bvFTD patients have behavioural abnormalities as their presenting symptom [11]. Disinhibition is reported in approximately 75% of patients, and often seen in the form of socially inappropriate behaviour (e.g. childish behaviour, loss of etiquette), loss of manners or decorum (e.g. offensive jokes often with a sexual reference, approaching strangers inappropriately), and impulsive, rash or careless actions (e.g. spending large amounts of money, gambling, falling for financial scams) [7]. Passivity (apathy) and decreased generating ability (inertia) in pursuing work, activities and hobbies is reported in around 85% of patients [7]. Early loss of sympathy or empathy makes patients with

bvFTD display a diminished response to other people's feelings and needs, general social interest or personal warmth – often causing patients being described as "cold" or "indifferent" [12]. A wide range of perseverative, stereotyped or compulsive/ritualistic behaviours is seen, including clapping hands, lip smacking, repeating phrases, hoarding, object counting, obsessive time keeping and hyperreligiosity [4, 10]. Altered food preferences (e.g. sweet cravings, rigid preferences) and abnormal eating behaviours (e.g. over- and binge eating) affects over 80% of patients [13-14].

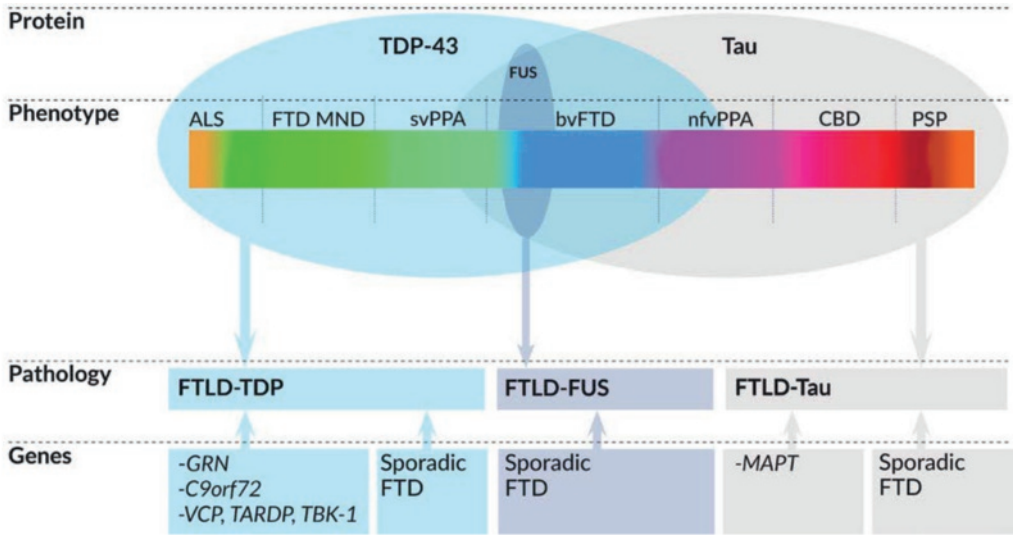

Figure 1.1 | **Clinical, pathological and genetic spectrum of FTD.** *Abbreviations:* TDP-43, transactive response DNA-binding protein 43; ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; MND, motor neuron disease; svPPA, semantic variant PPA; FUS, fused in sarcoma; bvFTD, behavioural variant frontotemporal dementia; nfvPPA, non-fluent variant primary progressive aphasia; CBD, corticobasal degeneration; PSP, progressive supranuclear palsy; FTLD, frontotemporal lobar degeneration; *GRN*, progranulin; *C9orf72*, chromosome 9 open reading frame 72; *VCP*, valosin-containing protein; *TARDP*, TAR-DNA binding protein; *TBK1*; TANK-binding kinase 1; *MAPT*, microtubule-associated protein tau. Modified with permission from BMJ Publishing Group © Seelaar H et al. J Neurol Neurosurg Psychiatry 2011; 82: 476–86.

Box 1.1 | Clinical criteria for bvFTD (Rascovsky et al., 2011 [7])

I. Neurodegenerative disease

The following symptoms must be present to meet criteria for bvFTD:

A. Shows progressive deterioration of behaviour and/or cognition by observation or history (as provided by a knowledgeable informant)

II. Possible bvFTD

Three of the following behavioural/cognitive symptoms (A-F) must be present to meet criteria. Ascertainment requires that symptoms be persistent or recurrent, rather than single or rare events

A. Early behavioural disinhibition [one of the following symptoms (A.1-A.3) must be present]:
   - A.1 Socially inappropriate behaviour
   - A.2 Loss of manners or decorum
   - A.3 Impulsive, rash or careless actions

B. Early apathy or inertia [one of the following symptoms (B.1-B.2) must be present]:
   - B.1 Apathy
   - B.2 Inertia

C. Early loss of sympathy or empathy [one of the following symptoms (C.1-C.2) must be present]:
   - C.1 Diminished response to other people's needs and feelings
   - C.2 Diminished social interest, interrelatedness or personal warmth

D. Early perseverative, stereotyped or compulsive/ritualistic behaviour [one of the following symptoms (D.1-D.3) must be present]:
   - D.1 Simple repetitive movements
   - D.2 Complex, compulsive or ritualistic behaviours
   - D.3 Stereotypy of speech

E. Hyperorality and dietary changes [one of the following symptoms (E.1-E.3) must be present]:
   - E.1 Altered food preferences
   - E.2 Binge eating, increased consumption of alcohol or cigarettes
   - E.3 Oral exploration or consumption of inedible objects

F. Neuropsychological profile: executive/generation deficits with relative sparing of memory and Visuospatial functions [all of the following symptoms (F.1-F.3) must be present]:
   - F.1 Deficits in executive tasks
   - F.2 Relative sparing of episodic memory
   - F.3 Relative sparing of visuospatial skills

III. Probable bvFTD

All of the following symptoms (A-C) must be present to meet criteria:

A. Meets criteria for possible bvFTD

B. Exhibits significant functional decline (by caregiver report or as evidenced by Clinical Dementia Rating scale or Functional Activities Questionnaire scores)

C. Imaging results consistent with bvFTD [one of the following (C.1-C.2) must be present]:
   - C.1 Frontal and/or anterior temporal atrophy on MRI or CT
   - C.2 Frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

Box 1.1 | Continued

IV. Behavioural variant FTD with definite FTLD pathology

Criterion A, and either B or C must be present to meet criteria:

A. Meets criteria for possible or probable bvFTD

B. Histopathological evidence of FTLD on biopsy or at post-mortem

C. Presence of a known pathogenic mutation

V. Exclusion criteria for bvFTD

Criteria A and B must be answered negatively for any bvFTD diagnosis. Criterion C can be positive for possible bvFTD, but must be negative for probable bvFTD:

A. Pattern of deficits is better accounted for by other non-degenerative nervous system or medical disorders

B. Behavioural disturbances are better accounted for by a psychiatric diagnosis

C. Biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process

PPA

PPA has been described as a clinical syndrome, characterized by progressive loss of verbal communication as a result of degeneration of the brain's language networks [15]. An international group of PPA researchers developed the current diagnostic criteria for PPA in 2011, in which patients are first diagnosed with PPA, and subsequently divided into one of the three clinical variants based on specific speech and language features [16]. Classification can be further specified into "imaging-supported" or "with definite pathology" if respectively imaging, pathologic or genetic data are available [16].

1. *Semantic variant PPA (svPPA)*

   In svPPA, patients gradually lose their semantic memory – the memory system that stores the knowledge about words, objects, and concepts [4,10]. Anomia (word-finding and naming problems) and single-word comprehension deficits belong to the core diagnostic features [16]. This leaves the speech circumlocutory and empty, ultimately meaningless [4,10]. Semantic paraphasias (e.g. "smoker" instead of "pipe") are often heard in spontaneous speech, and also surface dyslexia and dysgraphia occur (impairment in reading and writing words with an irregular or atypical spelling and/or pronunciation) [4]. In later disease stages, the semantic knowledge is affected beyond the language-domain, so that patients also develop symptoms of visual agnosia (e.g. impaired recognition of faces and objects) [10]. Also behavioural disturbances, are common in later stages of svPPA [17].

2. *Non-fluent variant PPA (nfvPPA)*

   In nfvPPA, patients present with a non-fluent, effortful, slow and/or halting speech that is characterized by apparent agrammatism and inconsistent sound errors (e.g. deletions, substitutions, insertions) [16]. Sentences are often shortened and simplified, omitting grammatical morphemes such as function words. Phonematic paraphasias (e.g. "cap" instead of "cat") are often heard [4,16]. The prosody of speech also becomes disrupted [16]. Although comprehension is relatively spared, the understanding of syntactically complex sentences is often impaired. Eventually, patients become mute, and can also develop concomitant atypical parkinsonism features (e.g. PSP, CBS) [10,16,18].

3. *Logopenic variant PPA (lvPPA)*
   LvPPA is the most recently described variant of PPA, and the Gorno-Tempini criteria state word retrieval (e.g. word-finding problems, confrontation naming deficits) and sentence repetition deficits as the core clinical features [16]. Paraphrases are often heard in the form of phonematic errors in spontaneous speech and naming, although well-articulated without distortions [19]. In contrast to nfvPPA, spontaneous speech is considerably non-fluent due to word-finding difficulties in the absence of agrammatism, and also prosody and articulation are relatively spared [16].

Parkinsonian and motor neuron diseases

In addition to bvFTD and PPA, the clinical spectrum of FTLD includes parkinsonism (e.g. PSP, CBS) and motor neuron diseases (FTD-MND, ALS). Patients with PSP or CBS can develop behavioural disturbances similar to bvFTD or PPA, and vice versa, patients with bvFTD or PPA can also develop neurological signs characteristic for PSP or CBS [20]. Approximately 15% of patients with FTD also have symptoms of ALS, and 5% of ALS patients fulfill the clinical criteria for bvFTD or PPA [21-22]. Core clinical criteria for PSP include ocular motor dysfunction (e.g. vertical gaze palsy, slowing of vertical saccades), postural instability (e.g. repeated unprovoked falls), akinesia (e.g. progressive gait freezing, bradykinesia and rigidity with axial predominance), and cognitive dysfunction (e.g. speech and language disorders, frontal disturbances) [23]. CBS was previously described as a primary motor disorder, with symptoms as asymmetrical akinesia/bradykinesia, rigidity, and limb dystonia – but more recent research also points to significant cognitive deficits (e.g. speech and language disturbances, alien limb behaviour, apraxia, and visuospatial impairments) that can appear early in the disease and sometimes even before the onset of motor symptoms [24-25]. ALS, as the most common form of motor neuron disease (MND), presents with a combination of lower and upper motor neuron degeneration, leading to limb paralysis, fasciculations, muscular cramps and increased tonus, dysphagia, dysarthria, and respiratory failure [26].

Neuropsychological biomarkers

In patients with suspected dementia, a comprehensive neuropsychological assessment is an important and auxiliary element in the diagnostic process, as it can determine the existence of cognitive dysfunctions but also discriminate between different types of dementia [27]. Detailed neuropsychological assessment can also identify cognitive deficits that are not readily apparent in everyday life, especially in bvFTD where behavioural changes dominate or mask cognitive deficits [4]. According to the diagnostic criteria, the neuropsychological profile of bvFTD is characterized by executive and/or generating deficits, while memory and visuospatial functions are relatively spared [7]. Common executive dysfunctions include problems in working memory, response inhibition, planning, generating/formation of a strategy, and abstraction [10,28]. A growing number of studies shows that bvFTD can present with memory deficits similar to AD [29-30] – not solely explained by the leading executive dysfunctions (e.g. impaired retrieval strategies), but due to true disruption of memory storage and consolidation [31-32]. Due to this overlap in cognitive profiles, the differentiation between bvFTD and AD in early disease stages remains challenging [33]. It has therefore been suggested that longitudinal approaches are more informative

than cross-sectional studies in identifying disease-specific trajectories of cognitive decline [34]. Also the addition of specific tests for language and social cognition has found to be essential. bvFTD patients may present with verb naming deficits, disinhibited output and stereotypical perseverations [35]. As the disease progresses, patients may develop semantic problems identical for svPPA [36], or become non-fluent to mute – comparable to nfvPPA [37]. Social cognition refers to a number of implicit and explicit processes that form the basis of a complex and dynamic set of behaviours and mutually shared expectations, which enable people to successfully interact with others [37]. Overwhelming research points to a diverse range of social cognitive deficits in bvFTD, including the impaired ability to process facial emotions, perspective taking, solving social dilemmas, perceiving sarcasm, and reacting to fearful or sad stimuli [37]. The clinical diagnosis of PPA heavily relies on careful analysis of spontaneous speech and by using standardized language tasks and/or batteries. Language is often evaluated based on scores of speech (information content and fluency), comprehension, repetition, and naming [4]. In the first two years, other cognitive domains are relatively spared [16], but as the evaluation of these domains are often language-based (e.g. episodic memory), patients with PPA attain lower test performances due to their language impairments. Nevertheless, there is growing evidence of impairments in social cognition, executive function and memory early in the disease course of PPA [37].

Neuroimaging biomarkers

Structural imaging

Grey matter volume

Most imaging studies in FTD have been performed by means of T1-weighted MRI, revealing specific patterns of grey matter (GM) volume loss according to clinical phenotype [38-39] (Figure 1.2). Special visual rating scales have become available to quantify the FTD-specific patterns of GM atrophy [4]. bvFTD patients demonstrate an asymmetrical, disproportionate GM atrophy of the dorsomedial prefrontal, mesio- and orbitofrontal cortex, temporal lobes, anterior cingulate cortex (ACC), anterior insula, and a number of subcortical structures (e.g. amygdala, striatum, thalamus) [40-41]. svPPA is marked by an asymmetrical (left>right) anterior and inferior temporal lobe atrophy, whereas in nfvPPA the volumes of the left inferior frontal gyrus, insula, and premotor and supplementary motor areas are significantly reduced [42-44]. The atrophy pattern of lvPPA is also consistently asymmetrical, with volume loss of the left posterior middle/superior temporal and inferior parietal lobe, posterior cingulate, precuneus, and medial temporal lobe [45]. However early in the disease course, changes can be absent or subtle, therefore absence of apparent GM atrophy cannot rule out FTD [4].

White matter integrity

Although for a long period of time, FTD has been regarded as a GM disease, converging evidence points in the direction of FTD as a dementia in which the white matter (WM) tract pathology is early and widespread, extending beyond the zones of GM atrophy [46-48]. Diffusion tensor imaging (DTI) is now a commonly used technique to study WM integrity, and although patterns of integrity loss

overlap between the FTD subtypes, specific profiles have been defined according to clinical, genetic and pathological subtype [39,46,49-50] (Figure 1.2). Tracts found to be compromised in bvFTD include the uncinate fasciculus (UF), cingulum, corpus callosum, fornix, superior (SLF) and inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus, thalamic radiation and corona radiata [46-50]. Connecting the limbic regions in the temporal lobe to the frontal lobe, and involved in e.g. empathy and inhibition, the UF has been suggested to be the key hub of WM degeneration in bvFTD [51-52]. bvFTD patients have more WM integrity loss than PPA patients in the genu of the corpus callosum and frontal pole [39]. svPPA is characterized by bilateral WM alterations of the inferior longitudinal fasciculus and UF [47,49-50,53-58]. In contrast to svPPA, studies of nfvPPA have shown WM integrity loss of the dorsal language pathways, involving arcuate and premotor components of the SLF, UF, and subcortical projections [55,57-59]. lvPPA presents with bilateral, but predominantly left-sided, WM changes in the ILF and SLF, UF, and subcortical projections [57]. Recent research suggests that damage to the UF underlies the emergence of behavioural symptoms in patients with PPA [60].

Functional neuroimaging

Resting-state functional MRI (rs-fMRI)

Resting-state functional MRI (rs-fMRI) is a relatively new neuroimaging technique that, by measuring time-dependent fluctuations in blood oxygenation levels as a surrogate of neural activity, can measure the functional connectivity between brain networks [61]. bvFTD has consistently been associated with reduced connectivity of the salience network – whose major hubs include the frontoinsula, anterior cingulate, amygdala, ventral striatum and medial thalamus, regions known to be involved in evaluating the emotional significance of stimuli, task-switching and behavioural self-regulation [62-63]. Potentially as the result of salience network degeneration, compensatory increased functional connectivity has been found in the default mode network [64-66], although not consistently found across all studies in bvFTD [67]. Patients with svPPA demonstrate asymmetrically reduced functional connectivity in the semantic network involving the anterior temporal lobe, association cortices, anterior cingulum, orbitofrontal and frontoinsular cortices, striatum and thalamus [68]. Although studies in nfvPPA are lacking to date, there is some evidence for reduced functional connectivity in regions enabling fluent speech, e.g. frontal operculum, primary and supplementary motor areas, and inferior parietal lobule [61]. Higher anterior default mode network connectivity [69] and lower left language and working memory network connectivity [70] have been associated with lvPPA.

Perfusion by arterial spin labeling (ASL)

Arterial spin labeling (ASL) is a functional MRI technique that measures brain perfusion by magnetically labelling water protons in arterial blood, creating an endogenous marker of cerebral blood flow (CBF) – assumed to be tightly coupled to brain metabolism [71-73]. bvFTD patients have consistently been found to have lower brain perfusion in the bilateral frontal lobes, the anterior cingulate cortex, insula and thalamus [71,73-74]. Specific ASL studies in PPA are scarce. One study combining bvFTD, PPA and CBS patients found lower perfusion in the bilateral prefrontal cortex, right inferior frontoinsula, medial parietal cortex, precuneus and posterior cingulate cortex [75]. Another study in patients with svPPA

demonstrated hypoperfusion relative to controls in the left (middle) temporal lobe and insula, extending to the left superior temporal lobe, and bilateral precuneus and posterior cingulate cortex [76].

PET imaging

By means of positron emission tomography (PET) using a glucose tracer (e.g. 2-[Fluorine-18] fluoro-2-deoxy-D-glucose [^{18}F-FDG]) the cerebral glucose metabolism can be visualized. With metabolism decreasing with neurodegeneration, FDG-PET has been found to be very useful for early differential diagnosis in dementia [77]. Showing large spatial overlap with patterns found by means of ASL-MRI [78], hypometabolism on FDG-PET predominantly affects the frontal (dorsolateral, medial, orbitofrontal), anterior cingulate cortex, frontoinsula and subcortical structures (caudate nucleus, putamen and thalamus), with relatively sparing of the sensorimotor cortex and cerebellum in bvFTD [79-82]. Studies in PPA demonstrated that nfvPPA is associated with left frontal hypometabolism, svPPA is linked to left anterior temporal metabolism, and lvPPA is related to left temporal-parietal hypometabolism [83-85]. Another application, PET with an amyloid tracer such as Pittsburgh compound B (PiB-PET) or florbetapir, can be used to exclude the presence of AD pathology in FTD patients [4] as bvFTD, svPPA and nfvPPA are mostly amyloid-negative [38]. As 50% of lvPPA have an underlying AD pathology, the tracer binding can have a similar pattern to that seen in AD – whereas a negative scan can indicate an underlying FTD pathology [86]. The newest application of PET-imaging includes tau PET. Once validated, tau PET has the potential to become a useful diagnostic, prognostic and progression biomarker, and surrogate marker, for effect-monitoring and patient recruitment in future anti-tau clinical trials [87].

Familial FTD

FTD tends to be highly genetic, with approximately 40-60% of cases having a positive family history for dementia, and 10-30% is familial with an autosomal dominant pattern of inheritance [88-90]. Amongst the FTD phenotypes, bvFTD is the most and svPPA the least heritable form [91]. Mutations in the progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*) genes, and the more recently discovered repeat expansion in chromosome 9 open reading frame 72 (*C9orf72*) are the three most common causes [90]. Mutations in other genes (e.g. *VCP*, *CHMP2B*, *FUS*) have been described, but occur very sporadically [90].

GRN

Discovered in 2006, over 70 mutations in the *GRN* gene account for approximately 8% of familial FTD [92]. The age at which the first symptoms arise is highly variable between and within families, between 35 and 89 years of age [93]. The neuroimaging profile describes a strongly asymmetrical and widespread GM atrophy of the temporal, inferior frontal and parietal lobes, and insula [90,94-95] and the loss of WM integrity in the large intrahemispheric tracts (e.g. inferior and superior longitudinal fasciculus, inferior fronto-occipital fasciculus and cingulum). The clinical phenotype associated with *GRN* mutations ranges from bvFTD, nfvPPA to (concomitant) parkinsonism and CBS [92-93].

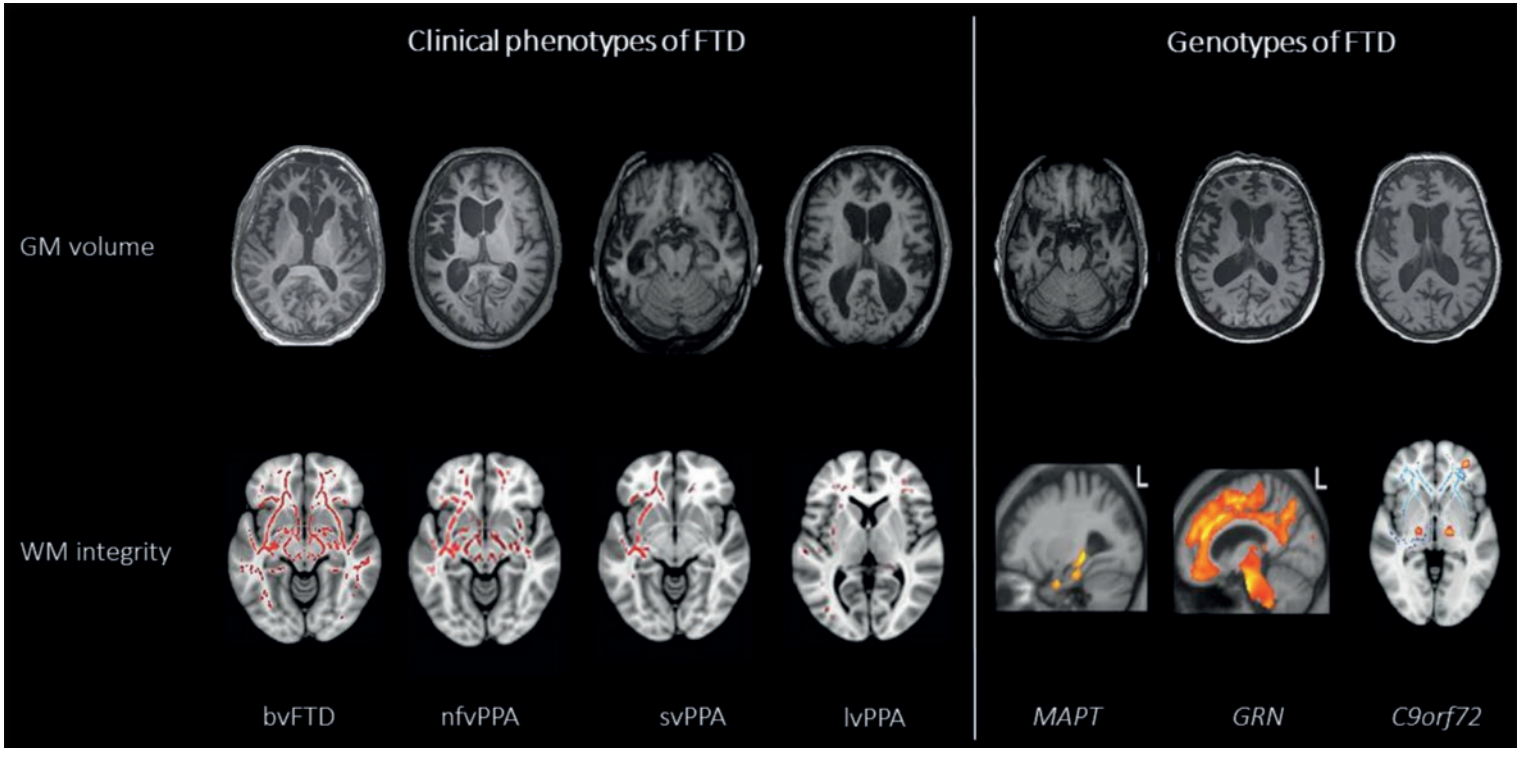

Figure 1.2 | **Pattern of GM volume and white matter integrity loss in the clinical phenotypes and genotypes of FTD.** Top row represents the grey matter volume loss per clinical phenotype (bvFTD, nfvPPA, svPPA, lvPPA) and genotypes of FTD (*MAPT*, *GRN*, *C9orf72*) on T1-weighted MRI scans (in the transversal plane – upper part of the image is the front of the brain, lower part is the back of the brain). Bottom row represents the white matter integrity loss per clinical phenotype (bvFTD, nfvPPA, svPPA, lvPPA) and genotypes of FTD (*MAPT*, *GRN*, *C9orf72*) on diffusion tensor weighted MRI scans (in the transversal plane - plane – upper part of the image is the front of the brain, lower part is the back of the brain or sagittal plane; images for *MAPT* and *GRN* are in sagittal plane – the left side is the front of the brain, the right side is the back of the brain. The red/blue lines and orange blobs represent the fractional anisotropy (FA) loss (one of the four measures for white matter integrity). *Abbreviations:* FTD, frontotemporal dementia; GM, grey matter; WM, white matter; bvFTD, behavioural variant frontotemporal dementia; nfvPPA, non-fluent variant primary progressive aphasia; svPPA, semantic variant primary progressive aphasia; lvPPA, logopenic variant primary progressive aphasia; *MAPT*, microtubule-associated protein tau; *GRN*, progranulin, *C9orf72*, Chromosome 9 open reading frame 72; L, left.

MAPT

Discovered in 1998, over 40 *MAPT* mutations account for approximately 5 to 17% of familial FTD and 30% of cases with a positive family history [96]. The age at onset tends to be lower in *MAPT* than *GRN* families [91]. The neuroimaging profile is a rather focal and symmetrical GM atrophy of the anterior temporal lobes and less involvement of the (orbito)frontal lobes [94-95], and WM integrity loss of the fornix, UF, corpus callosum, and inferior and superior longitudinal fasciculus [46,94]. Patients with *MAPT* mutations commonly present with bvFTD or atypical parkinsonism (PSP or CBS) [97].

C9orf72

The most recently discovered (2011) repeat expansion in *C9orf72* is the most common genetic cause of familial FTD and/or ALS, accounting for between 13 and 26% of cases [98]. There is a wide variation in symptom onset (between 43 and 68 years of age) [99]. A distinctive neuroimaging signature with GM atrophy of the frontal and temporal lobes, but in contrast to the other mutations also posterior cortical (parietal and occipital lobes) and subcortical (cerebellum and thalamus) atrophy is found [99-102]. GM atrophy is often more symmetrical and less pronounced [100]. With regards to WM pathology, diffusion abnormalities are found in the superior and longitudinal fasciculus, UF, corpus callosum, but also corticospinal tracts and anterior thalamic radiations [99]. The *C9orf72* repeat expansion is associated with a clinical phenotype of bvFTD, ALS, FTD-ALS, and less commonly PPA [103]. The disease progression is often slower [99-101], and patients often present with psychiatric symptoms such as obsessive-compulsive behaviour and psychosis [100,103].

The presymptomatic phase and biomarker development in familial FTD

The presymptomatic phase of dementia can be defined as the time-period in which there are no clinical symptoms of disease, but the underlying pathology has already become active – reflected by changes in biomarkers. The word biomarker refers to "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" (National Institutes of Health Biomarkers Definitions Working Group, 1998). Familial FTD forms the ideal disease-model, as we can identify pathogenic mutation carriers in their asymptomatic stage. Studies in other familial dementias, such as AD and Huntington's Disease, have demonstrated biomarker changes up to 25 years before estimated symptom onset [104-105], suggesting that the critical time-window to treat dementia lies most likely prior to clinical onset, when the pathological damage is at its minimum and potentially still reversible [106]. With promising avenues opening for disease-modifying therapies in clinical trials, there are however no robust biomarkers of familial FTD available yet. Figure 1.3 shows the hypothetical pattern of biomarker changes in familial FTD.

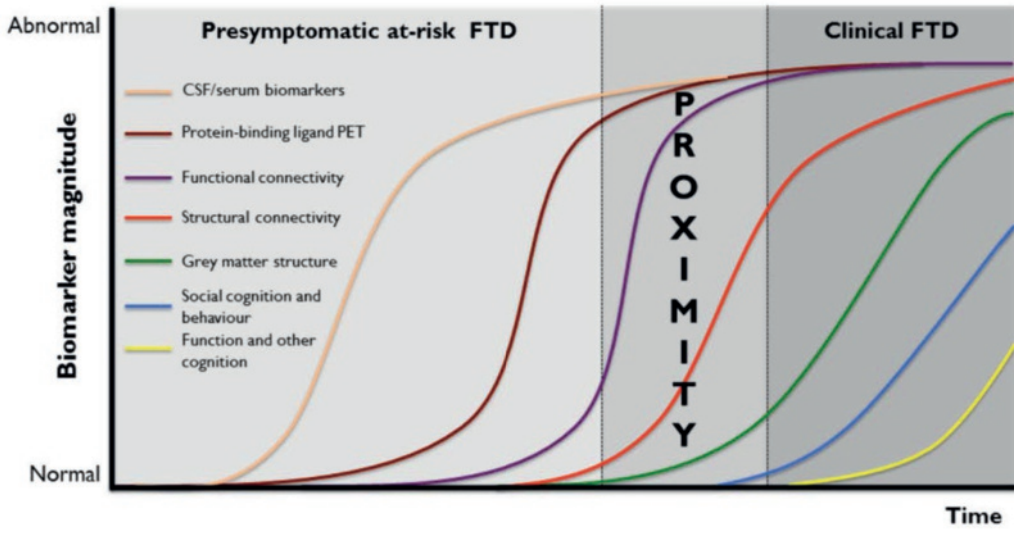

Figure 1.3 | **Hypothetical pattern of biomarker changes in familial FTD.** In the early presymptomatic phase, changes in cerebrospinal fluid and blood biomarkers are visible, followed by changes in PET tracer binding. In the proximity of symptom onset, neuroimaging changes in the form of lower functional and structural connectivity and grey matter volume, become apparent. Shortly before or around symptom onset, behavioural symptoms and deficits in social cognition can be objectified. Functional changes and deficits in other cognitive domains are often only quantifiable after symptom onset. *Abbreviations:* CSF, cerebrospinal fluid; PET, positron emission tomography, FTD, frontotemporal dementia. Used with permission from J.D. Rohrer, GENFI2 study protocol (2015).

Required applications of familial FTD biomarkers include [38]:

- *Diagnosis* | Ideally, diagnostic biomarkers discriminate patients with FTD from other types of dementia or individuals without dementia, or between clinical, genetic and pathological subtypes [38]. Despite large improvements in the clinical characterization of FTD, there remains a large diagnostic latency between symptom onset and the correct diagnosis, highlighting the diagnostic challenge of this heterogeneous disorder [107-108]. A timely and certain diagnosis can take away a part of the stress and burden experienced by caregivers [109]. Moreover, a correct diagnosis allows treatment (pharmacological or non-pharmacological) in an early phase [4]. From a clinical trial perspective, robust stratification of FTD clinical and pathological subtypes into the correct treatment groups increases chances of their success [46].
- *Staging & prognosis* | Staging biomarkers will allow the assessment of diseases severity and progression, and discrimination between the disease stages – presymptomatic, early or late symptomatic [38], helping group stratification in clinical trials. More importantly, these biomarkers will help informing patients and caregivers about what time-line to expect, determining the best treatment approach, and benefit communication between health providers and caregivers.
- *Onset prediction & monitoring diseases progression and treatment response* | Identifying disease onset and tracking disease progression are key elements in clinical trial design, as they can signify when therapy ideally should be initiated ("proximity biomarkers") and how treatment response can be monitored [106]. Pharmacodynamic biomarkers will become important to evaluate target

engagement and potential surrogate endpoints. The prediction of the future phenotype and the underlying neuropathology are also essential when disease-modifying agents become available [38].

Longitudinal studies in presymptomatic FTD

The understanding of the importance of longitudinal studies in familial FTD came from the success of previous studies into other genetic dementias [104-105]. Following both young at-risk mutation carriers far from symptom onset to older mutation carriers close to conversion to the clinical stage provides clear insight into the temporal and spatial cascade of pathological events that lead to dementia in a timespan of decades, and allows the investigation and eventually validation of prediction and monitoring disease biomarkers. Additionally, collaboration in larger consortium studies enables pooling of presymptomatic FTD cohorts, which is important given the fact that FTD is a rare disease and individual research centres most often have only relatively small total sample sizes, that range across different genes and ages [106]. Furthermore, clinical trials require large numbers of patients over longer time periods due to the generally slow onset and progression of clinical symptoms [104].

The *Frontotemporal Dementia Risk Cohort (FTD-RisC)* is the first large longitudinal study of presymptomatic mutation carriers and non-carriers from Dutch FTD families due to mutations in the *MAPT* and *GRN* genes, and the *C9orf72* repeat expansion. Since December 2009, participants are monitored on a two-year basis by means of an extensive standardized clinical assessment, including MRI scanning of the brain, a neuropsychological test battery, a neurological and physical examination, venipuncture, and an optional skin biopsy and/or lumbar puncture. Currently, over 160 participants are enrolled in this monocentre study. The *Genetic Frontotemporal dementia Initiative (GENFI)*, started in 2012, is a collaboration between University College London (UK), the Erasmus Medical Center and 24 other FTD expertise research centres across Europe and Canada, following first-degree presymptomatic mutation carriers and non-carriers from families with mutations in *MAPT* and *GRN*, and the *C9orf72* repeat expansion [110]. Currently, over 650 participants have been enrolled; the ultimate goal is to include 800 participants at three annual time points. The next phase of GENFI constitutes the creation of a robust methodological platform to run clinical trials, requiring strong collaborations between academia and the pharmaceutical industry. More recently initiated multicentre studies based in the United States include the Longitudinal Evaluation of *Familial Frontotemporal Dementia Subjects (LEFFTDS)* and *Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL)*. GENFI, LEFFTDS and ARTFL, together with the Australian Dominantly Inherited Non-Alzheimer Dementias (DINAD) study, are now working together in the *FTD Prevention Initiative (FPI)* in order to bring together knowledge in e.g. a minimum shared dataset across all worldwide projects.

Outline of this thesis

With promising avenues opening for disease-modifying therapies in clinical trials, we currently lack robust biomarkers for (familial) FTD. These biomarkers will be essential for improving diagnostic accuracy, staging and prognosis, onset prediction, and monitoring disease progression and treatment

response. In this thesis, we have therefore investigated the clinical application of neuroimaging and neuropsychological biomarkers in the familial and sporadic FTD spectrum. The two main research questions of this thesis are as follows:

1. What are the most promising candidate MRI biomarkers in presymptomatic familial FTD?
   Chapter 2.1 reports on the four-year follow-up within that same cohort, describing the spreading of WM integrity and GM volume loss in mutation carriers converting from the presymptomatic to the symptomatic stage of FTD, as well as the use of multimodal imaging biomarkers in prediction that conversion. In **Chapter 2.2** we define the first cross-sectional changes in WM integrity and GM volume in presymptomatic *C9orf72* repeat expansion carriers at higher risk (age >40 years of age) for developing FTD and/or ALS. **Chapter 3.1** lists the WM tracts involved in speech and language. It describes the anatomy and tractography of the main language tracts, and the use of DTI in language impairments due to cerebrovascular disease and PPA. **Chapter 3.2** reports on presymptomatic white matter integrity loss by means of cross-sectional DTI, performed in a large international cohort (GENFI) of FTD mutation carriers associated with *MAPT*, *GRN* and *C9orf72*.

2. What is the value of neuropsychological assessment in presymptomatic to symptomatic FTD?
   Chapter 4.1 describes the two-year neuropsychological follow-up of presymptomatic *MAPT* and *GRN* mutation carriers in FTD-RisC, investigating cognitive decline over time, and in relation to estimated years to symptom onset. **Chapter 4.2** investigates the same cohort, describing the four-year follow-up – but also the use of longitudinal neuropsychological trajectory biomarkers in predicting symptom onset. **Chapter 4.3** reports on the use of qualitative properties of verbal fluency tasks in characterizing bvFTD and PPA patients. **Chapter 4.4** lists a meta-analytic review quantifying the nature and extent of memory impairments in bvFTD, in comparison to AD and controls.

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Chapter 2

Neuroimaging biomarkers – multimodal imaging

2.1

Longitudinal multimodal MR imaging as prognostic and diagnostic biomarker in presymptomatic familial frontotemporal dementia

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Provisional accept - Brain

Abstract

Developing and validating sensitive biomarkers in the presymptomatic stage of familial frontotemporal dementia (FTD) is an important step in early diagnosis and the design of future therapeutic trials. In the longitudinal Frontotemporal Dementia Risk Cohort (FTD-RisC), we track presymptomatic mutation carriers and healthy controls from families with familial FTD due to *microtubule-associated protein tau* (*MAPT*) and *progranulin* (*GRN*) mutations. This study describes a 4-year follow-up multimodal MRI study, with three time points: 4 years and 2 years before symptom onset, and after symptom onset. In the total cohort of 73 participants, eight mutation carriers developed symptoms of FTD ('converters'). Longitudinal whole-brain decline in white matter integrity and grey matter volume was compared between these converters, non-converters (n=35), and healthy controls (n=30) from the same families. We also assessed the prognostic performance of decline within white matter and grey matter regions-of-interest by means of receiver operating characteristics analyses followed by stepwise logistic regression. Whole-brain analyses demonstrated extensive loss of white matter integrity and grey matter volume over time in converters, present from 2 years before symptom onset. The largest decline was found in the genu corpus callosum, forceps minor, uncinate fasciculus, and superior longitudinal fasciculus, as well as the prefrontal, temporal, cingulate, and insular cortex. White matter integrity loss of the right uncinate fasciculus and genu corpus callosum provided significant classifiers between converters, non-converters, and healthy controls. Our study confirms the presence of spreading predominant frontotemporal pathology towards symptom onset and highlights the value of multimodal MR imaging as a prognostic biomarker in familial FTD.

Introduction

Frontotemporal dementia (FTD) is the second most common presenile dementia disorder (onset <65 years), with a clinical profile of behavioural disturbances and/or language deterioration (bvFTD or PPA), associated with focal neurodegeneration of the frontal and/or temporal lobes [1-3]. FTD can have an autosomal dominant inheritance pattern, with mutations in the *progranulin* (*GRN*) or *microtubule-associated protein tau* (*MAPT*) genes, and the *chromosome 9 open reading frame 72* (*C9orf72*) repeat expansion as its three major causes [4]. Converging evidence from cross-sectional studies in familial FTD demonstrates the presence of a presymptomatic stage, characterized by early neuroimaging and clinical changes [5-8]. Longitudinal studies in the presymptomatic stage are still lacking, but may provide valuable information on 1) imaging-based disease staging, 2) characterization of disease trajectories, 3) validation of prognostic biomarkers, and 4) establishing the sensitivity of various neuroimaging techniques in early disease stages [9].

Structural neuroimaging studies in symptomatic FTD have shown predominant grey matter (GM) volume loss of the prefrontal cortex, anterior temporal lobe, insula and anterior cingulate cortex early in the disease course, with atrophy increasing as the disease progresses [10-13]. Additionally, studies now also suggest white matter (WM) integrity loss as the hallmark of FTD, in location and severity exceeding GM atrophy [1-3,14]. The uncinate fasciculus (UF), connecting the orbitofrontal cortex, temporal pole, insula and amygdala, has been suggested as the key target of network-led neurodegeneration early in the disease process [15-16] (*see also literature review in Supplementary data*). Recent studies of familial FTD have shown WM integrity loss of the UF [5,8] and inferior frontooccipital fasciculus (IFOF) [8] in the presymptomatic stage, and GM volume loss of e.g. the frontal, temporal, insular, and cingulate cortices [7,17-18]. However, follow-up studies describing the longitudinal trajectories of WM integrity and GM volume loss in the presymptomatic stage of FTD are still lacking.

In this study, we aimed to investigate the progression of GM volume loss and WM integrity from the presymptomatic to symptomatic stage in *MAPT* and *GRN* mutation carriers and healthy controls from the same families in the Frontotemporal Dementia Risk Cohort (FTD-RisC). This study forms the 4-year follow-up within our cohort [5]. The study aims are threefold: 1) to investigate whole-brain cross-sectional and longitudinal WM integrity and GM volume differences between mutation carriers and healthy controls from 4 years before to after symptom onset; 2) to determine the prognostic value of longitudinal decline in multimodal neuroimaging parameters in predicting symptom onset; and 3) to establish the best combination of multimodal neuroimaging parameters in predicting symptom onset.

Materials and methods

Participants

Within FTD-RisC, we are following healthy 50% at-risk family members from Dutch genetic FTD families on a 2-year basis. This paper reports on the 4-year follow-up of 83 participants from *MAPT* or *GRN* families, that were included between December 2009 and October 2012 [5,6,19]. DNA genotyping assigned participants either to the mutation carrier or healthy control group: 43 mutation carriers (30 *GRN*, 13 *MAPT*) and 40 healthy controls (31 *GRN* family members, nine *MAPT* family members). At study entry, mutation carriers were asymptomatic according to established diagnostic criteria for behavioural variant FTD (bvFTD) [20] or primary progressive aphasia (PPA) [21]. Their selection was based on the presence of at least one follow-up MRI scan. Only healthy controls that had undergone all three study visits were selected to ascertain stability of the data points. As such, we excluded 10 healthy controls, leaving 73 eligible participants in the final dataset (Figure 2.1.1).

Procedure

Every 2 years, all participants underwent a standardised clinical assessment consisting of a brain MRI, medical history, a neurological examination, and an extensive neuropsychological test battery. Knowledgeable informants (e.g. siblings, spouses) were asked about functional, cognitive, behavioural and/or neuropsychiatric changes by means of a structured interview and a well-validated questionnaire (Neuropsychiatric Inventory; NPI) [22], either during the study visit or afterwards in a telephone interview. In study participants, depressive symptoms were rated by means of the Beck's Depression Inventory (BDI) [23]. Neuropsychological testing consisted of screening tests for global cognition – the Mini-Mental State Examination (MMSE) [24] and Frontal Assessment Battery (FAB) [25] – and tests within the domains language, attention and mental processing speed, executive function, memory, visuoconstruction, and social cognition (test battery was described previously; [6]).

Converters

Using abovementioned clinical assessment, we determined symptom onset in mutation carriers, following clinical diagnostic criteria for bvFTD [20] or PPA [21]. Eight mutation carriers developed symptoms of FTD, five carrying a *MAPT* mutation and three carrying a *GRN* mutation. Two mutation carriers (one *GRN* and one *MAPT*) developed bvFTD between baseline and follow-up after 2 years. Two mutation carriers (both *GRN*) developed non-fluent variant PPA (nfvPPA) and four mutation carriers (all *MAPT*) developed bvFTD between follow-up after 2 and follow-up after 4 years. Mutation carriers remaining without FTD symptoms are referred to as 'non-converters' (n=35). See Supplementary Table 2.1.1 for demographic, clinical and neuropsychological data of the converters, and Figure 2.1.1 for converters' symptom onset within the study time-window.

Standard Protocol Approvals, Registrations, and Patient Consents

The clinical investigators and participants were blind for the participants' genetic status, except for the status of participants that decided to undergo predictive testing. In converters, we offered the patient and family members genetic counselling and we unblinded the genetic status, in order to confirm the

presence of the pathogenic mutation. All participants gave written informed consent at study entry. The study was approved by the Medical and Ethical Review Committee of the Erasmus Medical Center.

Study design

All converters were grouped into one converter group, and compared to healthy controls and non-converters at three time points: baseline, follow-up after 2 and 4 years, rearranged as (Figure 2.1.1):

- *4 years before symptom onset* – the MRI scan acquired 4 years before symptom onset was used. Analyses were performed on six out of eight converters, as two mutation carriers developed symptoms between baseline and first follow-up visit, and therefore no scans 4 years prior to symptom onset were available. Converter data were compared to baseline data of non-converters and healthy controls;
- *2 years before symptom onset* – the MRI scan acquired 2 years before symptom onset was used. Data was available for all converters (n=8). Of one *MAPT* converter, the diffusion scan had to be excluded due to insufficient data quality. Converter data were compared to data of the follow-up after 2 years of non-converters and healthy controls;
- *after symptom onset* – we used the MRI scan acquired at the visit the FTD diagnosis was set (n=8). Of one *MAPT* converter, only the T1 scan was available, as the participant terminated MR imaging prematurely, and therefore no diffusion scan could be acquired. Converter data were compared to data of the follow-up after 4 years of non-converters and healthy controls.

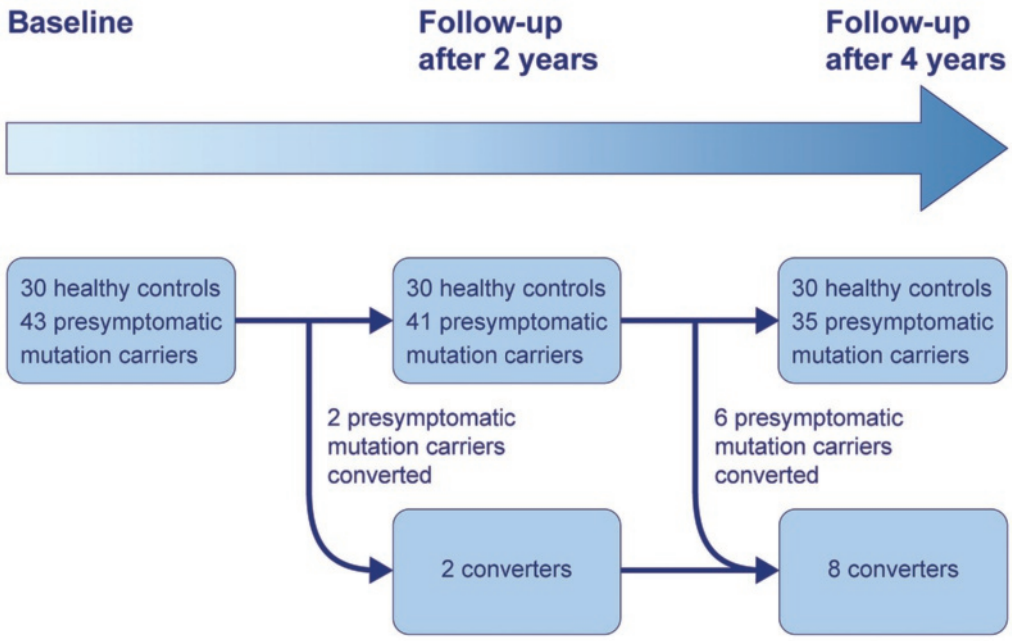

Figure 2.1.1 | **Study design.** A schematic timeline of the 4-year follow-up of presymptomatic mutation carriers, converters and healthy controls within FTD-RisC. Eight mutation carriers converted to clinical FTD within the study window; two between baseline and follow-up after two years, and six between follow-up after two and four years. For the data analysis, the data were restructured into three new time points: four years before symptom onset, two years before symptom onset, and symptom onset.

Image acquisition and (pre)processing

On each study visit, we acquired volumetric T1-weighted and diffusion tensor images on a Philips 3T Achieva MRI scanner (Philips Medical Systems, Best, the Netherlands) using an 8-channel SENSE head coil. Images were pre-processed by means of standard FMRIB Software Library (FSL; version 5.0.6) Voxel-Based Morphometry (VBM) and Tract-Based Spatial Statistics (TBSS) pre-processing tools (http://www.fmrib.ox.ac.uk/fsl). See Supplement 2.1.2 for specific image acquisition parameters and pre-processing pipelines. The resulting images were fed into whole-brain voxelwise statistics and region-of-interest (ROI) analyses (see below).

Whole-brain voxelwise statistics – TBSS and VBM

We investigated cross-sectional WM diffusion (fractional anisotropy; FA) and GM volume differences between converters, non-converters and healthy controls at the three time points by means of permutation-based testing using 5,000 permutations, applying one-way ANCOVAs with age and gender as covariates. Moreover, in order to generate change over time maps for repeated measures analyses, we subtracted the WM and GM maps calculated at the after symptom onset visit from the maps calculated at the 4 years before symptom onset visit in FSL. Using TFCE in Randomise, the significance level was set at FWE-corrected $p<0.05$. As the field-of-view (FOV) of the diffusion tensor images provided incomplete coverage of the lower brain areas, including cerebellum, the cerebellum was masked out from the TBSS analyses. In one of the converters we found a large (asymptomatic) cerebellar cyst, we therefore performed the VBM analyses in two steps, ascertaining that this subject was not driving the results in the cerebellum: 1) the entire group with the cerebellum included in all subjects; 2) the analysis excluding abovementioned converter.

ROI selection

We based our ROI selection on an extensive literature search into WM and GM changes in FTD (see Supplement 2.1.3 and Supplementary Table 2.1.2). We selected the following WM tracts: UF, superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), IFOF, genu, body and splenium of the corpus callosum (respectively gCC, bCC, and sCC), fornix, cingulum bundle, and forceps minor (FM). The John Hopkins University 1-mm atlas in FSL was used to parcel the entire WM into predefined ROIs (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases; [26]. Using FSL tools, the ROIs were restricted to voxels included in the mean FA skeleton mask – after which they were applied to the FA skeleton, giving left and right FA values per tract for each participant. The Harvard-Oxford 2-mm structural Atlas in FSL was applied to each subjects' native space GM segmentation, after which the mean voxel GM partial volume estimation per region (48 left, 48 right ROIs) was multiplied with the total volume of the image (in $mm^3/1000$), giving the GM per region in ml. For the GM ROIs, we selected the following regions: frontal lobe, prefrontal cortex (PFC), anterior temporal lobe, total temporal lobe, anterior cingulate cortex, total cingulate cortex, and insular cortex. The total cortical lobes and cingulate were the sum of all regions belonging to that area. The insula and anterior cingulate cortex were taken directly from the atlas. The prefrontal ROI was the sum of the frontal pole, orbitofrontal cortex, and superior, middle and inferior frontal gyrus. The anterior temporal ROI was the sum of the temporal pole, and the anterior divisions of the superior, middle and inferior temporal gyrus. All GM ROIs were corrected for head size by expressing

it as a percentage of the total intracranial volume in ml (%TIV), as automatically calculated in SPM12 (Wellcome Trust Centre for Neuroimaging, UCL, London, UK) running in MATLAB (version R2013b).

Statistical analysis

Statistical analyses were performed using SPSS Statistics 21.0 (IBM Corp., Armonk, NY) and GraphPad Prism 7 (La Jolla, California, USA). The significance level was set at $p<0.05$ (two-tailed) across all comparisons. We compared baseline demographic data between groups by means of one-way ANOVA, with Bonferroni post-hoc testing. Differences in sex between groups were analysed using Pearson χ^2 tests. We analysed longitudinal data points of global cognition and questionnaires using one-way repeated measures ANOVA. We investigated the classification abilities of ROI WM integrity and GM volume loss in discriminating between converters, non-converters and healthy controls by determining the area-under-the-curve (AUC) with 95% confidence intervals obtained by receiver operating characteristics (ROC) analyses, with optimal cut-off levels at the highest Youden's index (sensitivity + specificity-1; [27]). First, for ease of interpretation, we standardised all raw FA and GM volumes by converting them into z-scores per time-point (i.e. raw score minus the mean of healthy controls, divided by the standard deviation of healthy controls). Then, we calculated delta z-scores between time-points per ROI (after onset minus 4 years before symptom onset). To assess the performance of combinations of neuroimaging parameters, we performed logistic regression analyses, taking group (converter vs. non-converter and converter vs. healthy controls) as dependent variable and the delta z-scores as independent variables. The models were selected with a forward stepwise method according to the likelihood ratio test and applying the standard p-values for variable inclusion (0.05) and exclusion (0.10), with age and gender as covariates. Goodness of fit was evaluated with the Hosmer-Lemeshow (HL) χ^2 test. Nagelkerke R^2 is reported as measure of effect size.

Results

Demographics and clinical data

Demographic and clinical data of converters, non-converters and healthy controls are shown in Table 2.1.1. The mean familial age at symptom onset in converters was lower than in non-converters and healthy controls (both $p=0.006$). After symptom onset, converters had lower MMSE scores than non-converters and healthy controls (both $p<0.001$) and had significantly more neuropsychiatric symptoms, reflected in higher BDI (converters vs. non-converters $p=0.031$ – converters vs. healthy controls $p=0.054$) and NPI (converters vs. non-converters $p=0.075$ – converters vs. healthy controls $p=0.011$) scores. In converters, a significant decline over time was found for the MMSE ($p=0.002$). No significant changes in global cognition or neuropsychiatric symptoms were found in non-converters and healthy controls.

Table 2.1.1 | Demographics and clinical data

Demographics		Converters (n=8)	Non-converters (n=35)	Healthy controls (n=30)	*p*-value
Age at study entry, y		49.5 ± 9.6	50.3 ± 10.2	50.6 ± 10.7	0.966
Sex, female (%)		4 (50)	21 (60)	19 (63.3)	0.790
Education (Verhage)[1]		6.0 ± 0.6	5.5 ± 1.0	5.4 ± 1.0	0.365
Gene, *GRN* (%)		3 (37.5)	27 (77.1)	24 (80)	0.050
Onset age family, y		52.4 ± 7.0	59.2 ± 5.5	59.4 ± 4.7	0.005
Years from estimated onset at study entry		5.0 ± 4.7	8.9 ± 8.1	N/A	0.596
Clinical data	**Years to onset**				
MMSE	**4**	29.3 ± 0.8	29.2 ± 1.5	29.4 ± 0.9	0.685
	2	29.1 ± 1.1	28.8 ± 1.9	29.4 ± 1.1	0.288
	0	26.3 ± 3.3	29.3 ± 1.2	29.4 ± 0.9	<0.001
FAB*	**4**	–	–	–	–
	2	17.3 ± 0.8	17.5 ± 0.9	17.5 ± 0.8	0.888
	0	15.7 ± 1.6	17.1 ± 1.1	16.9 ± 1.4	0.057
BDI	**4**	1.3 ± 1.6	3.5 ± 4.8	4.0 ± 4.3	0.414
	2	3.1 ± 3.9	3.2 ± 4.2	3.7 ± 4.1	0.897
	0	9.6 ± 10.5	3.0 ± 6.6	3.5 ± 4.3	0.032
NPI-Q*	**4**	–	–	–	–
	2	0.1 ± 0.4	2.9 ± 13.6	0.7 ± 1.3	0.638
	0	13.6 ± 16.4	3.9 ± 12.2	0.8 ± 1.5	0.015

Values indicate: mean ± standard deviation. *Abbreviations: GRN*, progranulin; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; BDI, Beck's Depression Inventory; NPI-Q, Neuropsychiatric Inventory. [1]Dutch educational system categorized into levels from 1=less than 6 years of primary education to 7=academic schooling [44]. *Data only available on follow-up visits.

Cross-sectional whole brain WM integrity and GM volume loss

Analyses between converters, non-converters and HC demonstrated no significant differences in FA or GM volume 4 years before symptom onset (Table 2.1.2; Figure 2.1.2A, Figure 2.1.3A). Two years before symptom onset, converters had lower FA values than both non-converters and healthy controls in the UF, SLF, IFOF, ILF, CC, FM, cingulum, anterior thalamic radiation (ATR) and anterior corona radiata (ACR; Table 2.1.3; Figure 2.1.2B, Figure 2.1.3B), and lower GM volume of the bilateral frontal and temporal lobes, insula and cingulate cortex, extending to the parietal lobe and cerebellum (Table 2.1.2; Figure 2.1.2B, Figure 2.1.3B). After symptom onset, converters had lower FA values across all WM tracts (Table 2.1.2, Figure 2.1.2C), and lower GM volumes of large areas covering the frontal and temporal cortices, but also subcortical areas (e.g. thalamus) and cerebellum – with relative sparing of the parietal and occipital lobes in comparison to non-converters (Table 2.1.2; Figure 2.1.2C). The differences were in similar locations, but more extensive in comparison to healthy controls (Table 2.1.2, Figure 2.1.3C). The results were not driven by the converter with the cerebellar cyst, as excluding him did not change abovementioned findings. There were no significant differences in FA or GM volume between non-converters and healthy controls at any time point (Table 2.1.2).

Table 2.1.2 | Whole brain comparisons (TBSS, VBM) between converters, non-converters and healthy controls

	WM/GM	Cluster	Size	*p*	MNI coordinates			L/R	Area (peak voxel)
					x	y	z		
Converters vs. non-converters									
4 years before symptom onset	WM	–	–	ns	–	–	–	–	–
	GM	–	–	ns	–	–	–	–	–
2 years before symptom onset	WM	1	21781	0.004	15	42	-12	R	IFOF, UF, forceps minor
		2	1882	0.023	34	1	-32	R	cingulum
		3	144	0.047	48	-36	-4	R	SLF
		4	66	0.049	-48	-10	22	L	SLF
		5	19	0.050	-56	0	15	L	SLF
	GM	1	27122	<0.001	10	12	-28	R	orbitofrontal cortex
		2	4660	0.004	-40	2	-26	L	planum temporale
after symptom onset	WM	1	61066	<0.001	35	-8	-37	R	ILF
	GM	1	88222	<0.001	50	-12	-46	R	inferior temporal gyrus
longitudinal decline	WM	1	894	0.047	-3	153	84	n/a	gCC
	GM	1	18601	0.001	-30	22	2	L	insula
		2	6318	0.001	44	-32	-26	R	inferior temporal gyrus
Converters vs. healthy controls									
4 years before symptom onset	WM	–	–	ns	–	–	–	–	–
	GM	–	–	ns	–	–	–	–	–
2 years before symptom onset	WM	1	21781	0.004	15	42	-12	R	IFOF, UF, forceps minor
		2	1882	0.023	34	1	-32	R	cingulum
		3	144	0.047	48	-36	-4	R	SLF
		4	66	0.049	-48	-10	22	L	SLF
		5	19	0.050	-56	0	15	L	SLF
	GM	1	23126	<0.001	40	-38	-30	R	fusiform gyrus
		2	538	0.021	-16	50	32	L	frontal pole
after symptom onset	WM	1	62308	<0.001	14	50	-15	R	IFOF, UF
	GM	1	81558	<0.001	42	-10	-48	R	inferior temporal gyrus
		2	439	0.030	-14	-62	44	L	precuneus
		3	150	0.036	-18	-78	-4	L	lingual gyrus
		4	41	0.047	20	-86	-4	R	occipital fusiform gyrus
longitudinal decline	WM	1	914	0.026	-2	153	84	n/a	gCC
	GM	1	25216	0.001	-44	6	-30	L	temporal pole
		2	11300	0.001	46	-32	28	R	inferior temporal gyrus
		3	1165	0.014	18	-88	12	R	occipital pole
		4	391	0.029	-34	-70	22	L	lateral occipital cortex
		5	82	0.046	-20	-90	-4	L	occipital pole

Table 2.1.2 | Continued

	WM/GM	Cluster	Size	*p*	MNI coordinates			L/R	Area (peak voxel)
					x	y	z		
Non-converters vs. healthy controls									
4 years before symptom onset	WM	–	–	ns	–	–	–	–	–
	GM	–	–	ns	–	–	–	–	–
2 years before symptom onset	WM	–	–	ns	–	–	–	–	–
	GM	–	–	ns	–	–	–	–	–
after symptom onset	WM	–	–	ns	–	–	–	–	–
	GM	–	–	ns	–	–	–	–	–
longitudinal decline	WM	–	–	ns	–	–	–	–	–
	GM	–	–	ns	–	–	–	–	–

Abbreviations: TBSS, Tract-Based Spatial Statistics; VBM, Voxel-BasedMorphometry; MNI, Montreal Neurological Institute; R, right; L, left; gCC, genu corpus callosum; IFOF, inferior fronto-occipital fasciculus; UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus; ns, non-significant; n/a, not applicable. Clusters >50 voxels have been reported. $P<0.05$, FWE-corrected for multiple comparisons.

Longitudinal whole brain WM integrity and GM volume loss

Converters demonstrated longitudinal decline of FA in the gCC and FM over time in comparison to non-converters (Table 2.1.2, Figure 2.1.4A), and even more extensive (left UF, left SLF and posterior CC) compared to healthy controls (Table 2.1.2, Figure 2.1.4B). The longitudinal trajectories of the right UF and gCC are shown in Figure 2.1.5A. Furthermore, converters had significant GM volume loss of the prefrontal cortex, cingulate cortex, insula, temporal poles and inferior temporal gyrus in comparison to non-converters (Table 2.1.2, Figure 2.1.4A), and again more extensive (most of the frontal and temporal lobes, extending to the occipital cortex and cerebellum) compared to healthy controls (Table 2.1.2, Figure 2.1.4B). The results were not driven by the converter with the cerebellar cyst, as excluding him did not change abovementioned findings. There were no significant differences in FA or GM volume loss between non-converters and healthy controls (Table 2.1.2).

Classification

Between converters and non-converters, longitudinal decline in the WM integrity of the right UF and gCC provided significant classifiers (Table 2.1.3a, Figure 2.1.5B). Decline in the gCC provided the best fit for classifying between converters and non-converters (χ^2=0.738; $p<0.001$). The model correctly classified 85.0% of cases. Between converters and healthy controls, longitudinal decline of the right UF, gCC, FM, right IFOF, right insula and left anterior temporal lobe provided significant classifiers (Table 2.1.3b, Figure 2.1.5B). Decline in the gCC and right ILF provided the best fit for classifying between converters and healthy controls (χ^2=1.000; $p<0.001$). The model correctly classified 100% of cases.

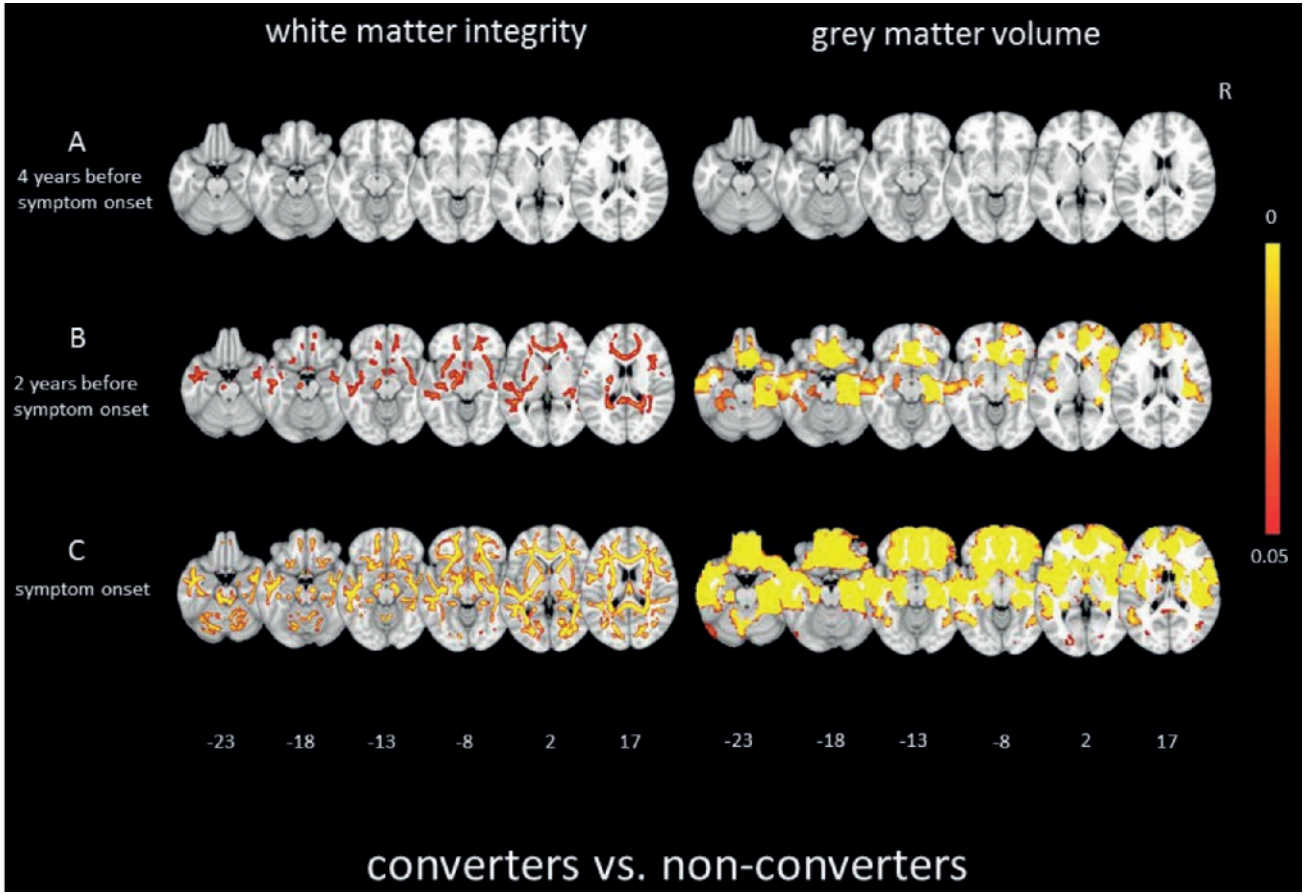

Figure 2.1.2 | **Cross-sectional whole brain grey matter volume and white matter integrity differences between converters, non-converters and healthy controls.** Maps illustrate significant differences in white matter integrity (FA; left) and grey matter volume (right) between converters and non-converters at 4 years before onset A) 2 years before onset B) and at symptom onset (C). FA thresholded ($p<0.05$) statistical images were thickened using tbss_fill in FSL for better visibility. Color bars represent *p*-values.

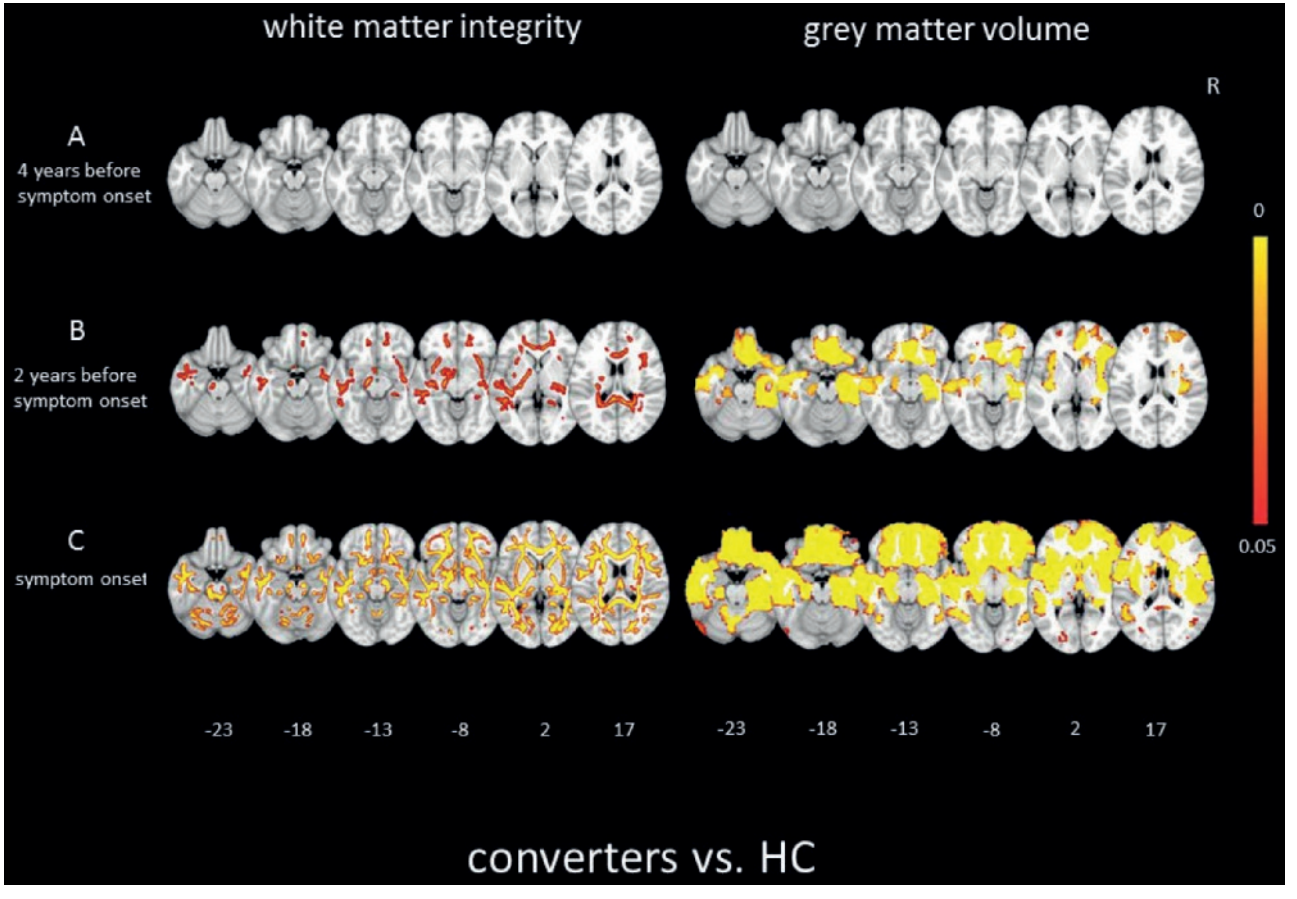

Figure 2.1.3 | **Cross-sectional whole brain grey matter volume and white matter integrity differences between converters, non-converters and healthy controls.** Maps illustrate significant differences in white matter integrity (FA; left) and grey matter volume (right) between converters and healthy controls at 4 years before onset A) 2 years before onset B) and at symptom onset C) FA thresholded ($p<0.05$) statistical images were thickened using tbss_fill in FSL for better visibility. Color bars represent *p*-values. *Abbreviation:* HC, healthy controls.

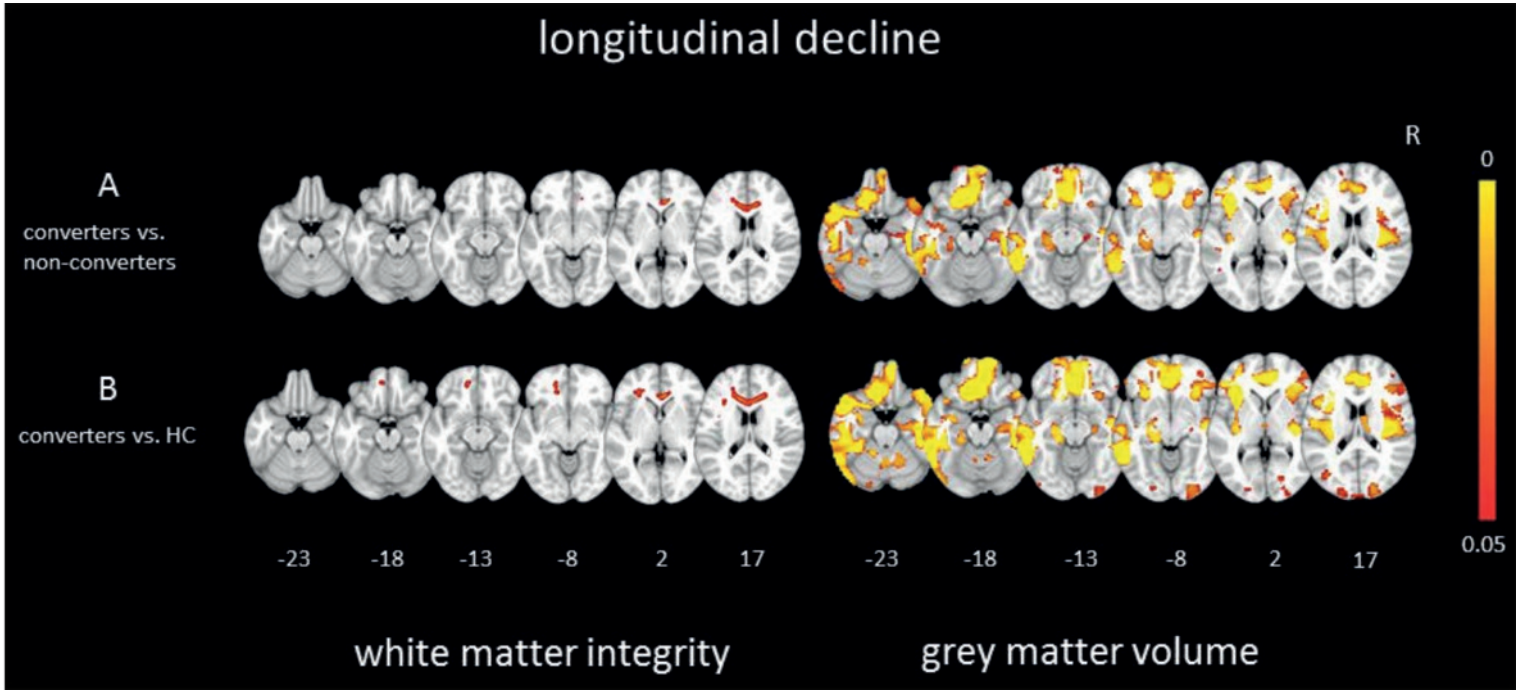

Figure 2.1.4 | **Longitudinal whole brain grey matter volume and white matter integrity differences between converters, non-converters and healthy controls.** Maps illustrate significant differences in white matter integrity (left) and grey matter volume (right) between converters and non-converters A) and between converters and healthy controls (HC; B). FA thresholded ($p<0.05$) statistical images were thickened using tbss_fill in FSL for better visibility. Color bars represent p-values.

Table 2.1.3a | Diagnostic performance of white matter integrity and grey matter volume loss between converters and non-converters

	L/R	AUC [95% CI]	*p*	Optimal cut-off	Sensitivity	Specificity
White matter tracts						
UF	R	0.83 [0.62-1.00]	**0.047**	-0.51	100%	62.5%
	L	0.81 [0.61-1.00]	0.059	–	–	–
SLF	R	0.72 [0.50-0.93]	0.186	–	–	–
	L	0.64 [0.31-0.97]	0.395	–	–	–
gCC	n/a	0.91 [0.86-1.00]	**0.014**	-0.85	100%	81.3%
bCC	n/a	0.59 [0.26-0.93]	0.571	–	–	–
sCC	n/a	0.72 [0.46-0.97]	0.186	–	–	–
fornix	n/a	0.80 [0.54-1.00]	0.073	–	–	–
forceps minor	n/a	0.73 [0.47-0.99]	0.156	–	–	–
cingulum bundle	n/a	0.72 [0.36-1.00]	0.186	–	–	–
IFOF	R	0.77 [0.54-0.99]	0.108	–	–	–
	L	0.67 [0.41-0.94]	0.299	–	–	–
ILF	R	0.64 [0.37-0.91]	0.395	–	–	–
	L	0.63 [0.28-0.97]	0.450	–	–	–
Grey matter areas						
frontal lobe	R	0.53 [0.22-0.84]	0.832	–	–	–
	L	0.66 [0.30-1.00]	0.235	–	–	–
prefrontal cortex	R	0.52 [0.20-0.83]	0.899	–	–	–
	L	0.66 [0.31-1.00]	0.218	–	–	–
temporal lobe	R	0.69 [0.35-1.00]	0.137	–	–	–
	L	0.61 [0.33-0.89]	0.396	–	–	–
ATL	R	0.51 [0.25-0.78]	0.932	–	–	–
	L	0.76 [0.47-1.00]	0.051	–	–	–
insula	R	0.66 [0.38-0.94]	0.218	–	–	–
	L	0.60 [0.34-0.86]	0.445	–	–	–
cingulate cortex	R	0.61 [0.31-0.91]	0.396	–	–	–
	L	0.78 [0.50-1.00]	**0.034**	-0.29	83.3%	86.7%
ACC	R	0.74 [0.37-0.92]	0.270	–	–	–
	L	0.65 [0.36-0.94]	0.252	–	–	–

Abbreviations: L, left; R, right; AUC, area under the curve; UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; gCC, genu corpus callosum; bCC, body corpus callosum; sCC, splenium corpus callosum; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; ATL, anterior temporal lobe; ACC, anterior cingulate cortex. White matter tract values represent FA (fractional anisotropy), ranging between 0 and 1. Grey matter area values are expressed in milliliters, corrected for total intracranial volume (TIV). The optimal cut-off level was determined by the highest Youden's index (i.e. sensitivity + specificity-1) (Youden et al., 1950). Significant *p*-values are given in bold.

Table 2.1.3b | Diagnostic performance of white matter integrity and grey matter volume loss between converters and healthy controls

	L/R	AUC [95% CI]	*p*	Optimal cut-off	Sensitivity	Specificity
White matter tracts						
UF	R	0.86 [0.69-1.00]	**0.024**	-0.39	100%	69.6%
	L	0.70 [0.44-0.95]	0.219	–	–	–
SLF	R	0.71 [0.47-0.94]	0.195	–	–	–
	L	0.66 [0.30-1.00]	0.306	–	–	–
gCC	n/a	0.96 [0.88-1.00]	**0.004**	-0.87	100%	91.3%
bCC	n/a	0.59 [0.36-0.82]	0.585	–	–	–
sCC	n/a	0.62 [0.36-0.88]	0.453	–	–	–
fornix	n/a	0.70 [0.43-0.96]	0.219	–	–	–
forceps minor	n/a	0.85 [0.64-1.00]	**0.029**	-0.06	100%	65.2%
cingulum bundle	n/a	0.72 [0.37-1.00]	0.172	–	–	–
IFOF	R	0.81 [0.65-0.98]	**0.048**	-0.35	100%	73.9%
	L	0.72 [0.52-0.92]	0.172	–	–	–
ILF	R	0.66 [0.37-0.95]	0.306	–	–	–
	L	0.58 [0.23-0.93]	0.633	–	–	–
Grey matter areas						
frontal lobe	R	0.57 [0.27-0.86]	0.621	–	–	–
	L	0.62 [0.27-0.97]	0.365	–	–	–
prefrontal cortex	R	0.51 [0.20-0.81]	0.967	–	–	–
	L	0.64 [0.31-0.97]	0.284	–	–	–
temporal lobe	R	0.71 [0.43-0.99]	0.108	–	–	–
	L	0.58 [0.29-0.87]	0.537	–	–	–
ATL	R	0.60 [0.32-0.88]	0.434	–	–	–
	L	0.80 [0.50-1.00]	**0.023**	-0.24	83.3%	90.3%
insula	R	0.76 [0.54-0.98]	**0.048**	-0.30	66.7%	77.4%
	L	0.63 [0.39-0.88]	0.303	–	–	–
cingulate cortex	R	0.57 [0.25-0.89]	0.592	–	–	–
	L	0.72 [0.45-0.99]	0.091	–	–	–
ACC	R	0.52 [0.24-0.81]	0.869	–	–	–
	L	0.61 [0.29-0.93]	0.410	–	–	–

Abbreviations: L, left; R, right; AUC, area under the curve; UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; gCC, genu corpus callosum; bCC, body corpus callosum; sCC, splenium corpus callosum; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; ATL, anterior temporal lobe; ACC, anterior cingulate cortex. White matter tract values represent FA (fractional anisotropy), ranging between 0 and 1. Grey matter area values are expressed in milliliters, corrected for total intracranial volume (TIV). The optimal cut-off level was determined by the highest Youden's index (i.e. sensitivity + specificity-1) (Youden et al., 1950). Significant *p*-values are given in bold.

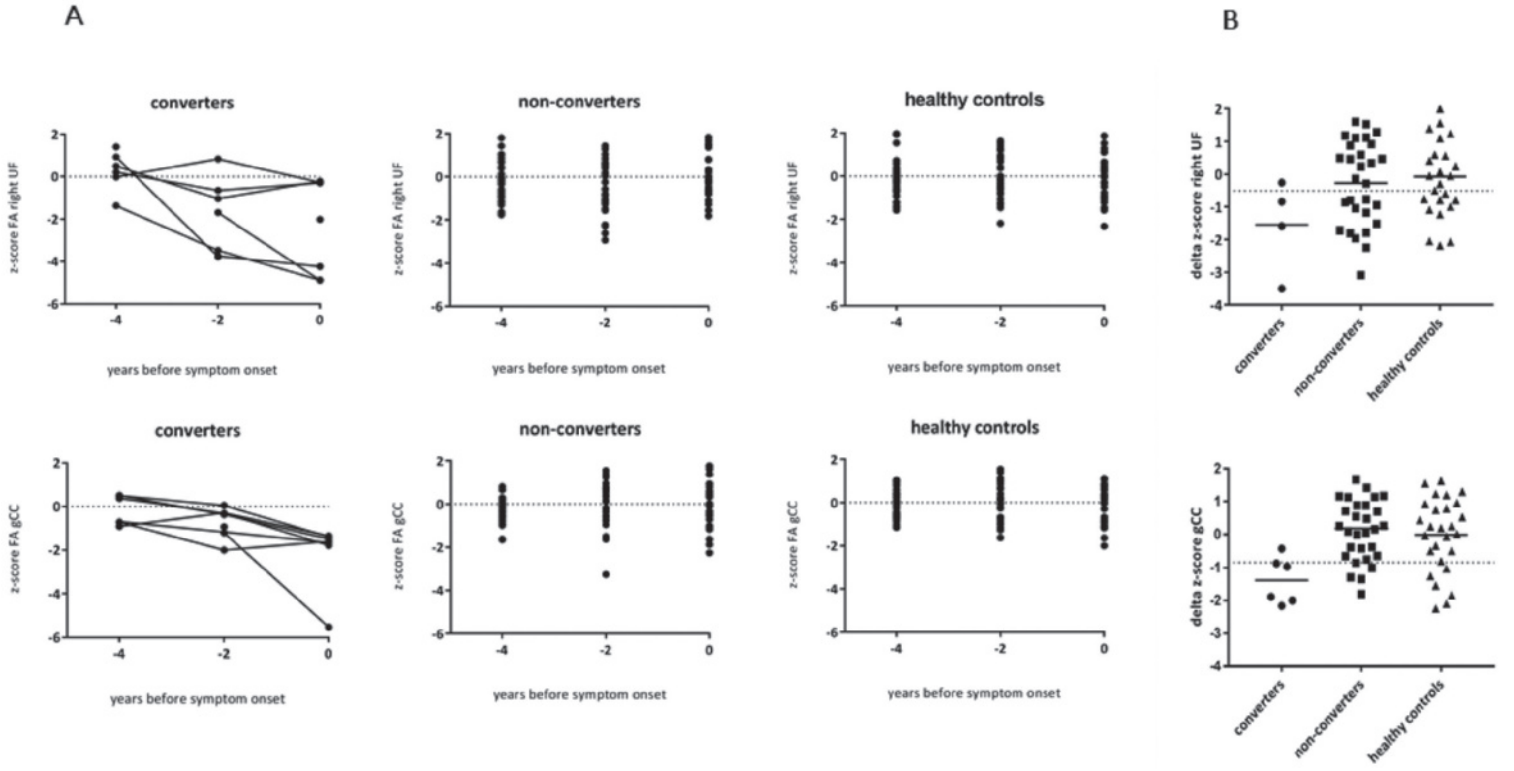

Figure 2.1.5 | **Longitudinal trajectories and classification accuracy of WM integrity decline from the presymptomatic to symptomatic phase.** A) Longitudinal trajectories of white matter integrity (FA) loss (z-score) in the right uncinate fasciculus (UF; top) and genu of the corpus callosum (gCC; bottom) in converters, non-converters and healthy controls. In converters, individual trajectories are drawn due to different sample sizes per time-point. B) Classification between converters, non-converters and healthy controls using the z-score delta fractional anisotropy (FA) of the right uncinate fasciculus (UF; top) and the genu of the corpus callosum (gCC; bottom). The dashed line represents the optimal cut-off to separate converters and non-converters (UF: delta FA=-0.51; sensitivity=100%, specificity=62.5% – gCC: delta FA=-0.85; sensitivity=100%, specificity=81.3%). The optimal cut-off between converters and healthy controls (not shown) is -0.39 (sensitivity=100%, specificity= 69.6%) and -0.87 (sensitivity=100%, specificity=91.3%) for the UF and gCC respectively.

Discussion

The present study is the first longitudinal study examining different neuroimaging modalities in a large cohort of at-risk participants from *GRN* and *MAPT* FTD families. Whole brain analyses demonstrated extensive loss of WM integrity and GM volume in converters, present from 2 years before symptom onset. The largest decline over time was found in the gCC, FM, UF and SLF, and the prefrontal and cingulate cortex, insula, temporal pole and inferior temporal gyrus. Classifiers between converters, non-converters and healthy controls were WM integrity loss of the right UF and gCC. WM integrity loss of the gCC provided the best measure for classifying between converters and healthy controls, while decline in the gCC and right ILF provided the best measures for classifying between converters and non-converters.

The most interesting finding of the present study is the relatively acute development of WM integrity and GM volume loss in the group of converters between 4 and 2 years before symptom onset, suggesting a rather explosive onset of pathophysiological changes shortly before symptom onset. The lower WM integrity of the UF in converters 2 years before symptom onset confirms this WN tract as the molecularly most vulnerable hub, already in the presymptomatic stage, as also found by two previous studies into familial FTD [5,8]. Tracts known to be involved in symptomatic frontotemporal dementia (*see literature review in Appendix 3*), the SLF, ILF, CC, FM, cingulum, ATR and ACR, are now also being confirmed as involved in the presymptomatic stage from 2 years before symptom onset. Moreover, the lower GM volume of the frontal, temporal, insular and cingulate cortex, extending to the parietal lobe, thalamus and cerebellum, largely overlaps with the presymptomatic spatial distribution found in the Genetic Frontotemporal dementia Initiative (GENFI) consortium [7]. The findings from this study greatly add to our understanding of the earliest structural MRI changes in FTD, in which both large WM [2,15,28] and GM [7] networks involved in social-emotional, executive, and language functioning become disrupted. A related key aspect concerns the spatial and temporal relationship between lower WM integrity and GM volume loss. Prior studies have suggested that WM abnormalities are the earliest marker of FTD, with GM atrophy occurring later in the disease process, and that the location and severity of WM integrity loss tends to exceed the GM atrophy [1-3,14]. In our study, not only did the spatial patterns of WM integrity and GM volume loss reveal a strong co-localization – confirming some previous studies [29-30], but contrasting others [2,15,31-34] – we also found a simultaneous onset of both WM integrity as well as GM volume loss. Although the latter seems incongruent with the hypothesis that WM pathology precedes GM abnormalities, it should be considered that direct comparisons of WM integrity and GM volume needs to be done with caution, as the imaging modalities investigating the tissue types differ considerably [14].

Our longitudinal study, in which mutation carriers are followed from the presymptomatic into the early symptomatic stage, provides crucial pathophysiological information about the disease progression over time. Longitudinal decline in converters was most prominent in the gCC, FM, prefrontal cortex, cingulate cortex, insula, and temporal lobes. Our findings thereby support the hypothesis of a network-led framework, in which neurodegeneration propagates along large-scale distributed WM networks with disease progression [35]. Although cross-sectional in nature and using a proxy for symptom onset, a

similar cascade of presymptomatic GM change was found in Rohrer et al. [7], with the first atrophy found in the insula, temporal and frontal cortices, spreading to the cingulate, parietal and occipital cortices with approaching estimated symptom onset. Longitudinal multimodal MRI studies in symptomatic FTD thus far have demonstrated significant loss of both WM integrity and GM volume over time [3,14-15,36], with more extensive progression of WM pathology than GM abnormalities across all FTD subtypes [3,14]. However, in our study the progression of GM atrophy visually seems larger than the WM integrity loss. As aforementioned, the imaging modalities differ, hampering a true comparison of patterns. Alternatively, this phenomenon does not occur initially in the presymptomatic stage, but later in the disease process [14].

Independently contributing to the prediction of symptom onset, presymptomatic decline in WM integrity of the right UF and gCC and GM volume loss of the left cingulate cortex, was found in converters. Our results greatly add to the current knowledge, as multimodal studies into FTD are scarce so far [37]. The few studies into the classification between frontotemporal and Alzheimer's disease (AD) patients demonstrated that both unimodal WM and GM neuroimaging significantly distinguished between the two groups (albeit weaker for GM than WM), but the optimal classification (87% sensitivity, 83% specificity) was attained by using a combination of techniques [38]. Möller et al. [39] furthermore showed that while GM atrophy measures contributed most to AD diagnosis, WM integrity measures added complementary information to GM atrophy measures in FTD. A possible explanation for this finding is the notion of FTD as a network disease – whereas AD is assumed to be a cortical dementia – in which loss of specific WM tracts connecting GM areas results in large network failure. The fact that in our search for the best combination of neuroimaging parameters we only found the gCC as significant discriminator between converters and non-converters is in line with this hypothesis. It would be interesting for future studies to replicate the present classification findings, preferably with different and/or more techniques (e.g. resting-state fMRI, ASL) or other statistical algorithms (e.g. support vector machines, machine learning techniques) to determine which combination of approaches achieves the highest classification accuracy for conversion to the symptomatic stage of FTD.

With upcoming clinical trials, ongoing studies are investigating the potential of longitudinal MRI as sensitive disease biomarkers. These interventions should ideally be applied in the earliest stage when the neuronal damage is still at its minimum [40], i.e. the presymptomatic stage. With both WM integrity and GM volume loss present at 2 years prior to symptom onset and increasing pathology when moving into the symptomatic stage, multimodal neuroimaging confirms its utility as disease staging and tracking biomarker. Longitudinal DTI changes in the gCC and as the strongest predictor for symptom onset is interesting, as Elahi et al. [36] have also found this region as the most consistent finding across all FTD syndromes; making this a potential WM tract to track disease progression in clinical trials that might include more than one FTD subtype. Interestingly, the WM integrity loss between 4 and 2 years before symptom onset seem to parallel the steep increase in NfL levels, found in a few converters in our previous study [41]. Future research should focus on the association between DTI parameters and NfL levels in a larger sample, as they may serve as potential biomarkers in future therapeutic trials.

The key strength of our study constitutes our longitudinal design, spanning a 4-year follow-up period of tracking at-risk participants from both *MAPT* and *GRN* families. The non-carriers from the same families were an ideal control group, as they had the same genetic and social background. Secondly, we have used the true onset instead of estimated symptom onset. Thirdly, all subjects underwent DTI imaging on the same scanner with the same sequencing parameters in a 4-year follow-up period. A first drawback is the relatively small sample size with respect to statistical power, and warrant replication in larger longitudinal cohorts with more converters. At this moment, our group of converters is too small to perform subgroup analyses, but for future research it would be informative to further explore the presymptomatic genotypic or phenotypic prognostic and diagnostic value of multimodal neuroimaging. In the current study we only describe changes in FA, as our baseline study [5] demonstrated this to be the most sensitive parameter in the presymptomatic phase. Furthermore, alterations in FA have found to be most pronounced with disease progression [14,29] and provided the best classification accuracy for FTD, making FA a justified metric for longitudinal studies in FTD. However, to interpret the exact neuropathological processes underlying the DTI changes, future studies should also include other diffusivity measures. Secondly, DTI scan-rescan reliability in neurodegeneration is scarcely studied and can be potentially hampered by its unequal distribution throughout different brain regions (i.e. highly anisotropic WM tracts have lower within-subject variability) and higher susceptibility to partial volume effects in smaller tracts [42]. Lastly, the DTI FOV in the present study was too small to include the lower WM tracts in our analyses – although this would have been interesting considering recent findings of corticospinal tract degeneration in both bvFTD and nfvPPA [43].

Conclusions

Our longitudinal study demonstrates the presence of presymptomatic structural neuroimaging changes in FTD mutation carriers, starting two years before onset, with predominant frontotemporal pathology spreading towards and into symptom onset. Presymptomatic decline of WM integrity of the UF and gCC, and GM volume loss of the left cingulate cortex, are consistent predictors of symptom onset in converters. Our results confirm the presence of a presymptomatic neuroimaging stage of familial FTD, and highlight the potential value of longitudinal multimodal structural MR imaging as a sensitive prognostic and diagnostic biomarker for presymptomatic to early symptomatic familial FTD.

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Supplementary Table 2.1.1 | Demographic, clinical and neuropsychological data of the converters

Demographics	Converter							
	1	2	3	4	5	6	7	8
Clinical diagnosis	bvFTD	bvFTD	bvFTD	nfvPPA	nfvPPA	bvFTD	bvFTD	bvFTD
Age at onset	67	56	57	51	57	42	45	43
Mean onset age family	59.7	53.2	53.2	59.7	59.7	44.5	44.5	44.5
Gene	*GRN*	*MAPT*	*MAPT*	*GRN*	*GRN*	*MAPT*	*MAPT*	*MAPT*
Mutation	S82VfsX174	P301L	P301L	S82VfsX174	S82VfsX174	G272V	G272V	G272V
Gender	Female	Female	Male	Female	Female	Male	Male	Male
Global cognition and questionnaires								
MMSE	28	30	27	29	26	26	26	27
FAB	16	16	13	18	15	15	16	17
NPI-Q	29	0	23	2	1	15	1	39
CBI-R	46	0	32	4	0	42	25	55
Neuropsychological test								
Social cognition								
Happé Cartoon Test	-1.8	-1.5	-2.2	1.2	-1.4	-2.6	-1.2	0.2
Ekman Faces Test	-0.7	-3.3	-2.0	0.6	-3.0	-3.0	-1.6	-0.4
Language								
Boston Naming Test 60-item	-0.1	0.4	-0.6	0.7	0.2	>-3.0	>-3.0	0.1
ScreeLing – phonology (/24)	23.5/24	24/24	24/24	23/24	23/24	24/24	24/24	24/24
Semantic Association Test (/30)	29/30	29/30	26/30	28/30	29/30	21/30	28/30	28/30
Similarities WAIS-III	-0.7	-1.0	-1.0	0	-1.7	-1.4	1.4	-1.0

Abbreviations: bvFTD, behavioural variant FTD; PNFA, progressive non-fluent aphasia; *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; NPI-Q, Neuropsychiatric Inventory-Questionnaire; CBI-R, Cambridge Behavioural Inventory-Revised; WAIS, Wechsler Adult Intelligence Scale; TMT, Trailmaking Test; WCST, Wisconsin Card Sorting Test; RAVLT, Rey Auditory Verbal Learning Test. Test scores are at the visit after symptom onset. Scores have been transformed to z-scores (if applicable) or are expressed as their score/total score.

Supplementary Table 2.1.1 | Continued

Demographics	Converter							
	1	2	3	4	5	6	7	8
Executive function								
Categorical fluency (animals)	-1.3	-1.1	-2.3	0.2	-1.5	-2.3	-1.3	-1.5
Phonological fluency	-2.0	-2.1	-1.7	-0.4	-1.1	-1.0	-0.1	-0.4
TMT part B | A	-2.8	-2.0	-1.1	-1.6	>-3.0	-2.1	1.0	-0.5
Stroop card 3 | 2	-0.7	0	-0.2	-0.9	-0.6	1.3	1.1	-0.1
WCST – concepts	-2.2	-2.2	-2.0	-1.4	-1.0	0.2	0.3	0.2
Attention & mental processing speed								
TMT part A	-0.9	-0.7	-1.5	1.1	-1.1	1.7	1.3	-0.2
TMT part B	-2.9	-2.1	-1.6	-0.9	>-3.0	-0.1	1.6	-0.4
Stroop card 1	-2.0	0	-1.9	-1.4	-1.4	-1.4	-0.6	-2.3
Stroop card 2	-1.3	-1.2	-3.1	-1.6	-1.4	-1.5	-1.1	-1.9
Stroop card 3	-1.5	-0.9	-2.1	-1.8	-1.5	0	0.1	-1.3
Letter Digit Substitution Test	-0.4	0	-1.1	0.42	-0.4	0.42	0.8	>-2.3
Memory								
RAVLT immediate recall	0.7	0.7	-2.3	2.6	-1.8	-2.2	0	-2.0
RAVLT delayed free recall	0.4	0.2	-2.1	1.9	-0.2	-4.2	-0.2	-1.8
RAVLT delayed cued recall (/30)	30/30	29/30	29/30	30/30	29/30	19/30	29/30	27/30
Visual Association Test	<-0.6	<-0.6	<-0.8	<-0.6	<-0.6	>-3.0	<-0.8	<-0.6
Digit Span WAIS-III	-0.4	-0.4	-0.4	-1.0	-2.0	1.0	-2.0	-0.4
Visuoconstruction								
Clock Drawing (/14)	13/14	13/14	13/14	13/14	12/14	11/14	12/14	13/14
Block Design WAIS-III	-1.4	-0.7	0.4	0.4	-1.0	-0.4	2.0	-0.4

Abbreviations: bvFTD, behavioural variant FTD; PNFA, progressive non-fluent aphasia; *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; NPI-Q, Neuropsychiatric Inventory-Questionnaire; CBI-R, Cambridge Behavioural Inventory-Revised; WAIS, Wechsler Adult Intelligence Scale; TMT, Trailmaking Test; WCST, Wisconsin Card Sorting Test; RAVLT, Rey Auditory Verbal Learning Test. Test scores are at the visit after symptom onset. Scores have been transformed to z-scores (if applicable) or are expressed as their score/total score.

Supplement 2.1.2 | Image acquisition parameters & pre-processing pipeline

Image acquisition parameters

For grey matter volumetric comparisons and anatomical reference, T1-weighted images were acquired using the following scanning parameters: repetition time (TR)=9.8 ms, echo time (TE)=4.6 ms, flip angle=8°, 140 slices, voxel size=0.88 x 0.88 x 1.20 mm, total scan time=4.50 min. Diffusion tensor images were acquired by means of single-shot echo planar images (EPI) with gradients applied along 61 diffusion-weighted directions (maximum b-value s/mm^2 1000), using the following acquisition parameters: TR=8250 ms, TE=80 ms, flip angle=90°, 70 contiguous axial slices, voxel size=2 x 2 x 2 mm, field of view=256 x 208 x 140 mm, total scan time=8.48 minutes.

Pre-processing pipeline

We corrected raw diffusion data for motion artefacts and Eddy currents, we extracted binary brain masks using BET, and we fitted the diffusion tensor model at each voxel using DTIFIT – resulting in fractional anisotropy (FA) maps for each participant. We aligned the images to an FA standard template through nonlinear registration. A mean FA image was created and thinned to obtain a skeleton with tracts common to the entire group. Individual FA data was projected onto this skeleton (threshold 0.2). We performed pre-processing of the T1-weighted images through brain extraction followed by tissue segmentation and alignment to MNI-152 standard space (Montreal Neurological Institute, Montreal, QC, Canada) using non-linear registration. A study-specific template was created and native grey matter images were non-linearly re-registered to this template. The registered partial volume images were modulated to correct for local expansion or contraction by dividing by the Jacobian of the warp field. These modulated grey matter images were smoothed with an isotropic 4 mm Gaussian kernel (FWHM ~9 mm).

Supplement 2.1.3 | Overview of literature search for ROI selection

Paper selection

Papers were selected on the basis of the following Pubmed searches: "(Diffusion* OR DTI) AND (frontotemporal* OR FTD)"; "(White matter OR WM) AND (frontotemporal* OR FTD)"; "(Diffusion tensor imaging OR DTI) AND (primary progressive aphasia* OR PPA)"; "(White matter OR WM) AND (primary progressive aphasia* OR PPA)"; "(grey matter OR gray matter OR GM) AND (frontotemporal* OR FTD)"; "(grey matter OR gray matter OR GM) AND (primary progressive aphasia* OR PPA)"; "(atrophy) AND (frontotemporal* OR FTD)"; "(atrophy) AND (primary progressive aphasia* OR PPA)". Reference lists of the identified papers were examined for further leads. The search was limited to full-text papers published in English over the past ten years. Case studies were excluded. The final selection was based on relevance, as judged by the authors. Due to the scarcity of presymptomatic papers, and regions corroborated with those of the symptomatic stage, ROI selection was primarily based on papers describing symptomatic FTD. We selected white matter tracts and grey matter regions if they were described to be affected in >75% of the selected papers.

Supplementary Table 2.1.2 | Summary literature ROI WM and GM selection

Author	Technique	Patient groups	Regions
White matter tracts			
Presymptomatic studies			
Borroni et al. 2008	VBM	*GRN* carriers	UF, IFOF
Dopper et al. 2014	TBSS	*GRN* and *MAPT* carriers	UF
Lee et al. 2017	TBSS	*C9orf72* carriers	CC, cingulum, internal and external capsule
Symptomatic studies			
Agosta et al. 2010	VBM	svPPA	ILF, arcuate fasciculus, UF, SLF, gCC
Agosta et al. 2012	TBSS	bvFTD, PPA	CC (anterior-posterior gradient), cingulum bundles, corona radiata, external and internal capsule, fornix, cerebral and cerebellar peduncles, subcortical WM subjacent to frontal and parietal cortex, temporal and occipital WM, orbital and dorsolateral frontal WM
Acosta-Cabronero et al. 2011	TBSS, tractography	svPPA	UF, arcuate fasciculus
Borroni et al. 2007	Voxel-wise	fvFTD, tvFTD	SLF, ILF
D'Anna et al. 2016	ROI	PPA	UF, IFOF, ILF
Daianu et al. 2016	tractography	bvFTD, EOAD	UF, CC, ATR, cingulum, SLF
Hornberger et al. 2011	TBSS	bvFTD, AD	Frontal and anterior temporal regions
Lam et al. 2014	TBSS	bvFTD, PPA (nfPPA, svPPA)	ATR, anterior cingulum, SLF, ILF, IFOF, UF, CC
Lillo et al. 2012	TBSS	ALS, ALS-FTD, bvFTD	Forceps minor, anterior CC, ILF, CST
Lu et al. 2014	ROI	bvFTD, EOAD	Frontal lobes, genu CC
Mahoney et al. 2013	TBSS	PPA, AD	UF, ILF, SLF, subcortical projections
Mahoney et al. 2014	Voxel-wise	Familial/sporadic bvFTD, AD	UF, cingulum, CC, SLF, ILF, ATR, fornix
Mahoney et al. 2015	ROI	Sporadic bvFTD, *MAPT* carriers, *C9orf72* carriers	UF, cingulum
Matsuo et al. 2008	tractography	fvFTD, tvFTD	UF, ILF, arcuate fasciculus, CC (anterior-posterior gradient)
McMillan et al. 2012	ROI	bvFTD, PPA, CBS, AD	CST, IFOF, ILF, SLF, UF, CC (anterior-posterior gradient)
Meijboom et al. 2017	TBSS, tractography	bvFTD, svFTD	Forceps minor and major, CC, IFOF, ATR, cingulum, UF, ILF, SLF
Möller et al. 2015	TBSS, ROI	bvFTD, AD	Fornix, CC, forceps minor, thalamus, ATR, SLF, ILF, IFOF, UF, CST

Supplementary Table 2.1.2 | Continued

Author	Technique	Patient groups	Regions
White matter tracts			
Presymptomatic studies			
Rohrer et al. 2010	VBM	Familial FTD (*GRN*, *MAPT*)	ILF, SLF, IFOF, cingulum, CC, brainstem, fornix, UF
Steketee et al. 2016	TBSS, tractography	bvFTD, AD	ATR, cingulum (cingulate gyrus, hippocampus), forceps major and minor, IFOF, ILF, SLF, UF
Schwindt et al. 2013	TBSS	svPPA, nfPPA	UF, IFOF, ILF, forceps minor, gCC, SLF, corona radiata, ATR, internal capsule
Whitwell et al. 2010	ROI	bvFTD, nfPPA, svPPA	ILF, UF, SLF, genu CC, anterior and posterior cingulate, corticospinal tract
Yoshiura et al. 2006	ROI	bvFTD	Frontal gyri, orbitofrontal gyri, anterior temporal lobes
Zhang et al. 2009	ROI, voxel-wise	fvFTD, AD	Anterior CC, ACC, cingulum, UF, thalamic radiation in ALIC, SLF, posterior CC
Zhang et al. 2011	Voxel-wise	FTD, AD	Frontal and temporal lobes, anterior CC, anterior cingulum
Zhang et al. 2013	VBM, ROI	bvFTD, svPPA, nfPPA	Arcuate fasciculus, UF, ILF, parahippocampus, anterior CC, fornix
Author	**Technique**	**Patient groups**	**Regions**
Grey matter regions			
Presymptomatic studies			
Lee et al. 2017	VBM	*C9orf72* carriers	Midcingulate, thalamus, dorsolateral PFC
Rohrer et al. 2015	ROI	*MAPT*, *GRN* and *C9orf72* carriers	Insula, temporal, frontal, parietal, cingulate
Symptomatic studies			
D'Anna et al. 2016	Cortical hickness, ROI	PPA	Orbitofrontal cortex, anterior temporal lobe
Lillo et al. 2012	VBM	ALS, ALS-FTD, bvFTD	Frontal pole, OFC, ACC, superior frontal gyrus, (pre)motor cortices, anterior insula, temporal poles, thalamus, striatem
Mahoney et al. 2014	VBM	Familial/sporadic bvFTD, AD	Orbitofrontal, super/inferior frontal gyri, insula, cingulate, amygdala, middle/inferior temporal gyri
McMillan et al. 2012	Voxel-wise	bvFTD, PPA, CBS, AD	Frontal cortex, anterior temporal cortex
Möller et al. 2015	VBM, ROI	bvFTD, AD	Superior, middle and inferior frontal gyrus, orbitofrontal gyrus, insula, temporal gyrus

Supplementary Table 2.1.2 | Continued

Author	Technique	Patient groups	Regions
Grey matter regions			
Presymptomatic studies			
Rohrer et al. 2010	VBM	Familial FTD (*GRN*, *MAPT*)	Frontal, temporal, parietal lobes, cingulate cortex, thalamus
Rohrer et al. 2015	ROI	*MAPT*, *GRN* and *C9orf72* carriers	Insula, temporal, frontal, parietal, cingulate
Steketee et al. 2016	ROI	bvFTD, AD	Frontal, temporal and parietal cortices, basal ganglia
Schwindt et al. 2013	VBM	svPPA, nfPPA	Insula, inferior frontal, medial frontal, temporal regions, precuneus, medial temporal lobe, putamen, nucleus accumbens
Whitwell et al. 2009	VBM	Familial FTD with *MAPT* and *GRN*	Frontal, temporal and parietal lobes (all mutation carriers); *GRN* vs. controls in posterior temporal and parietal; *MAPT* vs. controls in anteriomedial temporal lobes; *MAPT* vs. *GRN*: medial temporal, insula, putamen
Whitwell et al. 2010	VBM	bvFTD, nfPPA, svPPA	Frontal and temporal lobes, insula, supplemental motor area, medial and lateral parietal lobes and occipital lobes
Zhang et al. 2011	VBM	FTD, AD	Frontal (frontoinsula) and temporal lobes, ACC, uncus, parietal lobes, caudate, thalamus
Zhang et al. 2013	VBM, ROI	bvFTD, svPPA, nfPPA	ACC, striatem, (fronto)insula, frontopolar regions, temporal pole, inferior frontal gyrus, superior frontal gyrus, caudate nucleus

Abbreviations: VBM, voxel-based morphometry; TBSS, tract-based spatial statistics; ROI, region of interest; *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; *C9orf72*, chromosome 9 open reading frame 72; bvFTD, behavioural variant FTD; PPA, primary progressive aphasia; svPPA, semantic variant PPA; fvFTD, frontal variant FTD; tvFTD, temporal variant FTD; EOAD, early-onset Alzheimer's disease; AD, Alzheimer's Disease; nfPPA, non-fluent PPA; ALS, Amyotrophic Lateral Sclerosis; CBS, corticobasal syndrome; UF, uncinate fasciculus; IFOF, inferior fronto-occipital fasciculus; CC, corpus callosum; gCC, genu corpus callosum; WM, white matter; SLF, superior longitudinal fasciculus; ILF, inferior longitudinal fasciculus; ATR, anterior thalamic radiation; CST, corticospinal tract; ALIC, anterior limb internal capsule; PFC, prefrontal cortex; OFC, orbitofrontal cortex; ACC, anterior cingulate cortex.

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2.2

Defining cognitive function, grey matter and white matter in presymptomatic *C9orf72* repeat expansion

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Abstract

To investigate cognitive function, grey matter volume and white matter integrity in the presymptomatic stage of *C9orf72RE*. Presymptomatic *C9orf72RE* carriers (n=18), and first-degree family members without a pathogenic expansion (controls, n=15) underwent a standardized protocol of neuropsychological tests, T1-weighted MRI and diffusion tensor imaging. We investigated group differences in cognitive functions, grey matter volume through voxel-based morphometry and white matter integrity by means of tract-based spatial statistics. We correlated cognitive change with underlying grey or white matter. Our data demonstrate lower scores on letter fluency, Stroop card I, and Stroop card III, accompanied by white matter integrity loss in tracts connecting the frontal lobe, the thalamic radiation and tracts associated with motor functioning in presymptomatic *C9orf72RE* compared with controls. In a subgroup of *C9orf72RE* carriers above 40 years of age, we found grey matter volume loss in the thalamus, cerebellum, and the parietal and temporal cortex. We found no significant relationship between subtle cognitive decline and underlying grey or white matter. This study demonstrates that a decline in cognitive functioning, white matter integrity, and grey matter volumes are present in presymptomatic *C9orf72RE* carriers. These findings suggest that neuropsychological assessment, T1w MRI and diffusion tensor imaging might be useful to identify early biomarkers in the presymptomatic stage of FTD and/or ALS.

Introduction

The pathogenic chromosome 9 open reading frame 72 repeat expansion (*C9orf72RE*) underlies the majority of familial frontotemporal dementia syndromes (FTD), and amyotrophic lateral sclerosis (ALS) [1]. The clinical presentation is variable, comprising behavioural variant FTD (bvFTD) and/or ALS as well as prominent neuropsychiatric symptoms and episodic memory disorders [2-4]. In accordance, neuroimaging studies have shown a variable pattern of both cortical and subcortical grey matter atrophy involving frontal, temporal, and parietal regions, the cerebellum and thalamus [5-10]. Scarce diffusion tensor imaging studies indicated white matter degeneration localized in the cingulum, corticospinal tract, corpus callosum, and cerebellar peduncle in *C9orf72RE* patients [8,11-13].

The field of disease-modifying treatment in FTD and ALS, and particularly in *C9orf72RE*-related disease [14], shows important progress. Ideally, a therapy would be instituted early in the disease process, when neurodegeneration is still limited. This increases the need for markers that identify early disease-related changes, and track disease progression. When studying early markers in autosomal dominant disease, the presymptomatic stage offers unique opportunities [15-16]. Studies into the presymptomatic stage of *C9orf72RE*-associated FTD or ALS are scarce, but have shown evidence for behavioural changes [17], and grey matter volume loss in temporal, parietal, frontal and cerebellar regions [17-18], though this was contradicted by an absence of atrophy in a study of 7 presymptomatic *C9orf72RE* carriers [10].

In order to expand the knowledge on biomarkers for early-stage *C9orf72RE*, the present study examines presymptomatic cognition, grey and white matter, through neuropsychological assessment, T1-weighted magnetic resonance imaging (T1w MRI), and diffusion tensor imaging (DTI), in a standardized cohort study of autosomal dominant FTD [15-16]. We furthermore relate presymptomatic *C9orf72RE* cognitive changes to potential underlying grey or white matter, to enable anatomical pinpointing of the clinical heterogeneity in *C9orf72RE*.

Methods

Participants

Between July 2013 and January 2017, we recruited 33 healthy at-risk first-degree family members of twelve Dutch pedigrees with an autosomal dominant inheritance pattern and the *C9orf72RE*. The clinical diagnosis in affected family members was bvFTD in seven families, bvFTD and FTD-ALS in three families, bvFTD and ALS in one family, and FTD-ALS in one family, see Appendix 1. All participants underwent a standardized work-up including MRI of the brain [15], neuropsychological assessment [16], neuropsychiatric and behavioural questionnaires, physical and neurological examination and a structured interview with a knowledgeable informant (e.g. siblings, spouses) covering functional, cognitive, behavioural or neuropsychiatric changes in daily living. We defined participants as presymptomatic when established criteria for FTD or ALS were not fulfilled [19-20], i.e. an absence of cognitive disorders on neuropsychological testing, an absence of significant behavioural/neuropsychiatric changes

(see Rascovsky et al. [20]), reported during a structured interview with knowledgeable informants or questionnaires, and an absence of signs of motor neuron disease during neurological examination. Two participants were included in the GENFI cohort study [17].

Genetic analysis

Venipuncture for DNA isolation was performed at study entry. The presence of the GGGGCC hexanucleotide repeat expansion in *C9orf72* was established by long-range PCR and tandem repeat-primed PCR analyses, as described before [1]. The presence of more than 30 repeats in *C9orf72* was considered pathogenic in this research setting, as this is rare in the healthy population [21]. Based on this analysis, we assigned the participants to the *C9orf72RE* carrier (n=18), or healthy control group (n=15).

Standard Protocol Approvals, Registrations, and Patient Consents

Investigators and participants were blind for the genetic status of the participants, unless participants underwent predictive testing (two participants). The study was approved by the Medical and Ethical Review Committee of the Erasmus Medical Center and written informed consent was obtained from all participants.

Neuropsychological assessment

Trained neuropsychologists (LCJ, JLP) administered a standardized battery of neuropsychological tests, neuropsychiatric and behavioural questionnaires. The battery [16], covered the following cognitive domains: global cognitive functioning using Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB), language through the 60-item Boston Naming Test (BNT), Semantic Association Test (SAT) verbal subtask, categorical (animals) and letter fluency; attention using Trail Making Test (TMT) part A, Stroop color-word test card I and II (Stroop I and II) and Letter Digit Substitution Test (LDST); executive functioning by means of TMT B, and Stroop III; the memory domain using Dutch version of the Rey Auditory Verbal Learning Test (RAVLT) learning and recall, and WAIS-III digit span total; visuoconstruction using Royall Clock drawing test and WAIS-III block design; social cognition through the Happé cartoon task and Ekman 60 Faces Test. We standardized all raw neuropsychological test scores by converting them to z-scores (individual test score minus mean of controls divided by SD of controls), and created composite domain scores. The presence of neuropsychiatric and behavioural symptoms was investigated using Beck's Depression Inventory (BDI) [16], Neuropsychiatric Inventory (NPI) [22], and Cambridge Behavioural Inventory-Revised (CBI-R) [23].

MRI acquisition and preprocessing

We acquired whole brain T1w MRI and DTI scans on a Philips 3.0-tesla Achieva MRI scanner, using an 8-channel or 32-channel (in 5 cases) SENSE head coil, with the exact same scanning parameters, as described previously [16]. FSL was used for imaging analyses, i.e. voxel-based morphometry (VBM) for T1w images, and tract-based spatial statistics (TBSS) for DTI (FMRIB's Software Library, www.fmrib.ox.ac.uk). We performed preprocessing of T1w images through brain extraction followed by tissue segmentation and alignment to MNI-152 standard space using non-linear registration. A study-specific template with a balanced set of *C9orf72RE* carriers and controls was created and native grey matter

images were non-linearly re-registered to this template. The registered partial volume images were modulated to correct for local expansion or contraction by dividing by the Jacobian of the warp field. These modulated grey matter images were smoothed with an isotropic Gaussian kernel with a sigma of 4 mm, corresponding with an FWHM kernel of 9 mm. We corrected diffusion tensor images for motion artefacts and eddy current by alignment to the b0 image using the FMRIB Diffusion Toolbox. Images were non-linearly registered to a study-specific template. The tensor was fitted at each voxel using DTIFIT to create fractional anisotropy (FA) images. We created and thinned a mean FA image to obtain a skeleton containing the center of all tracts. Individual FA data was projected onto this skeleton, resulting in skeletonised FA data for each subject, fed into voxelwise statistics. Mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AxD) were then projected onto the white matter skeleton, using the skeleton projection vectors estimated in the FA analysis.

Neuroimaging analysis

We performed permutation-based testing using 5,000 permutations, and created two separate models for two-sample t-tests (mutation carriers vs. controls) for grey matter volume or white matter diffusion parameters, with age, sex, and when applicable head coil, as covariates. Due to an acquisition artefact, one DTI scan could not be used in our analyses (mutation carrier). In FSL we performed two separate within-group correlation analyses between z-scores of neuropsychological tests differing between mutation carriers and controls at $p<0.05$, and grey matter or white matter. In these cognition-neuroimaging correlation analyses an additional covariate for education was added. The significance level was set at $p<0.05$ (two-tailed), corrected for multiple comparisons (FWE), using threshold-free cluster enhancement. We used the Harvard-Oxford cortical structural atlas, and John Hopkin's University DTI-based WM atlas implemented in FSL.

Neuropsychological and neuroimaging analyses in carriers and controls >40 years of age

We performed group comparisons in a subgroup of carriers and controls >40 years of age, i.e. closer to clinical onset age (n=13 *C9orf72RE* carriers and n=11 controls) [17,24], for neuropsychological tests, grey and white matter analyses. Due to the acquisition artefact, one DTI scan could not be used in the analysis (i.e. n=12 *C9orf72RE* mutation carriers).

Statistical analysis

Statistical analyses on neuropsychological and demographic data were performed with SPSS Statistics 21.0. We analysed demographic data using two sample t-tests or Pearson chi-square tests. We found a left-skewed distribution for the Royall clock drawing test, MMSE, and FAB, and a right-skewed distribution for the NPI, BDI and CBI-R. We reported the median and interquartile ranges, and performed Mann-Whitney U tests. In order to meet criteria for normality, we replaced one extreme outlier in the TMT B by the highest test scores (88 seconds) added up with 10 seconds. Given the left-skewed distribution of the Royall clock drawing test, the domain visuoconstruction consisted only of z-scores of WAIS-III block design. Z-scores for neuropsychological data were subsequently compared between groups by means of one-way ANCOVA with age, sex and education level as covariates. We set the significance level at $p<0.05$ (two-tailed) across all comparisons, with Bonferroni correction for multiple comparisons.

Results

Demographic data

Demographic and clinical data are showed in Table 2.2.1. In *C9orf72RE* carriers and controls the age range was distributed equally, with respectively 5 and 4 participants <40. MMSE, FAB, neuropsychiatric or behavioural measures did not differ between groups. For details on the presence of neuropsychiatric symptoms on NPI, see Appendix 2.2.2. Physical and neurological examination in our participants did not show abnormalities, specifically signs of motor neuron disease.

Table 2.2.1 | Demographic data of *C9orf72RE* carriers and controls

	C9orf72RE carriers (n=18)	controls (n=15)	*p*-value
Age (years)	45.8 (13.8)	47.8 (13.3)	0.689
Sex, female (%)	15 (83.3)	8 (53.3)	0.062
Education (Verhage[1])	5.6 (0.8)	5.5 (0.8)	0.784
Mean age of family onset (years)	53.0 (5.3)	53.5 (4.6)	0.804
Motor neuron disease signs (%)*	0 (0.0)	0 (0.0)	–
MMSE	30.0 (1)	29.5 (1)	0.630
FAB	17.0 (1)	17.5 (2)	0.602
NPI*	0 (1)	0 (0)	0.655
BDI*	3.0 (13)	3.0 (8)	0.455
CBI-R*	1 (6)	0 (5)	0.455

Values indicate: mean ± standard deviation, number (percentage), or in case of MMSE, FAB, NPI, BDI, CBI-R: median (interquartile range). *Abbreviations:* MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; NPI, Neuropsychiatric Inventory; BDI, Beck Depression Inventory; CBI-R, Cambridge Behavioural Inventory Revised. *Missing data for presence of motor neuron disease signs in one HC, for FAB in one carrier, for NPI in one carrier, for BDI in one carrier, for CBI-R in one HC. [1]Dutch educational system categorized into levels from 1=less than 6 years of primary education to 7=academic schooling. P-value by means of 2-sample t-test or chi-square test. MMSE, FAB, NPI, BDI and CBI-R data was not normally distributed and P-values were calculated by means of Mann-Whitney U test.

Neuropsychological assessment

The results of the neuropsychological assessment can be found in Table 2.2.2. None of the participants performed at disorder level (i.e. ≥2 SD below normative data mean). *C9orf72RE* carriers had lower scores than controls on letter fluency, Stroop card I, and Stroop card III. In the subgroup analysis of presymptomatic *C9orf72RE* carriers and controls over 40 years of age we found no between group differences, see Appendix 2.2.3. At a Bonferroni corrected threshold, there were no differences between groups for neuropsychological tests.

Grey matter volume and white matter integrity

Whole-group TBSS analyses demonstrated lower FA and higher RD in *C9orf72RE* carriers compared with controls within the right superior corona radiata, the right inferior longitudinal fasciculus, the right uncinate fasciculus, the bilateral anterior thalamic radiation, the corticospinal tract and the right internal and external capsule (Figure 2.2.1, Table 2.2.3). In the subgroup analysis over 40 years of age, we found

no differences for white matter parameters at a threshold of FWE $p<0.05$. We did find results for FA at a less stringent threshold of FWE, $p<0.15$ (Figure 2.2.2B, Table 2.2.3). Whole-group VBM analyses revealed no grey matter volume differences between *C9orf72RE* carriers and controls. When we confined our analyses to a subgroup >40 years of age, *C9orf72RE* carriers showed lower grey matter volume in the right inferior temporal gyrus, right cerebellum (VI), left post- and precentral gyrus, the left superior parietal lobe and the left thalamus compared with controls (Figure 2.2.2A, Table 2.2.3). Vice versa, we found no grey or white matter changes in controls compared with *C9orf72RE* carriers.

Table 2.2.2 | Neuropsychological data of *C9orf72RE* carriers and HC

Domain	Neuropsychological test	*C9orf72RE* carriers (n=18)[1]	controls (n=15)[1]	*C9orf72RE* carriers (n=18)[2]	*p*-value
Language	BNT	53.8 (3.7)	54.0 (3.9)	-0.04 (0.94)	0.850
	SAT	27.7 (1.0)	28.3 (1.0)	-0.62 (0.98)	0.428
	Animal fluency	25.9 (5.6)	27.8 (7.5)	-0.25 (0.74)	0.237
	Letter fluency	37.3 (9.1)	40.9 (12.2)	-0.30 (0.75)	0.026
	Total Language	–	–	-0.30 (0.47)	0.101
Memory	RAVLT learning	49.7 (7.9)	50.9 (10.9)	-0.11 (0.73)	0.476
	RAVLT recall	10.6 (2.3)	9.0 (4.0)	0.39 (0.56)	0.248
	Digit Span	16.3 (3.7)	17.9 (B.,ML5.1)	-0.31 (0.72)	0.159
	Total Memory	–	–	-0.01 (0.45)	0.605
Attention & mental speed	TMT A*	32.1 (8.2)	28.2 (7.8)	-0.50 (1.06)	0.247
	Stroop I*	45.7 (6.9)	41.8 (4.9)	-0.80 (1.43)	0.041
	Stroop II*	58.1 (11.2)	51.5 (8.3)	-0.79 (1.34)	0.096
	LDST	33.4 (6.0)	35.8 (8.2)	-0.29 (0.73)	0.255
	Total Attention	–	–	-0.81 (1.22)	0.069
Executive function	TMT B*	62.9 (18.1)	54.1 (12.4)	-0.71 (1.47)	0.283
	Stroop III*	92.8 (21.9)	77.7 (16.7)	-0.90 (1.31)	0.048
	Total Executive Functioning	–	–	-0.81 (1.22)	0.060
Social cognition†	Ekman faces	47.1 (4.7)	45.7 (7.6)	0.19 (0.62)	0.760
	Happé ToM	24.0 (7.5)	22.5 (3.5)	-0.20 (0.47)	0.100
	Total Social Cognition	–	–	-0.01 (0.50)	0.448
Visuoconstruction	Clock drawing	13.0 (1.0)	13.0 (1.0)	–	0.464
	Block Design	34.7 (13.9)	40.6 (13.8)	-0.43 (1.01)	0.091
	Total Visuoconstruction	–	–	-0.43 (1.01)	0.091

Values indicate: uncorrected mean (standard deviation), or in case of Clock drawing median (interquartile range). [1]raw scores, [2]z-scores. *Abbreviations:* BNT, Boston Naming Test; SAT, Semantic Association Test; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; RAVLT, Rey Auditory Verbal Learning Test. Average z-scores for HC were not reported as these were equal to zero per definition. *Higher scores indicate worse performance, Z-scores are inverted. †Missing data for social cognition tests for one carrier. *P*-value on Z-score comparisons of *C9orf72RE* carriers and HC, by means of univariate ANCOVA corrected for age, sex and education. In case of Clock drawing *p*-value by means of Mann-Whitney U test. At Bonferroni correction $p<0.002$ there are no significant results.

Relationship between neuropsychological assessment and grey or white matter

We found no correlation between letter fluency, Stroop card I, or Stroop card III and grey or white matter volumes within the whole group of *C9orf72RE* carriers or controls.

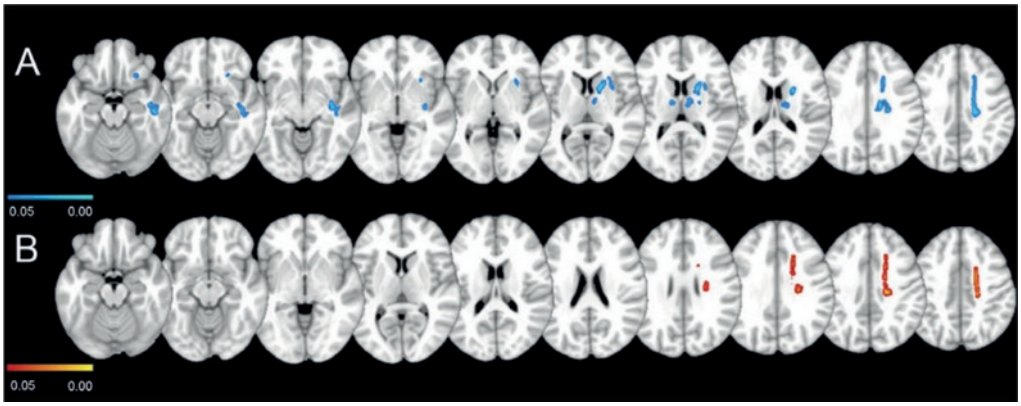

Figure 2.2.1 | **Differences in white matter integrity between the whole group of *C9orf72RE* carriers and HC.** A) White matter results for FA, for the contrast Carriers<HC in the entire cohort. B) White matter results for RD, for the contrast Carriers>HC in the entire cohort. Results are corrected for multiple comparisons (FWE $p<0.05$) using threshold-free cluster enhancement.

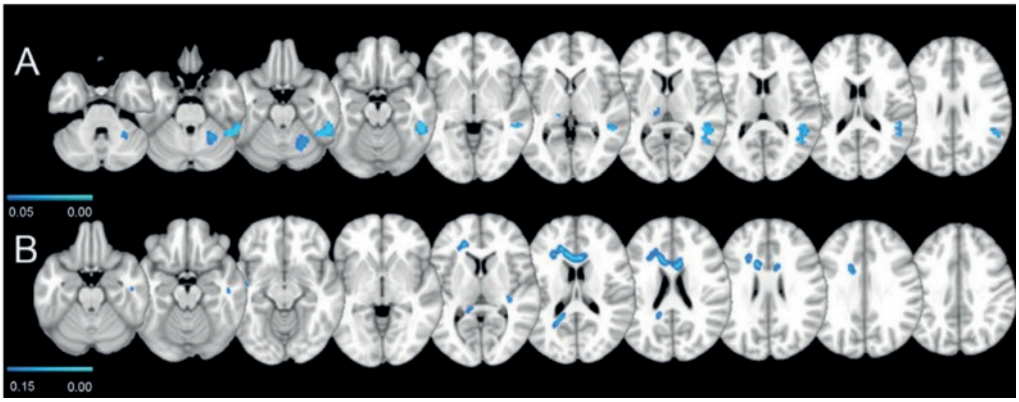

Figure 2.2.2 | **Differences in grey matter volume and white matter integrity between *C9orf72RE* carriers and HC for subgroup analysis >40 years of age.** A) Grey matter results for the contrast Carriers<HC. B) White matter results for RD, for the contrast Carriers>HC. Results are corrected for multiple comparisons (FWE $p<0.05$ in grey matter analysis and $p<0.15$ in white matter analysis) using threshold-free cluster enhancement.

Table 2.2.3 | GM volume clusters and white matter tracts in *C9orf72RE* compared with controls

	Cluster size	*p*-value	x	y	z	L/R	Peak voxel location
Grey matter volume differences in whole group							
–	–	–	–	–	–	–	–
White matter integrity differences in whole group							
FA: Carriers<HC	783	0.04	20	-22	38	R	Superior corona radiata
	379	0.044	48	-12	-26	R	Inferior longitudinal fasciculus
	194	0.042	16	9	6	R	Anterior limb internal capsule
	97	0.045	10	-10	13	R	Anterior thalamic radiation
	67	0.048	30	10	8	R	External capsule
	36	0.048	29	22	-19	R	Uncinate fasciculus
	24	0.047	-11	-9	12	L	Anterior thalamic radiation
RD: Carriers>HC	672	0.044	20	-21	38	R	Superior corona radiata, corticospinal tract
Grey matter volume differences > 40 years of age							
Carriers<HC	928	0.014	52	-40	-16	R	Inferior temporal gyrus
	198	0.035	26	-50	-30	R	Cerebellum (VI)
	104	0.039	-52	-24	44	L	Postcentral gyrus
	66	0.014	-36	-56	48	L	Superior parietal lobule
	39	0.044	-60	-6	40	L	Precentral gyrus
	38	0.033	-14	-24	4	L	Thalamus
White matter integrity differences > 40 years of age at a lower threshold							
FA: Carriers < HC	951	0.111	7	20	18	R	Forceps minor
	115	0.138	-14	-44	12	L	Forceps major
	46	0.145	-23	-58	14	L	Forceps major
	23	0.148	33	-25	4	R	Inferior fronto-occipital fasciculus
	23	0.147	-44	-9	-14	L	Inferior longitudinal fasciculus
	20	0.146	48	-16	-20	R	Inferior longitudinal fasciculus

Results are corrected for multiple comparisons (FWE) using threshold-free cluster enhancement at $p<0.05$. White matter integrity differences >40 years of age were found at a threshold FWE $p<0.15$.

Discussion

In this study we demonstrate lower cognitive test performance for letter fluency, Stroop card I, and Stroop card III, and white matter integrity loss within the superior corona radiata, the inferior longitudinal fasciculus, the uncinate fasciculus, the anterior thalamic radiation, the corticospinal tract and the internal and external capsule in presymptomatic *C9orf72RE* carriers compared with controls. Grey matter volume loss was found in a subgroup of presymptomatic carriers over 40 years of age, in the thalamus,

cerebellum, and parietal and temporal regions. We found no correlation between subtle cognitive changes and underlying grey and white matter substrates in presymptomatic *C9orf72RE*.

While participants in our study performed within the normative range of neuropsychological tests by definition, our results indicated a subtle decline in language (letter fluency), attention (Stroop card I), and executive function (Stroop card III) in presymptomatic *C9orf72RE* carriers compared with controls. These findings did not survive correction for multiple comparisons, but are in line with observations in symptomatic *C9orf72RE* FTD patients, showing a typical FTD profile with language impairment, attention deficits and executive dysfunction [2-3]. Also, approximately 50% of symptomatic C9 ALS patients developed executive dysfunctioning during the course of their disease [25]. In the present study we found no evidence for presymptomatic memory decline, neuropsychiatric or behavioural symptoms in *C9orf72RE* [4-5,25-26]. Therewith, our presymptomatic phenotypic profile contradicts the results of two other studies in presymptomatic *C9orf72RE* FTD and ALS relatives, in which behavioural changes were found present up to 15 years before estimated symptom onset [17], and cognitive decline was absent [17-18]. These presymptomatic phenotypic differences may either relate to the diversity in emerging clinical phenotype (i.e. ALS, FTD or FTD-ALS), reflect the large clinical heterogeneity observed in *C9orf72RE* [21], or relate to differences in disease stage. Interestingly, the latter explanation was contradicted by our non-significant results in the subgroup analysis in carriers and controls >40 years of age, i.e. approaching symptom onset. While these results could reflect a lack of power, it may also be suggested that cognitive deficits in *C9orf72RE* are long present, and do not merely mark clinical onset. If true, this would contradict with findings and hypotheses on cognitive decline emerging only years before symptom onset in presymptomatic *MAPT* and *GRN* [16-17].

In our study, presymptomatic *C9orf72RE* carriers demonstrated white matter integrity loss, reflected by lower FA and higher RD, within tracts connecting regions of significant grey matter loss in symptomatic FTD and/or ALS; such as the frontal lobe in case of the inferior longitudinal fasciculus and the uncinate fasciculus [11], the thalamus in case of the thalamic radiation [5], and motor regions in case of the corticospinal tract, corona radiata and internal/external capsule [27]. The uncinate fasciculus and inferior longitudinal fasciculus are tracts typically associated with bvFTD [28], while FA reduction in white matter within the frontal and cingulate gyrus or internal capsule was reported in ALS [29]. Our results of decreased FA and higher RD are concordant with the scarce DTI studies in symptomatic *C9orf72RE*. C9+ALS patients showed FA, RD and MD change in frontotemporal white matter, and bilateral thalamic tracts [8]. In *C9orf72RE* FTD, decreased FA and increased AxD was found in the corpus callosum, cingulum bundle [11], and the right and left superior cerebellar peduncle [12]. It has been demonstrated repeatedly that early white matter integrity alterations precede grey matter changes in FTD [15,30-31]. In accordance, our study shows white matter integrity loss in the entire group of *C9orf72RE* carriers, while grey matter volume loss was confined to a subgroup of presymptomatic carriers over 40 years of age. However, white matter integrity was not encountered in the >40 subgroup at a stringent threshold. Since a less stringent threshold did show results in frontal white matter, the lack of results in the subgroup could be explained as a lack of power, considering the small sample size in the subgroup analyses, and the fact that one extra DTI scan was not available due to an acquisition artefact. Longitudinal follow-up of preclinical cohorts

of *C9orf72RE* carriers, as well as the use of different analysis techniques (e.g. cortical thickness analysis), will have to elucidate the sequential order of grey and white matter change in specifically *C9orf72RE*. The finding of atrophy in the smaller group of older presymptomatic carriers, closer to clinical onset [32], contradicts the view that atrophy in *C9orf72RE* reflects developmental abnormalities [21], as in that case grey matter loss should be detectable across our entire cohort. This was supported by a presymptomatic *C9orf72RE* study showing grey matter abnormalities up to 25 years before symptom onset [17].

Pathological and T1w MRI studies suggest a symmetric cortico-thalamo-cerebellar network impairment to underlie symptomatic *C9orf72RE* [2,6,9,12,33]. In the present study we show that this pattern is already present in presymptomatic *C9orf72RE* carriers at risk for conversion. We found grey matter volume loss in the cerebellum (lobule VI) and thalamus, the inferior temporal gyrus, postcentral gyrus and superior parietal lobe. Cerebellar and thalamic pathology are increasingly recognized to contribute to cognition, behaviour and neuropsychiatric (dys)functioning, through their role as relay station [34]. The thalamus is involved in multiple functional networks, and has been related to *C9orf72RE* symptomatology by undermining salience network connectivity [7], compromised in bvFTD. Lobules VI and VII of the cerebellum are considered the 'cognitive cerebellum' [35], and showed atrophy in both bvFTD and ALS patients [36]. In correlation analyses though, particularly the superior cerebellum has been related to cognitive functioning in bvFTD [36]. Postcentral gyrus thinning, i.e. the primary somatosensory cortex, is associated with ALS patients, and inferior temporal gyrus thinning was related to faster clinical progression in a longitudinal study in ALS [37]. The precentral gyrus and superior parietal lobe were previously identified as regions associated with symptomatic *C9orf72RE* [9,26], as studies show more widespread atrophy in *C9orf72RE* compared with other FTD mutations, specifically *MAPT* mutation carriers [9].

In this study, subtle cognitive changes did not correlate with underlying grey or white matter in *C9orf72RE* carriers or controls. Possible explanations lie in the lack of power to detect such an association, or the heterogeneity in our cohort with respect to emerging phenotype (i.e. FTD or ALS), which could complicate pinpointing clinical features. On the basis of the present results it is hard to predict the clinical outcome of individual patients, as we have group level results indicative for both FTD and ALS phenotypes. Longitudinal studies extending into the symptomatic stage may further elucidate on the most sensitive biomarkers for phenotypic findings.

Important strengths of this study are the standardized protocol with single center MRI, and neuropsychological evaluation, and the use of a well-matched control group. Important drawbacks are the small sample of presymptomatic *C9orf72RE* carriers, and the fact that our diffusion-weighted field of view did not involve cerebellar white matter. Finally, in the presymptomatic stage we cannot account for incomplete penetrance associated with *C9orf72RE*. We did account for incomplete age-related penetrance, i.e. ages of onset fluctuating between 40 and 90 years of age [24], by performing analyses in a subgroup >40 years of age.

Conclusions

Our data demonstrates a presymptomatic *C9orf72RE* stage characterized by a subtle decline in attention, executive functioning, and language, and white matter changes in tracts connecting the frontal lobe, the thalamic radiation, and tracts associated with motor functioning. Grey matter loss was demonstrated in a subgroup of *C9orf72RE* carriers over 40 years. We found no correlation between subtle cognitive change and underlying white or grey matter substrates. This study expands on the knowledge of the presence of disease related changes in presymptomatic *C9orf72RE* carriers [17-18]. In the future, larger but foremost, longitudinal studies may confirm cognitive, grey and white matter abnormality patterns in presymptomatic *C9orf72RE*, and elucidate the sequential order of these potential markers in the *C9orf72RE* disease evolution.

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Appendix 2.2.1 | Carrier and control distribution for autosomal dominant ***C9orf72RE*** families

Family number and diagnosis	*C9orf72RE* carriers	controls	Total
Family 1 – bvFTD	3 (16.7)	2 (13.3)	5 (15.2)
Family 2 – bvFTD	1 (5.6)	0 (0.0)	1 (3.0)
Family 3 – FTD-ALS	1 (5.6)	0 (0.0)	1 (3.0)
Family 4 – bvFTD	3 (16.7)	5 (33.3)	8 (24.2)
Family 5 – bvFTD and ALS	1 (5.6)	0 (0.0)	1 (3.0)
Family 6 – bvFTD	1 (5.6)	0 (0.0)	1 (3.0)
Family 7 – bvFTD and FTD-ALS	4 (22.2)	4 (26.7)	8 (24.2)
Family 8 – bvFTD and ALS	1 (5.6)	2 (13.3)	3 (9.1)
Family 9 – bvFTD and FTD-ALS	1 (5.6)	0 (0.0)	1 (3.0)
Family 10 – bvFTD and FTD-ALS	1 (5.6)	0 (0.0)	1 (3.0)
Family 11 – bvFTD	0 (0.0)	1 (6.7)	1 (3.0)
Family 12 – bvFTD	1 (5.6)	1 (6.7)	2 (6.1)
Total	**18**	**15**	**33**

Values indicate: number (valid percentage).

Appendix 2.2.2 | Neuropsychiatric Inventory, presence of symptoms

	C9orf72RE carriers (n=17)*	control (n=15)
Delusions	0 (0)	0 (0)
Hallucinations	1 (5.9)	0 (0)
Agitation/Aggression	1 (5.9)	0 (0)
Depression/Dysphoria	2 (11.8)	2 (13.3)
Anxiety	0 (0)	0 (0)
Elation/Euphoria	1 (5.9)	0 (0)
Apathy/Indifference	0 (0)	0 (0)
Disinhibition	1 (5.9)	0 (0)
Irritability/Lability	2 (11.8)	1 (6.7)
Aberrant motor behaviour	0 (0)	0 (0)
Sleep and night-time behaviour disorders	0 (0)	0 (0)
Appetite and eating changes	0 (0)	1 (6.7)

Values indicate: number (valid percentage). *Missing data for NPI in one carrier.

Table e-2.2.3 | Neuropsychological data of *C9orf72RE* carriers and control >40 years of age

Domain	Test	*C9orf72RE* carriers (n=13)[1]	control (n=11)[1]	*C9orf72RE* carriers (n=13)[2]	*p*-value
Language	BNT	53.3 (3.7)	53.0 (3.8)	0.08 (0.96)	0.519
	SAT	27.9 (1.1)	28.3 (1.1)	-0.38 (0.97)	0.815
	Animal fluency	25.3 (6.4)	26.2 (6.7)	-0.13 (0.95)	0.504
	Letter fluency	36.1 (8.7)	38.5 (13.1)	-0.18 (0.67)	0.227
	Total Language	–	–	-0.15 (0.52)	0.656
Memory	RAVLT learning	46.6 (7.1)	48.7 (11.4)	-0.19 (0.63)	0.563
	RAVLT recall	9.6 (1.6)	7.7 (3.9)	0.48 (0.41)	0.121
	Digit Span	16.5 (4.2)	16.6 (4.5)	-0.00 (0.92)	0.853
	Total Memory	–	–	0.10 (0.41)	0.803
Attention and mental processing speed	TMT A*	34.2 (8.4)	30.7 (6.6)	-0.53 (1.28)	0.658
	Stroop I*	45.5 (6.9)	43.1 (4.9)	-0.50 (1.40)	0.238
	Stroop II*	59.7 (11.7)	53.3 (7.6)	-0.84 (1.53)	0.221
	LDST	32.6 (5.7)	33.5 (7.7)	-0.11 (0.73)	0.718
	Total Attention	–	–	-0.50 (1.03)	0.267
Executive function	TMT B*	68.9 (15.7)	58.0 (11.5)	-0.95 (1.37)	0.133
	Stroop III*	99.9 (21.6)	80.5 (16.7)	-1.16 (1.30)	0.083
	Total EF	–	–	-1.06 (1.12)	0.074
Social cognition[†]	Ekman faces	45.8 (4.6)	45.3 (8.8)	0.06 (0.53)	0.752
	Happé ToM	21.0 (2.5)	20.8 (6.0)	0.03 (0.42)	0.829
	Total Social Cognition	–	–	0.05 (0.43)	0.980
Visuoconstruction	Clock drawing	13 (1)	13 (1)	–	0.910
	Block Design	30.7 (13.0)	36.3 (13.3)	-0.42 (0.98)	0.409
	Total Visuoconstruction	–	–	-0.42 (0.98)	0.409

Values indicate: uncorrected mean (standard deviation), or in case of Clock drawing median (interquartile range). [1]raw scores, [2]z-scores. *Abbreviations:* BNT, Boston Naming Test; SAT, Semantic Association Test; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; EF, executive functioning. Average Z-scores for HC were not reported as these were equal to zero per definition. *Higher scores indicate worse performance, Z-scores are inverted. [†]Missing data for social cognition tests for one carrier. *P*-value on Z-score comparisons of *C9orf72RE* carriers and HC, by means of univariate ANCOVA corrected for age, sex and education. In case of Clock drawing p-value by means of Mann-Whitney U test. At Bonferroni correction $p<0.002$ there are no significant results.

Chapter 3

Neuroimaging biomarkers – white matter imaging

3.1

White matter tracts of speech and language

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Abstract

Diffusion tensor imaging (DTI) has been used to investigate the white matter (WM) tracts underlying the perisylvian cortical regions known to be associated with language function. The arcuate fasciculus (AF) is composed of 3 segments (1 long and 2 short) whose separate functions correlate with traditional models of conductive and transcortical motor or sensory aphasia, respectively. DTI mapping of language fibers is useful in pre-surgical planning for patients with dominant hemisphere tumours, particularly when combined with functional magnetic resonance imaging. DTI has found damage to language networks in stroke patients and has the potential to influence post-stroke rehabilitation and treatment. Assessment of the WM tracts involved in the default mode network has been found to correlate with mild cognitive impairment, potentially explaining language deficits in patients with apparently mild small vessel ischemic disease. Different patterns of involvement of language-related WM structures appear to correlate with different clinical subtypes of primary progressive aphasias.

Anatomy and tractography of the language tracts

The arcuate fasciculus and other language tracts

The best-known WM tract related to language is the AF. According to the classical model, described in the late 19th century [1], this perisylvian WM bundle connects the frontal expressive language area (classical Broca area) with the posterior temporoparietal receptive language areas (classical Wernicke area). A disruption of the AF results in conduction aphasia. Conduction aphasia is a heterogeneous clinical entity that is characterized by a patient's undisturbed ability to speak and to understand language, but the inability to repeat spoken text [2]. In recent years, insight into the anatomy of the AF, and the WM tracts related to language in general, has changed. On the one hand, it has become clear that the AF is not a single tract. On the other hand, several other WM tracts have been identified that are also involved in language. The AF is now also known as the dorsal language pathway. In a hallmark study, set out to explain the clinical heterogeneity of conduction aphasia, Catani et al. [2] further segregated this dorsal language pathway into one long direct segment – directly interconnecting the classical Broca and Wernicke areas – and two short indirect segments (Figure 3.1.1). These two indirect segments, an anterior and a posterior segment, run laterally to the long segment and both project into the so-called Geschwind territory (inferior parietal lobule). This region, where multi-modal sensory input comes together, is thought to play an important part in semantic processing. Its connection with classical Broca and Wernicke area through the indirect segments offers an explanation for the clinical aphasia syndromes of Brocalike or transcortical motor aphasia and Wernickelike or transcortical sensory aphasia. These aphasias are distinct from classical conduction aphasia, which is consistent with a lesion of the long segment of the AF. In transcortical motor aphasia, spontaneous speech is impaired, while comprehension is intact. In other words, there is failure to vocalise semantic content, which would be consistent with a disconnection between Broca's area and the Geschwind's territory, through a lesioned *anterior* short segment [4]. In transcortical sensory aphasia, fluency and repetition are intact, but comprehension is reduced, i.e. there is failure to comprehend auditory semantic content. This deficit would be consistent with a disconnection between Wernicke's area and Geschwind's territory, as a result from a lesioned *posterior* short segment [3].

In addition to the AF, several ventral pathways, connected with the perisylvian network, have now been recognised for their role in language processing. These include the uncinate fasciculus (UF), the inferior fronto-occipital fasciculus (IFOF) and the inferior longitudinal fasciculus (ILF) [2] (Figure 3.1.2). In a combined functional MRI (fMRI) and DT-tractography study, Saur et al. [5] confirmed the hypothesis of a dual functional language system. The dorsal pathway, i.e. the AF, was found to be involved in sound-to-motor mapping. The ventral pathway was associated with sound-to-meaning integration. This ventral pathway consisted of the UF, connecting the anterior temporal language areas with the frontal lobe [5,6]. The IFOF connects the frontal with the occipital lobes, and is thought to play a role in written language [2]. The ILF connects the temporal cortex to the occipital lobe, carrying visual information, and probably plays a role in visual object recognition [7].

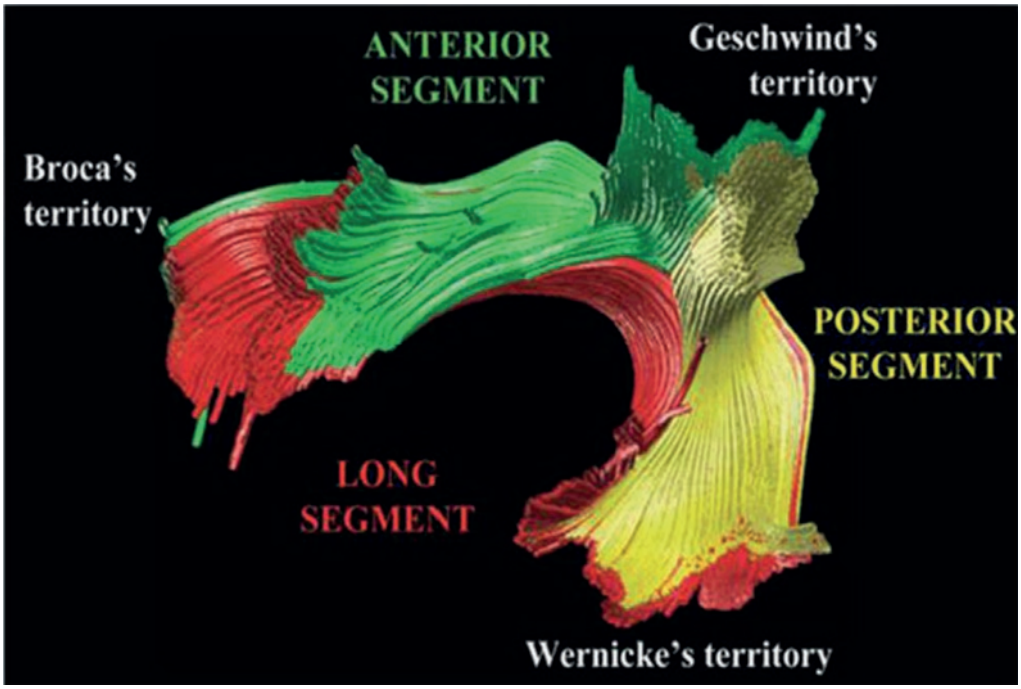

Figure 3.1.1 | **The dorsal language pathway.** There is one long segment (red) and two short segments (green and yellow). Reprinted with permission from Catani et al. [2].

Finally, several commissural tracts also seem to play a role in language processing. The anterior commissure directly connects the left and right anterior temporal lobes, including the left and right anterolateral superior temporal sulcus. The functional connectivity of these structures was found to be strongly correlated with language recovery after aphasic stroke [8]. The corpus callosum, the largest WM structure in the brain connecting the two hemispheres, has been associated with cognitive disorders in which functions from both hemispheres need to be integrated. It is in particular in the posterior part of the corpus callosum (CC), connecting the temporal and occipital cortices, that a lesion leads to functional deficit [9]. The most prominent deficit is word blindness (alexia), in which there is an inability to read aloud or to understand written script due to a disconnection of the visual and language areas. Interestingly though, the microstructural organisation of the CC seems to be inversely correlated with the degree of hemispheric lateralisation for language, i.e. the more language is lateralised to the left hemisphere, the lower is the microstructural organisation of the CC. This observation has been linked to the finding of *increased* microstructural organisation of the corpus callosum in dyslexia, presumably in relation to the finding of reduced hemispheric lateralisation for language with this condition [10].

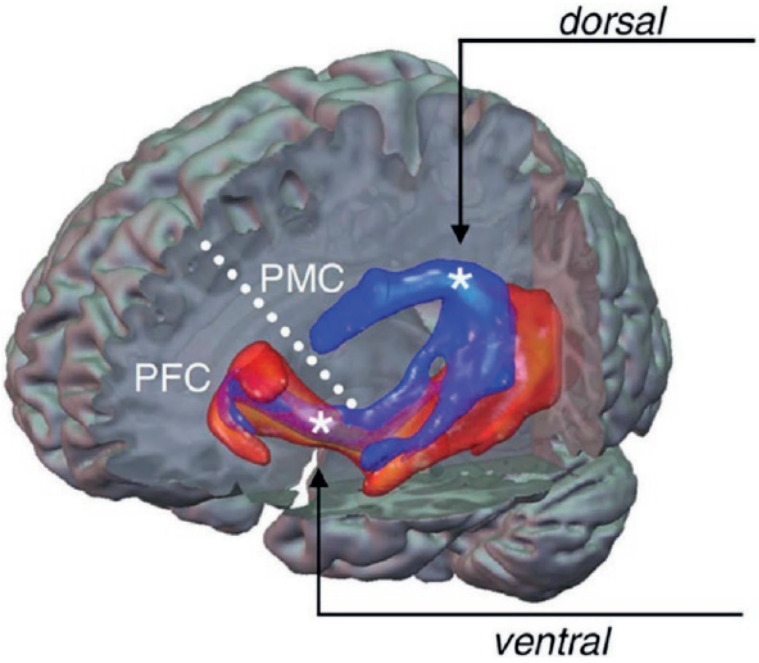

Figure 3.1.2 | **The dual functional language system. This consists of a dorsal pathway (blue) involved in sound-to-motor mapping and a ventral pathway (red) associated with sound-to-meaning integration.** PMC, premotor cortex; PFC, prefrontal cortex. Reprinted with permission from Saur et al. [4]

Hemispheric lateralisation

It is well established that language function is hemispherically lateralised, which is related to handedness: 95% of right handers have left sided functional hemispheric language lateralisation, while 15% of left handers show right sided functional lateralisation [11]. A clear structural asymmetry has also been described, with one of the consistent findings being a leftward asymmetry in volume of the planum temporale and the parietotemporal white matter [12-16]. In a DTI-tractography and anatomical study of all major WM tracts, Thiebault de Schotten et al. [17] also found a leftward asymmetry of the AF, which only concerned the long, direct segment. This finding was more pronounced in males than in females, the former showing a stronger leftward lateralisation. The anterior indirect segment of the AF on the other hand showed a slight rightward asymmetry. This finding is thought to represent the anatomical correlate of right hemisphere dominance for visuo-spatial processing, deficits of which result in neglect, which is typically a right hemispheric syndrome [17]. In right handed volunteers, the ventral language pathway could only be demonstrated in the left hemisphere, in line with the functional neuroimaging findings showing activation in only the left hemisphere activation for processing intelligible speech [6].

It is tempting to assume that the asymmetry of the AF is related to the known functional lateralisation of language areas [18-19], and some studies did indeed find such a relationship in right handed volunteers [6,18]. In a combined fMRI and DTI-tractography study we confirmed these findings in right handers

[20]. We demonstrated that the degree of structural asymmetry in these participants was correlated with the degree of functional lateralisation, i.e. the more asymmetrical the AF, the more lateralised language function. In left handers however, there was an overall significant leftward asymmetry of the AF, irrespective of functional language lateralisation. Similar results are reported by Propper et al. [21], also demonstrating a leftward asymmetry of the AF in both left and right handers, which was strongly correlated with the degree of handedness. In a study of monozygotic twins, however, a strong correlation between cerebral asymmetry for language and asymmetry in the arcuate fasciculus was found [22]. Overall, the relationship between structural and functional lateralisation therefore is not as straightforward as it seems.

DTI metrics and fibre tracking

The three maps that are commonly derived from a DTI scan are the quantitative apparent diffusion coefficient (ADC) and fractional anisotropy (FA) map, and the directionally encoded colour coded (DEC) map. The ADC is a voxel by voxel measure of the magnitude of diffusion. The FA is a measure of the degree of preferential diffusion directionality, where high FA indicates a great degree of preferential directionality (anisotropy) such as in the highly organised WM tracts, and low FA less preferential directionality such as in the GM and cerebrospinal fluid (CSF) where FA is 0 (isotropy). Related measures are the radial and axial diffusivity, respectively representing diffusion along and perpendicular to the diffusion tensor's principal direction. The DEC maps by convention colour code voxels with inferior-superior direction in blue, antero-posterior direction in green and left-right direction in red. Fibre tracking can be performed with a multitude of different computational algorithms that provide streamlines based on the measured preferential direction of diffusion within voxels.

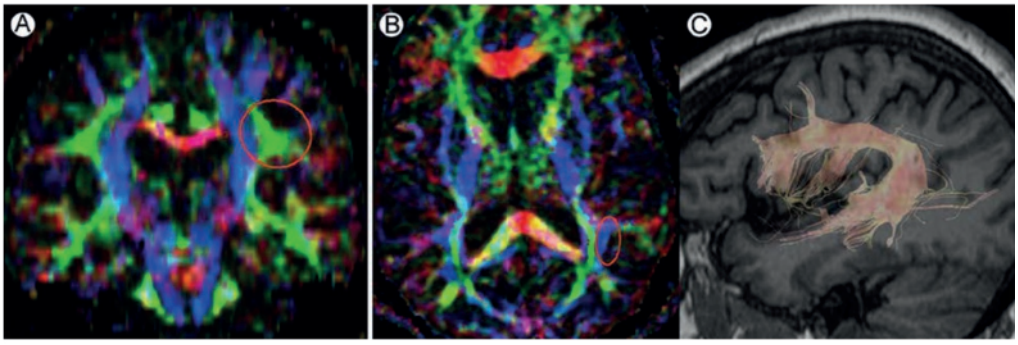

Figure 3.1.3 | **Tracking the arcuate fasciculus:** A) a seed region of interest (ROI) is placed in the green triangular-shaped superior longitudinal fasciculus (circled) in the coronal plane; B) a target ROI is placed in the vertical segment of the arcuate fasciculus in the transverse plane (circled) on the directionally encoded colour maps; and C) the 3D rended tract is superimposed on a sagittal T1 volume. 3D, 3-dimensional.

Because the AF is a subdivision of the superior longitudinal fasciculus (SLF), DTI-tractography is required to assess it separately. There is no consensus on how to perform fibre tracking of WM tracts and several approaches have been described. For our clinical routine, we use the methods described by Wakana et

al. [23], using both a seed and target region of interest (ROI). For tracking the AF (Figure 3.1.3c), the seed ROI is placed around the deep WM of the posterior parietal portion of the SLF, visible as a green triangular shape on the directionally encoded tensor map in the coronal plane (Figure 3.1.3a). The target ROI is placed around the descending portion of the SLF in the posterior temporal lobe, seen as a blue structure lateral to the splenium of the CC in the transverse plane (Figure 3.1.3b). With this method, both the long and the indirect short segments are commonly visualised, without separation of these segments. This is generally sufficient for clinical purposes.

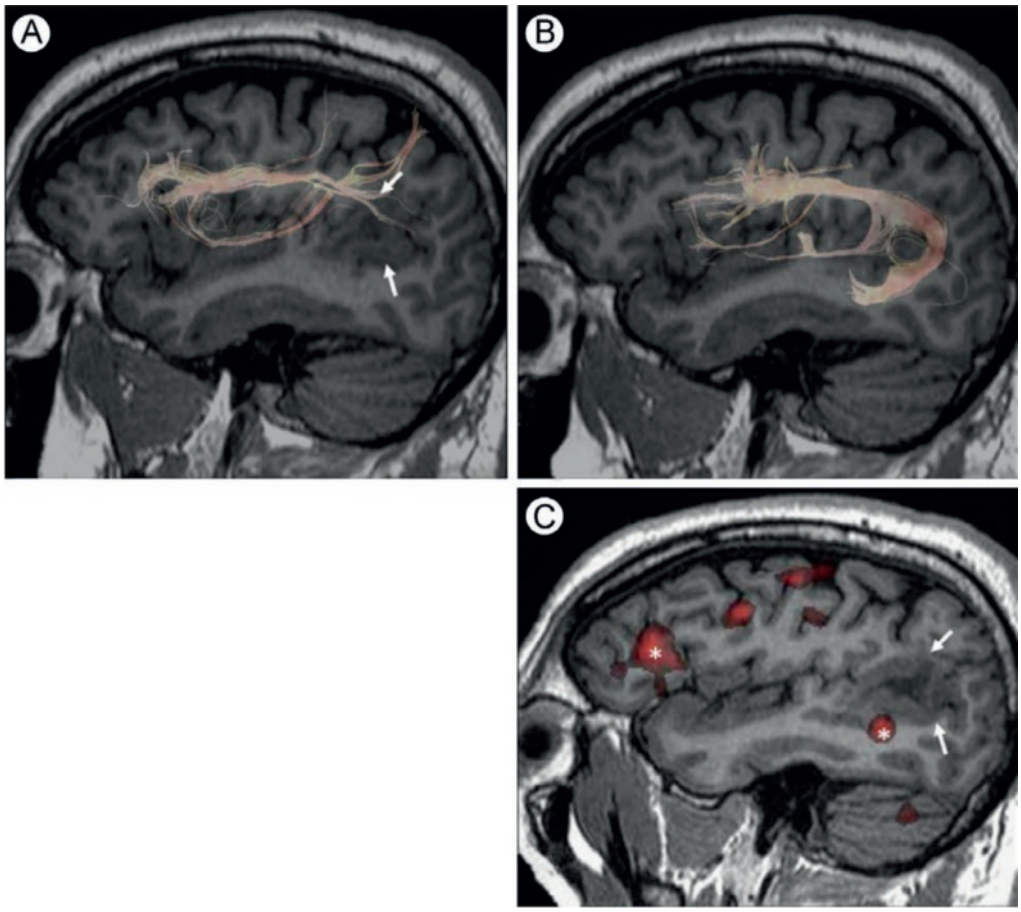

Figure 3.1.4 | **Tracking the arcuate fasciculus (AF) in the presence of a tumor in the left supramarginal and superior angular gyri:** A) note that with the default fractional anisotropy (FA) threshold at 0.18 the tracking algorithm fails to track the AF past the tumor (arrows); B) using additional regions of interest in the language areas as assessed by fMRI allows the lowering of the FA threshold to 0.12, resulting in successful tracking of the AF; and C) fMRI ROIs identified by * with activation superimposed on T1 volume.

If separation is required, we refer to the 2-ROI approach described by Catani et al. [24]. An alternative approach for tracking the AF is to use functional rather than structural anatomical landmarks for ROI placement. With fMRI, areas of language activation can be identified which could serve as seed and target ROIs. Such an approach is particularly useful in cases of severely distorted anatomy, for instance in brain tumour patients [25-27] (Figure 3.1.4). The UF (Figure 3.1.5c) is tracked by selecting the most posterior coronal slice in which the temporal lobe is separated from the frontal lobe (Figure 3.1.5a-b).

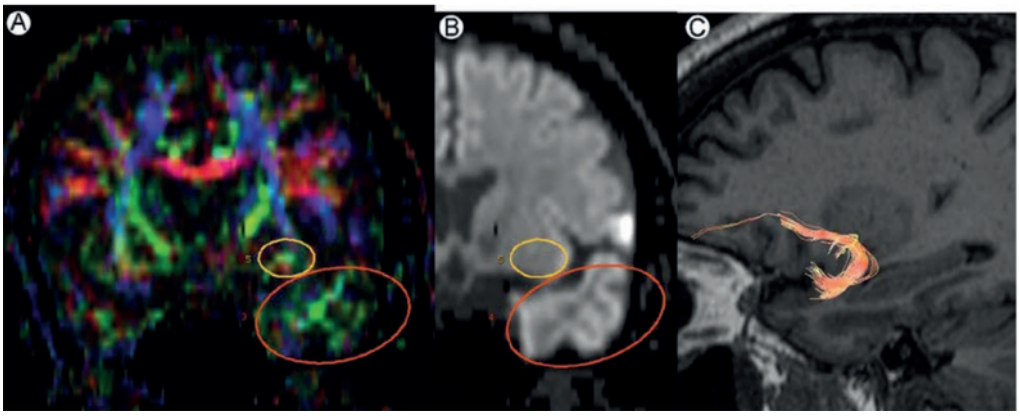

Figure 3.1.5 | **Tracking the uncinate fasciculus.** A) Regions of interest (ROIs) are placed in the most posteriorly located coronal slice where the frontal and temporal lobes are still separated. B) This can best be appreciated on the B0 image. A seed ROI is placed encompassing the entire temporal lobe (A and B: red) and a target ROI in the anterior-posterior projecting fibers in the frontal lobe (A and B: yellow). C) Projection of the uncinate fasciculus on to sagittal T1 volume.

The first ROI includes the entire temporal lobe and the second ROI includes the entire projections toward the frontal lobe. For tracking the IFOF (Figure 3.1.6d) the seed ROI is placed delineating occipital lobe, by identifying the middle coronal slice between the posterior edge of the cingulum and the posterior edge of the parieto-occipital sulcus, best visualised on an anatomical image rather than the colour coded map (Figure 3.1.6a-b). For the target ROI the entire hemisphere is delineated on a coronal slice at the anterior edge of the genu of corpus callosum (Figure 3.1.6c).

Presurgical assessment of language tracts

Inadvertent transection of the WM language tracts during surgery is avoided by their localisation with subcortical stimulation. Assessing the language tracts with subcortical stimulation was found to be useful in minimising permanent language deficits in patients undergoing surgical resection of glioma in the dominant hemisphere [28]. Although subcortical stimulation can be considered the gold standard for mapping the WM tracts, it is important to realise that this procedure is cumbersome: it requires close proximity to the resection bed, higher electrical currents and is less reliable than electrocortical mapping

[29]. It is time-intensive, which limits the number of tracts that can be localised. These tracts can only be assessed locally, i.e. there is no full overview of all tracts as can be achieved with DTI-tractography. It also seems that the technique not always gives sufficient warning, but rather seems to give information on damage that is already done [30]. Pre-operative DTI-tractography of the WM language tracts can be used as an adjunct to their intra-operative localisation with subcortical stimulation. This is currently the only real application of DTI of the language WM tracts in clinical practice. Current neuronavigational systems allow for the overlay of DTI derived fibre tracts on the anatomical reference scan during surgery, providing the surgeon with information about the relationship between his position and the location of these tracts (Figure 3.1.4). The advantages of pre-operative mapping of the language tracts include the ability to optimally plan the surgical approach, have a clear target for deep WM stimulation, reduce the duration of the surgical procedure, and lower the number of seizures [27].

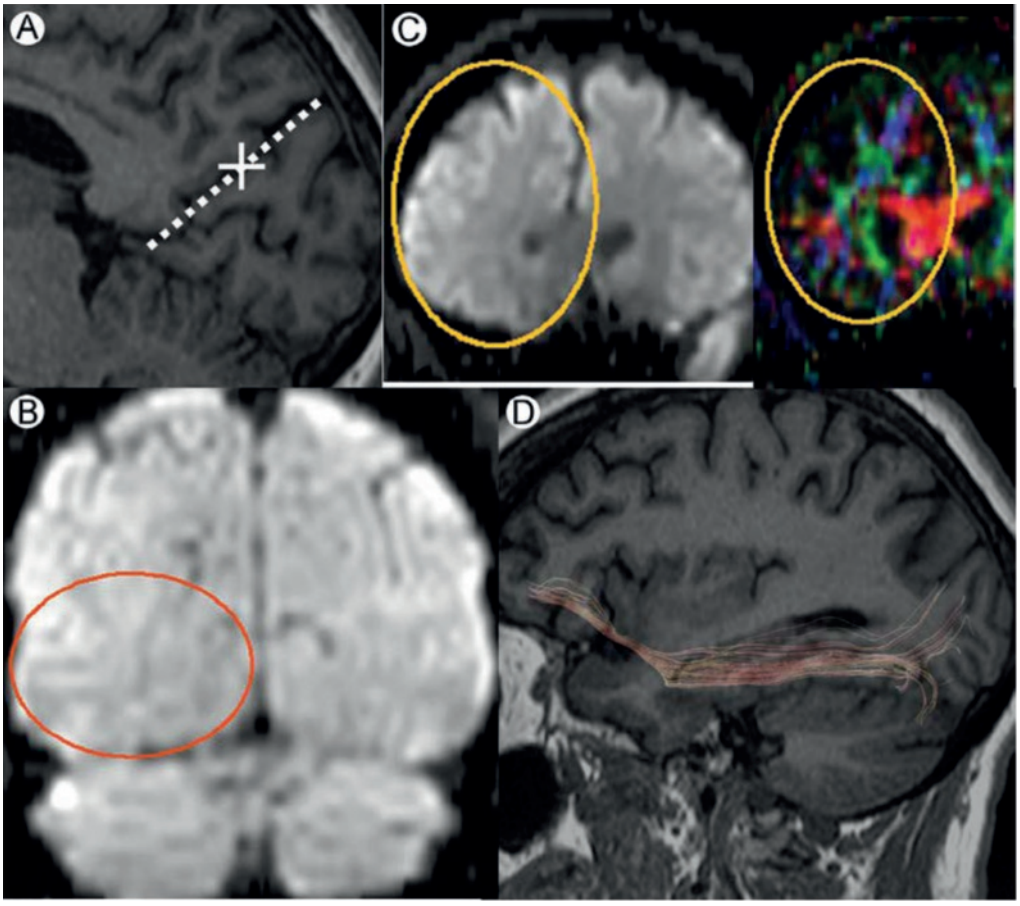

Figure 3.1.6 | **Tracking the inferior fronto-occipital fasciculus (IFOF)**: A) sagittal T1 image showing placement (cross) of the coronal region of interest (ROI) in the middle of the parieto-occipital sulcus (dashed line); B) the seed ROI encompassing the occipital lobe in a coronal section; C) a target ROI is placed around the entire frontal lobe at the level of the genu of the corpus callosum; and D) tractography of the IFOF projected onto a sagittal T1 volume.

Clinical benefit

While the advantages for the surgical procedure of pre-operative DTI fibre tracking as listed above are fairly well-established [27], studies assessing the benefit of this technique for patient outcome are rare. In a hallmark paper by Wu et al. longer overall survival and higher performance status was demonstrated in glioma patients that had undergone DTI prior to surgery compared to those that had not [31]. Several studies have assessed the combined use of fMRI and DTI-tractography and generally report a benefit in terms of impact on clinical decision making and modification of the surgical approach in up to 20% of cases [32]. Furthermore, Yu et al. reported a significantly greater extent of tumour resection in patients with pre-operative DTI-tractography [33], but the impact on overall survival was not assessed.

Validity of tract localisation

Bello et al. assessed the accuracy of DTI fibre tracking of both the language and motor tracts in 64 patients with high and low grade gliomas in comparison with intra-operative subcortical mapping [27]. They report a very high sensitivity (89-99%) and specificity (100%) for mapping the AF, UF and IFOF, although they note that the frontal fibres of the AF were often not depicted. Other studies combining subcortical stimulation with DTI fibre tracking reported 81-97% correspondence between positive subcortical sites and DTI fibre tracts [26].

Tract integrity

DTI can not only be used to localise a WM tract, but also to assess its infiltration or destruction by tumour. DTI-t has demonstrated a difference in the way WM tracts are involved in high and low grade tumours: with high grade gliomas, the WM tracts are commonly displaced by or in close proximity to the tumour, while in low grade tumours tracts are often found within the tumour itself, and are commonly infiltrated [27]. Additionally, as described by Hussain et al. in this issue four patterns of FA and ADC appearance can be distinguished to indicate tract integrity, ranging from tract displacement to tract destruction [34].

Combining fMRI with DT-t

By combining DTI-tractography with fMRI we can provide the surgeon with a comprehensive overview of both the subcortical and cortical language regions. The combination also has two important other advantages [25]. Firstly, in patients with a brain tumour, anatomical landmarks for fibre tracking may be deviated or obscured by the mass effect and presence of the tumour. Functional language regions identified with fMRI can in such cases serve as more reliable landmarks for the placement of seed and target ROIs. In patients with tumours in the language areas, fMRI based seed ROIs were found to improved tractography as compared with anatomic ROIs [26]. Secondly, tracking results vary according to the FA threshold applied to the tracking algorithm. This is commonly set at an FA around 0.2, such that the tracking algorithm terminates in areas with low FA where directionality is uncertain and tracking below such a threshold would result in many false positive tracts. In WM tracts that are infiltrated by tumour or are oedematous, however, FA may fall below this threshold, which can cause fibre tracking to terminate prematurely (Figure 3.1.4a). Lowering the FA threshold will solve this, but the tracking algorithm needs to be constrained to avoid the introduction of erroneous false positive tracts. Such constraint can be achieved by the use of multiple ROIs that need to be placed as accurately as possible, such as on the basis of fMRI (Figure 3.1.4b) [25,27].

Limitations

While DTI-tractography allows for the anatomical localisation of the WM tracts, it only provides structural and not functional information. There is still considerable controversy about the question whether severing the language WM tracts will actually cause – permanent – aphasia. This is particularly questionable for fibre tracts that appear to be infiltrated or destroyed by tumour [35]. A major limitation of the use of pre-operatively acquired data, including DTI maps, during surgery is the brain shift that occurs during surgery with the opening of the skull. Unfortunately, the direction and degree of shift is not always predictable, and repeated landmark checks are required at minimum to account for this effect, which is generally greater with larger than with smaller tumours. Other techniques to correct for brain shift during surgery are intra-operative ultrasound and MRI. Even without considering registration errors due to brain shift, there is some uncertainty regarding the architectural reproducibility of the WM tracts. In a study of 17 healthy volunteers who were scanned twice with the same protocol on the same scanner, the spatial correlation of the AF reconstructions from the 2 scans was maximum 69% [36]. The difference between the 2 reconstructions was the shift of about 1 voxel, suggesting a definition of tractography borders of about 2 mm of uncertainty. General limitations of DTI-t, not specific to the language tracts, include the inability to differentiate afferent from efferent fibres, to solve the ambiguity of fibre kissing and fibre crossing, and misregistrations from geometric distortions [37]. It is important to remember that DTI-tractography relies on computational algorithms that have multiple thresholds affecting the tract reconstruction, in particular in the presence of a brain tumour. As described above, the tracking algorithm may terminate prematurely due to low FA in tracts with oedema or tumour infiltration. Additionally, the angular threshold may terminate tracts with sharp angles due to displacement or distortion. Susceptibility artefacts, either due to (tumoural) haemorrhage or surgical material, result in signal drop-out which may not be apparent on the reconstructed images; source images therefore need to be scrutinised for these and other artefacts affecting the DTI signal. The non-visualisation of a white matter tract in any such cases needs to be interpreted with great care, and certainly does not equate tract disruption.

DTI of language deficits in cerebrovascular disease

The most common cause of aphasia is cerebrovascular disease (CVD), or 'stroke', the clinical term referring to the loss of brain function due to disturbance of blood supply. CVD is a heterogeneous condition in which large and small vessels can be affected, either by ischaemic infarction or haemorrhage. The type of aphasia and prognosis are highly influenced by lesion type, location and size. Most aphasia cases result from ischaemic occlusion of the left middle cerebral artery, supplying the perisylvian cortex, basal ganglia, internal capsule and periventricular WM. Haemorrhage is not constrained by vascular arrangements, and can vary from small to large bleedings dependent on the size of the blood vessel. Both infarction and haemorrhage may have devastating effects on cerebral WM [38], which can have great implications for language functioning.

DTI in acute and subacute stroke

Neuroimaging in stroke has evolved from the use of computed tomography (CT) to advanced MRI techniques [39-41]. In the hyperacute phase, diffusion weighted imaging (DWI) is widely used in clinical practice to delineate the presence, size and location of ischaemic infarction. In case of acute ischaemic infarction, intracellular water diffusion is reduced which translates as a pathological high signal on DWI (for more information see [42]). The cellular retention and even uptake of water leading to cytotoxic oedema in this stage of stroke, found to be well detectable using DWI [43], can pose problems for DTI as elevation in water content changes the diffusion anisotropy [44]. The exact impact of these hyperacute stroke stage processes on DTI is still largely unknown [45], but DTI findings in (cytotoxic) oedema are diverse, with several studies reporting reduced anisotropy at the site of the lesion [46-48], and others reporting increased anisotropy [49]. Sotak [47] states that substantial and reliable changes in diffusion anisotropy occur during the subacute and chronic stages of stroke, when disruption of the cytoarchitecture will lead to a loss of ordered anisotropic structures. In the meantime the use of DTI in acute clinical practice remains negligible [50]. For research purposes however, DTI is of great value, because we can study the development of microstructural WM damage directly after stroke up until the chronic phase on a microstructural level [46,48,51], and relate these findings to clinical outcome. Zelaya et al. [48] for example found a monotonic and significant decrease in anisotropy within an ischaemic lesion as a function of time. This may in the future be used to assess the severity of an ischaemic event and the impact on language functioning. Furthermore, the potential ability of DTI to distinguish acute primary stroke from chronic ischaemia may lead to enhanced clinical, pharmacological care in the acute phase [52], with associated positive clinical outcome. Despite brain repair in the subacute phase, WM damage is normally extending into the subacute and chronic phase of stroke due to Wallerian degeneration. Wallerian degeneration refers to the secondary degeneration of axons as the result of proximal axonal injury or neuronal death. As this degeneration cannot be detected by conventional MRI techniques (T2 FLAIR MRI) until 4-10 weeks after the stroke [53], DTI has a great advantage in these stages. Several studies have furthermore shown that vascular related white matter damage visualised as hyperintensities on T2 FLAIR MRI are just the tip of the iceberg [54-56]. By means of DTI we are able to sensitively examine microstructural WM changes as an effect of stroke.

Vascular white matter damage and cognitive decline

Cerebral small vessel disease (CSVD) is a vascular condition that affects the smallest vessels of the brain supplying the deep WM and subcortical GM structures. The condition is common in elderly and is found to be associated with deterioration of cognitive functions like executive functioning, memory functioning [57] and language functioning [58]. The mechanisms through which CSVD contributes to cognitive impairment however, are still a matter of debate. A recent paper of Papma et al. [54] examined the role of CSVD in affecting WM microstructural integrity underlying default mode network functioning, using DTI in a group of patients in an early stage of dementia. The default mode network is a functional network of brain regions known to play a role in cognitive functioning, which is preferentially active when individuals are not focused on the external environment, and when individuals are engaged in internally focused activities such as mind wandering. It includes the precuneus and the medial prefrontal, posterior and anterior cingulate, and parietal cortices. Structures of the DMN seem particularly vulnerable to atrophy

and amyloid deposition and its deterioration is often associated with dementia [59-60]. For the purpose of the study, Papma et al. [54] performed probabilistic tractography of DMN related tracts [61-62]. Figure 3.1.7 displays the results of the probabilistic tractography of the DMN related WM and control tracts. Tractography allows for 3D reconstruction and estimation of WM tracts, and provides useful information on the presence and severity of injury of fibre tracts which cannot be obtained using conventional MRI. The authors examined the relationship between extracted DTI measures within the normal appearing WM of the tracts displayed in Figure 3.1.7, and determinants of CSVD, but also demographic variables and dementia related variables. They found that within the tracts that underlie the DMN, WM hyperintensity as obtained by FLAIR MRI was one of the most important predictors. Interestingly, this postulates that even small vessel disease leading to mild WM damage can influence cognitive functioning, among which language functioning, by influencing network functioning.

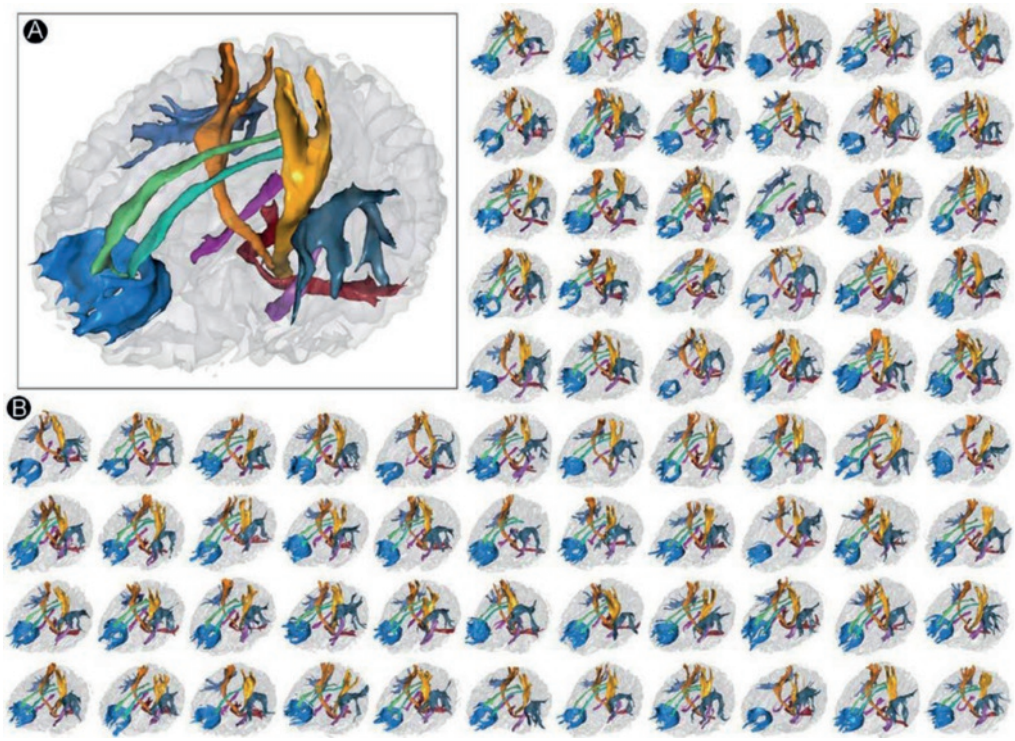

Figure 3.1.7 | **Tractography of the default mode network in mild cognitive impairment (MCI):** A) probabilistic tractography of the tracts of interest in a single subject (blue: forceps minor, light and dark green: left and right cingulum cingulate part, orange and yellow: left and right corticospinal tract, light and dark purple: left and right cingulum hippocampus part, light and dark grey: left and right superior longitudinal fasciculus, and red: middle cerebellar peduncle) and B) range of visibility of these tracts in all participants in the study (both healthy controls and patients with MCI and small vessel ischemic disease) in native space. Reproduced with permission from Papma et al. [53].

DTI in post-stroke aphasia

Much of DTI research in post stroke aphasia has focused on identifying WM tracts that connect nodes within the language network, like Broca and Wernicke areas using tractography. In aphasia research tractography has been extensively used to examine the status of the AF (for an overview see [63]). In the absence of Broca or Wernicke injury, damage to the AF, as assessed with FA value and fibre tracking, can lead to severe aphasia [64]. Tracking the AF, and identifying the region of damage, led to diagnostic reclassification of aphasia type in several patients in a study of Kim et al. [65], e.g. they found that a disconnection of the left AF could be the cause of Broca's aphasia instead of conduction aphasia (Figure 3.1.8). These findings can have important clinical implications, as this would imply a more favourable outcome. In addition, using an ROI method several studies found that lower FA values of the AF and the SLF are associated with more severe aphasia [65-66]. By means of voxelwise lesion-behaviour mapping (VLBM), a technique used to identify brain structures associated with acute language impairment after stroke, Kümmerer et al. [67] found that language problems were foremost associated with subcortical tissue, in particular the dorsal SLF and AF. According to the authors this does not necessary imply that acute aphasia represents a disconnection syndrome, but rather demonstrates that WM damage critically contributes to language impairment.

DTI in post-stroke aphasia therapy

When evaluating the effects of aphasia therapy on brain structure and function, the selection of patients at least 6 months after the onset of stroke (chronic phase) is crucial [68], as during the chronic phase functional or structural changes due to natural recovery are minimal. In general it has been found that regardless the type of therapy used, the effectiveness increases when the intensity of therapy is increased, both in terms of time investment and difficulty. Whether language recovery after intensive rehabilitation is supported by the recruitment of preserved structures or by morphological changes in damaged white matter pathways can be determined by means of DTI. Schlaug et al. [69] examined changes within the density of the right hemisphere WM tracts before and after melodic intonation aphasia treatment in chronic stroke patients with left AF damage, with a significant increase in the absolute number of fibres of the right AF. On the other hand, a case study focusing on the left AF reported that aphasia treatment in a chronic patient led to immediate FA increase along with improvement of language [66]. Some researchers claim that the repair of left hemisphere language networks will have more favourable outcomes than the recruitment of homologous regions in the opposite hemisphere [70]. To further elucidate this we can use DTI measures of left and right WM structures before and after language therapy, and relate the structural changes to clinical outcome. In addition, DTI can serve as a proxy in pharmacological vascular treatment, as it was shown that microstructural axonal changes on DTI can be reversible [71].

The clinical implication of DTI in post-stroke aphasia

Although DTI has potential clinical value the clinical implication of DTI in post-stroke aphasia so far is minimal. The use of DTI can have implications for treatment, both behavioural and pharmacological. With the potential of DTI to distinguish between acute lesion sites and older lesions [52] enhanced clinical, pharmacological care may lead to better clinical outcome. Therapy success can be enhanced by using DTI to re-evaluate an aphasia type diagnosis [65]. In addition, several studies have examined

the prognostic value of the integrity of white matter structures in predicting language outcome in post-stroke aphasia patients. Song et al. [72] found that lesion load within the AF was predictive for language outcome in post-stroke aphasia. Kim and Jang found that the prognosis in post-stroke aphasia patients in whom the left AF could be reconstructed using tractography had better clinical outcome when compared with patients without a trackable AF [63,65]. And finally, Schlaug et al. [51] demonstrated that the use of ADC threshold values in the acute phase can be useful in predicting tissue viability and stroke outcome.

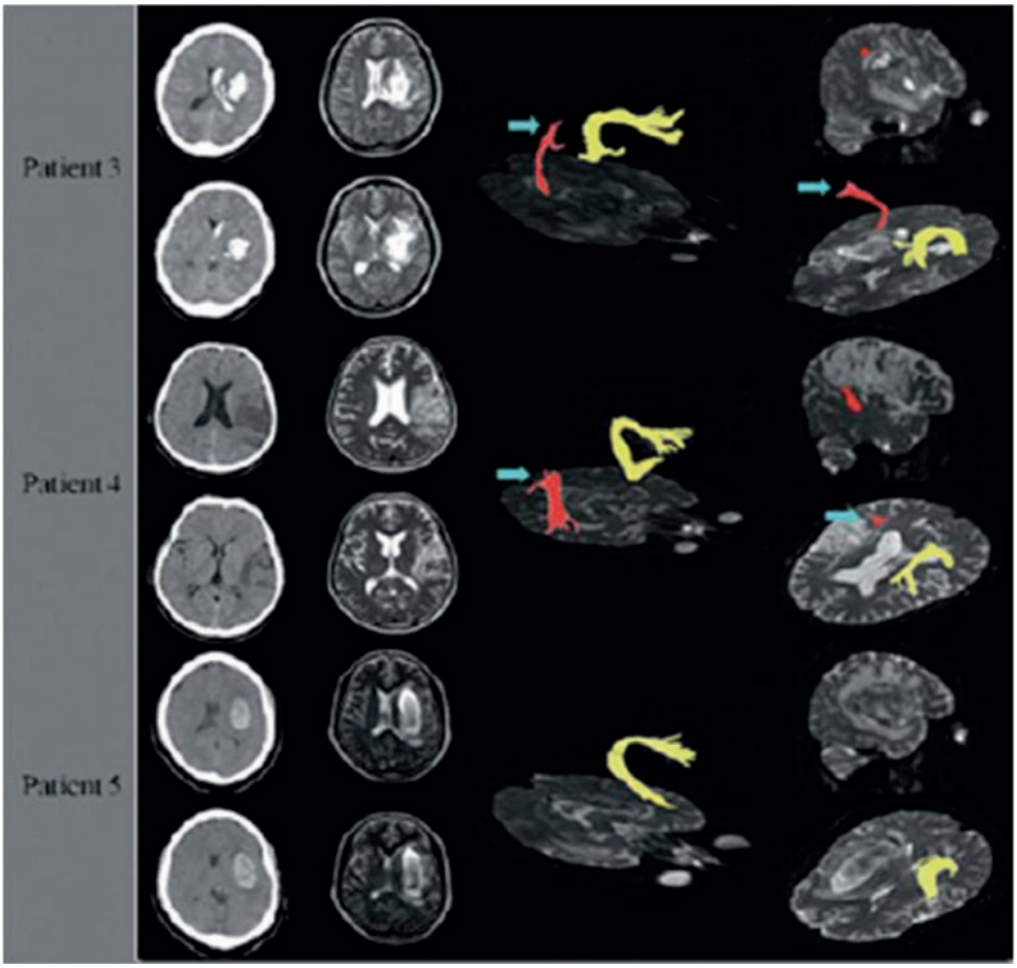

Figure 3.1.8 | **Arcuate fasciculus lesions in Broca aphasia.** Patient 3 and 4 both presented with a Broca-type aphasia but showed no lesion in the inferior frontal gyrus; DTI tractography of the arcuate fasciculus shows disconnection (arrows) near Wernicke area. Patient 5 presented with global aphasia; the arcuate fasciculus could not be reconstructed at all. Reproduced with permission from Kim et al. [64].

DTI of language deficits in dementia

Language deficits in dementia

Research into the white matter tracts involved in speech and language is increasingly directing its attention to the field of neurodegenerative diseases. A common misconception is that memory impairments are always the presenting symptom of dementia; however, language deficits are frequently found [73-74]. For example, even in the earliest stages of Alzheimer's disease (AD), deficits in the language abilities have been revealed [75]. Initially, language deficits comprise subtle problems regarding naming, output rate and comprehension, but develop into prominent paraphrases (e.g. "rypamid" instead of "pyramid" [phonemic paraphrase] or "bus" instead of "train" [semantic paraphrase]), automatic repetitions ('echolalia') and stereotypic output in the moderate to severe stages of the disease process [75]. Furthermore, in frontotemporal dementia (FTD), the second most common cortical dementia syndrome, language impairments range from lower or stereotypical speech output to echolalia, perseverations, and eventual mutism [74,76]. Of special interest in this neurodegenerative spectrum are the so called primary progressive aphasias (PPA): dementia subtypes in which isolated speech and language abnormalities are the most salient features from the initial disease phase onwards [1,77]. Clinically, the PPA spectrum comprises three different variants: 1) *semantic variant PPA (svPPA)*, 2) *non-fluent variant PPA (nfvPPA)*, and 3) *logopenic variant PPA (lvPPA)* [1] (Box 3.1.1). As these syndromes vary considerably in terms of their clinical presentation, important information regarding the function of different parts of the language network and their specific underlying white matter tracts can be demonstrated.

Neuroimaging in PPA

Recent advances in the neuroimaging of language-related dementias have been predominantly driven by the clinical refinement of the underlying syndromes as well as the search for new genetic and pathological aspects [77]. Despite aforementioned advances, making an accurate diagnosis or predicting underlying disease pathology has especially proved challenging due to the symptomatic, anatomical and pathological overlap between the clinical subtypes. Furthermore, the detection of the exact disease onset and tracking of disease progression was previously hampered by the lack of sensitive *in vivo* biomarkers [78]. With the development of diffusion MRI, and specifically DTI, aforementioned restrictions could be circumvented [79]. Therefore, DTI could hold the promise to improve our understanding of the pathophysiology of network disintegration across the PPA spectrum and therefore yield more insight into the microstructural organization of the different language networks [78,80].

DTI in language-related dementia research

Thus far, no DTI study has specifically looked into the affected WM tracts involved in language processing in AD. DTI changes, however, have amongst others been found in WM diffusion metrics of the corpus callosum and cingulum, as well as the frontal, parietal and temporal lobes, including several cortico-cortical association fibres such as the external capsule, ILF, SLF and UF [81-83].

Box 3.1.1 | **Clinical classification of PPA and its subtypes** [1]

1. **Semantic variant PPA (svPPA):** both core features (1. Impaired confrontation naming, 2. Impaired single-word comprehension), and at least three out of four other diagnostic features (1. Impaired object knowledge, particularly for low-frequency or low-familiarity items, 2. Surface dyslexia or dysgraphia, 3. Spared repetition, 4. Spared speech production (grammar and motor speech).
2. **Non-fluent variant PPA (nfvPPA):** at least one core feature (1. Agrammatism in language production; 2. Effortful, halting speech with inconsistent speech sound errors and distortions (apraxia of speech), and at least two out of three other diagnostic features (1. Impaired comprehension of syntactically complex sentences, 2. Spared single-word comprehension, 3. Spared object knowledge).
3. **Logopenic variant PPA (lvPPA):** both core features (1. Impaired single-word retrieval in spontaneous speech and naming, 2. Impaired repetition of sentences and phrases), and at least three out of four other diagnostic features (1. Speech (phonologic) errors in spontaneous speech and naming, 2. Spared single-word comprehension and object knowledge, 3. Spared motor speech, 4. Absence of frank agrammatism).

The WM alterations associated with AD have found to be less extensive than those with FTD, with no region in AD showing greater diffusivity changes when directly compared to FTD [81]. FTD disease-specific damage has amongst others been identified in WM tracts of the anterior frontal (e.g. cingulate, corpus callosum and SLF) lobes, as well as those connecting to the temporal (e.g. UF, ILF) lobes [81,84]. A growing amount of studies have investigated the similarities and differences in patterns of WM integrity loss in the PPA subtypes, as will be described below.

Semantic variant PPA (svPPA)

First, in svPPA the most significant changes in DTI metrics were identified most prominently in ventral tracts, connecting the temporal lobes to respectively the occipital and orbitofrontal, and the parietal and frontal lobes [80]. Specifically, in both the left, and to a lesser degree in the bilateral, UF and ILF, diffusional restrictions have been found [77,78,80,84-88]. For instance, both using fibre tracking, Galantucci et al. [80] and Agosta et al. [86] demonstrated an increase of all diffusivity measures (mean [MD], radial [DR] and axial diffusivity [DA]) and lower FA in the UF, and an increase of diffusivities without a reduction of FA in the ILF. Furthermore, Mahoney et al. [78] deemed DR to be the most sensitive metric in svPPA – followed by FA and DA – affecting the greatest degree of WM tracts in this particular subtype. In contrast to the ventral tracts, the dorsal pathways, as well as the more posterior located WM tracts, seem to be less significantly affected in svPPA [77,78,80,86]. Significant DTI changes could only be demonstrated when investigating the different components of the SLF individually [80]. Clinically, svPPA is characterised by fluent speech but impaired comprehension of word meaning and word-finding difficulties, as well as the loss of semantic knowledge [77,78,80,85]. The ILF and UF have been suggested to play a role in respectively visual object recognition i.e. linking objects to lexical labels and the mediation of semantic processing [86,89-90]. Damage to these tracts, therefore, seems to be consistent with the clinical picture of svPPA, with profound lexical deficits and relatively spared sound production and sentence construction.

Non-fluent variant PPA (nfvPPA)

In contrast to svPPA, nfvPPA primarily affects the frontal pathways. WM tract degeneration is consistently revealed in the left SLF (in particular AF) – leaving the ventral pathways relatively spared [77,78,80,86-88]. In a comparison between nfvPPA patients and control subjects, lower FA and higher MD values were demonstrated across the entire left SLF, while DA was not significantly altered. Furthermore, the ventral tracts connecting the temporal lobe to respectively the occipital and orbitofrontal cortex were not different from controls [80]. Clinically, nfvPPA is characterized by hesitant and halting, effortful speech production, agrammatism (using the wrong verb tense or word order), phonemic paraphrases and difficulty with understanding grammatically complex sentences [77,78,80,85]. In concordance with aforementioned findings, decreased integrity of the SLF, with sparing of the ILF has been suggested to best differentiate nfvPPA from svPPA [77,80] and LPA [80]. In this way, the SLF might be specifically involved in the language deficits seen in nfvPPA [84]. This seems consistent with the notion of the SLF as the neuroanatomical substrate for normal articulatory, phonemic and grammar processing [78]. Furthermore, it has been recently recognised that patients with nfvPPA can also present with so called 'apraxia of speech', in which speech production is affected on the motor level, i.e. impaired programming of syllables across or within words [91]. Therefore, the finding that damage to the SLF has been associated with apraxia of speech [77,89,90], as well as deficits in sentence comprehension and production [85], seems to correspond well to the clinical picture of nfvPPA. The latter could also be related to diffusivity changes in the anterior corpus callosum, which in turn seems to be consistent with evidence of the stroke literature that showed correlations between corpus callosum dysfunction and grammatical performance in Broca's aphasia [92].

Logopenic variant PPA (lvPPA)

DTI research between lvPPA patients and controls found bilateral fronto-temporo-parietal white matter tracts to be involved, including the ILF, UF, SLF, cingulum and fornix [78,88,93]. One study found no significant differences between patients and control subjects when entire tracts were investigated, but did find lower FA and higher MD values when taking separate SLF components into account [80]. However, the direct comparison between lvPPA and the other PPA variants showed somewhat mixed results. While Galantucci et al. [80] found no tract to be more damaged between the PPA subtypes, Mahoney et al. [78] revealed lvPPA to be associated with greater DTI metric alterations in posterior bilateral WM tracts (including ILF, SLF, UF, corpus callosum) when compared to nfvPPA and differences in only the splenium of the corpus callosum relative to SD. The discrepancy between studies might e.g. be caused by the use of different diffusion tensor-based techniques or the use of relatively small study sample sizes. Another plausible explanation is the notion that lvPPA WM damage encompasses both the ventral (as in SD) and dorsal (as in nfvPPA) pathways [88], thereby somewhat hampering the radiological differentiation between lvPPA and the other PPA subtypes. In concordance with the latter line of reasoning lies the language profile of lvPPA, which also shows some overlap with the clinical presentation of both svPPA and nfvPPA [88]. LPA is symptomatically characterised by slowed speech output, (sentence and phrases) repetition deficits, word finding pauses/difficulties and phonological errors in both naming and spontaneous speech [1,78,80]. According to Migliaccio et al. [93] the neuroanatomical basis of the disease-specific symptoms of lvPPA can, however, be found in the profound parietal WM atrophy. Along with the GM damage, the predominant posteriorly located white matter damage has been suggested

to particularly hamper the transition of information from the parietal to frontal-temporal areas, resulting in the lexical retrieval problems and phonological errors seen in this syndrome [1,93]. This is consistent with the finding of Galantucci et al. [80], showing that particularly the posterior segment of the SLF (connecting the posterior temporal and parietal cortex) is significantly damaged in lvPPA patients.

Diagnostic & prognostic value of DTI in PPA

From a direct comparison between the extent of GM and WM alterations in the AD-FTD language spectrum it becomes apparent that WM damage not only matches well with the GM degeneration, but also exceeds it in terms of magnitude, suggesting WM pathology to be not only the most salient, but also the earliest feature of language-related dementias. A possible explanation for this finding could be that WM damage precedes or leads to GM atrophy. Evidence for this notion can be found in a recent DTI study in presymptomatic FTD mutations carriers, demonstrating a widespread pattern of reduced WM integrity in frontotemporal areas without any cerebral GM changes, as well as a correlation with age, i.e. WM damage expands as gene carriers approach the symptomatic disease stage [94]. Detailed longitudinal studies, incorporating larger sample sizes and both volumetric and diffusion information are needed to investigate whether DTI could have greater diagnostic accuracy than conventional structural MRI modalities, especially in the earliest disease stages.

Conclusion

In addition to the well-known arcuate fasciculus, other WM tracts have now been identified as being involved in language processing. These include the uncinate fasciculus, the IFOF, and the ILF. These can all be separately visualised using tractography. In cerebrovascular disease, DTI provides us information on the presence and severity of WM injury, prognosis and recovery mechanisms in post-stroke aphasia. While its clinical impact, in particular in the early stages of stroke, is as yet negligible, research by means of DTI in post-stroke aphasia, brings us closer to a better understanding of the effects of stroke on cerebral WM. In time DTI may be used to increase the diagnostic and prognostic accuracy and aid in clinical, pharmacological intervention in an (sub)acute stage. In dementia, DTI research into the syndromic variants of AD and FTD thus far supports the notion of disease-specific breakdown of the different language networks. In svPPA, the greatest changes have been revealed in the ventral WM tracts, while nfvPPA is primarily characterised by diffusion deficits in the dorsal network. lvPPA in turn seems to affect both the ventral and dorsal pathways, with a specific prediliction for the more posteriorly oriented (parietal) tracts. This suggests that – in addition to frontotemporal GM atrophy – WM damage is related to the specific language profiles associated with each dementia or PPA subtype. DTI provides significantly greater diagnostic accuracy for early clinical classification of PPA subtypes as compared to macrostructural GM and WM atrophy alone and has the potential to become a sensitive biomarker for tracking disease progression. In this way, DTI might hold the promise to gain additional insight into both the pathophysiological molecular substrate as well as the normal functioning of the human language networks and the different WM tracts underlying them. At present, however, presurgical evaluation of brain tumour patients is the only clinical application of DTI-tractography to localise the language tracts and assess their integrity. Despite demonstrated advantages for the surgical procedure, outcome studies and randomised trials are still needed to show the benefit of using DTI-tractography in the pre-operative evaluation of brain tumour patients.

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3.2

Presymptomatic white matter integrity loss in familial frontotemporal dementia in the GENFI cohort: a cross-sectional diffusion tensor imaging study

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Abstract

We aimed to investigate mutation-specific white matter (WM) integrity changes in presymptomatic and symptomatic mutation carriers of the *C9orf72*, *MAPT* and *GRN* mutations by use of diffusion-weighted imaging within the Genetic Frontotemporal dementia Initiative (GENFI) study. 140 mutation carriers (54 *C9orf72*, 30 *MAPT*, 56 *GRN*), 104 presymptomatic and 36 symptomatic, and 115 non-carriers underwent 3T diffusion tensor imaging. Linear mixed effects models were used to examine the association between diffusion parameters and years from estimated symptom onset in *C9orf72*, *MAPT* and *GRN* mutation carriers versus non-carriers. Post-hoc analyses were performed on presymptomatic mutation carriers only, as well as left-right asymmetry analyses on *GRN* mutation carriers versus non-carriers. Diffusion changes in *C9orf72* mutation carriers are present significantly earlier than both *MAPT* and *GRN* mutation carriers – characteristically in the posterior thalamic radiation and more posteriorly located tracts (e.g. splenium of the corpus callosum, posterior corona radiata), as early as 30 years before estimated symptom onset. Early involvement of the uncinate fasciculus and cingulum was found in *MAPT*, sparing the internal capsule, whereas involvement of the anterior and posterior internal capsule was found in *GRN*. Restricting analyses to presymptomatic mutation carriers only, similar – albeit less extensive – patterns were found: posteriorly located WM tracts (e.g. posterior thalamic radiation, splenium of the corpus callosum, posterior corona radiata) in presymptomatic *C9orf72*, the uncinate fasciculus in presymptomatic *MAPT*, and the internal capsule (anterior and posterior limbs) in presymptomatic *GRN* mutation carriers. In *GRN*, most tracts showed significant left-right differences in one or more diffusion parameter, with the most consistent results being found in the UF, EC, RPIC and ALIC. This study demonstrates the presence of early and widespread WM integrity loss in presymptomatic FTD, and suggests a clear genotypic 'fingerprint'. Our findings corroborate the notion of FTD as a network-based disease, where changes in connectivity are some of the earliest detectable features, and identify diffusion tensor imaging as a potential neuroimaging biomarker for disease-tracking and -staging in presymptomatic to early stage familial FTD.

Introduction

Genetic FTD with an autosomal dominant inheritance pattern has a heterogeneous clinical profile, including behavioural variant FTD (bvFTD) and primary progressive aphasia (PPA). The *Chromosome 9 open reading frame 72* (*C9orf72*) repeat expansion, and mutations in the *microtubule-associated protein tau* (*MAPT*) and *progranulin* (*GRN*) genes are the three most common causes of familial FTD [1-3]. At-risk subjects within the presymptomatic stage allow a unique time-window into the earliest disease stages of FTD, important for diagnostic improvement and the development of robust and sensitive biomarkers [4-5]. The Genetic Frontotemporal dementia Initiative (GENFI) is a longitudinal cohort study of familial FTD across Europe and Canada, investigating carriers of the *C9orf72*, *MAPT* or *GRN* mutations and their healthy first-degree relatives. Cross-sectional analyses on volumetric MR images in GENFI demonstrated frontotemporal grey matter (GM) volume loss from 10 years before estimated symptom onset, confirming that the disease process precedes the clinical onset by several years in familial FTD [6].

White matter (WM) alterations, as measured by diffusion tensor imaging (DTI) are found to be early and widespread in the symptomatic phase of FTD, extending beyond the zones of GM atrophy [7-9], with distinct profiles in clinical and genetic subtypes [7,10-14]. The pattern of WM integrity loss includes the uncinate fasciculus (UF), cingulum, (anterior) corpus callosum, fornix, superior and inferior longitudinal fasciculi, thalamic radiation and corona radiata [7,12,14-16]. Also, previous studies in presymptomatic FTD caused by *GRN* and *MAPT* mutations demonstrated respectively lower integrity of the UF [17-18], and inferior frontooccipital fasciculus [17], whereas studies into presymptomatic *C9orf72* have shown more inconsistent results [19-21]. This underlines that, although a promising candidate, larger studies are needed in order to validate DTI as a neuroimaging biomarker for presymptomatic FTD.

In the current study we compared baseline DTI parameters between mutation carriers and non-carriers in families with autosomal dominant FTD caused by *C9orf72*, *MAPT* and *GRN* mutations within the GENFI consortium [6]. We hypothesized that the three different pathogenic groups have distinct profiles, with increasing WM integrity loss when moving from the presymptomatic to symptomatic stage.

Methods

Participants

Within the second GENFI data freeze [6], 365 participants from genetically confirmed FTD families with either a *C9orf72* repeat expansion, *MAPT*, or *GRN* pathogenic mutation were recruited from 13 research centres between January 30, 2012 and May 4, 2015. Six participants did not have MR imaging performed, and were therefore excluded. To improve data homogeneity, we excluded images from 1.5T scanners (n=50). All images were subjected to strict visual quality control, which led to 54 participants being excluded from further analysis, mainly due to motion and artefacts. The final sample consisted of 255 subjects, of which 140 were mutation carriers (54 *C9orf72,* 30 *MAPT*, 56 *GRN*) and 115 were non-carriers (see Figure 3.2.1 for the sample flowchart).

Standard Protocol Approvals, Registrations, and Patient Consents

Written informed consent was obtained from all participants at study enrolment. The study was approved by the local Medical and Ethical Review committees at each research site. DNA genotyping was performed locally at each research site. We defined a pathogenic repeat expansion in *C9orf72* as more than 30 repeats [22]. If presymptomatic participants had not undergone predictive testing, the clinical investigators were blind to their genetic status.

Clinical assessment

All participants underwent a standardised clinical assessment consisting of a medical and family history, neurological examination, neuropsychological testing and MR imaging of the brain. We determined clinical status according to established diagnostic criteria [23-24], based on this assessment and information from a structured interview with knowledgeable informants. The interview consisted of questions regarding behavioural, neuropsychiatric, cognitive, (instrumental) activities of daily living, motor, and autonomic symptoms. Furthermore, we quantitatively measured functional and/or behavioural changes by means of the Cambridge Behavioural Inventory Revised (CBI-R) [25]. Global cognition was assessed by means of the Mini-Mental State Examination (MMSE) [26].

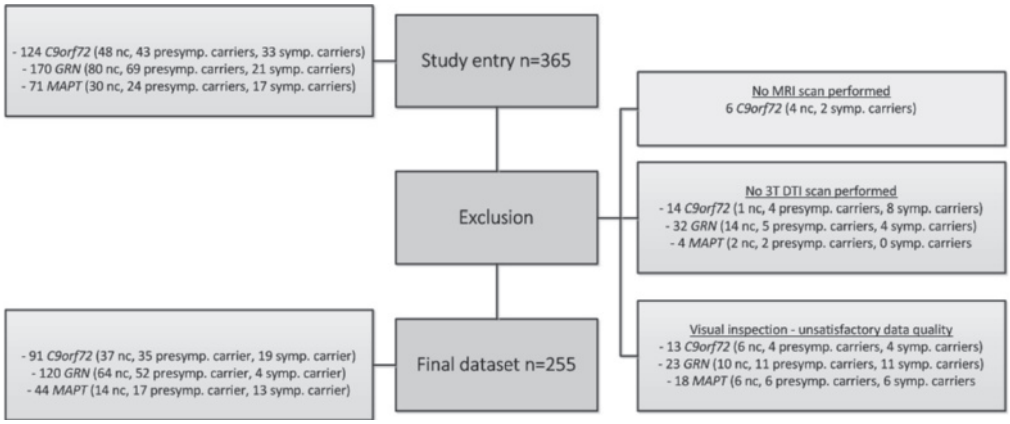


Figure 3.2.1 | **Overview of participant in- and exclusion.** 365 subjects were eligible for study participation. Six subjects did not undergo MRI scanning, and were therefore excluded. Only 3T scans were considered, therefore 1.5T (n=34) scans were first excluded from further analysis. Visual quality control of the images resulted in exclusion of another 54 images, leading to a final dataset of 255 subjects (115 non-carriers ("nc"), 104 presymptomatic mutation carriers, 36 symptomatic carriers.

DTI acquisition and (pre)processing

We performed 3T diffusion-weighted and volumetric T1-weighted MRI. Scanning was performed on MRI scanners from 5 vendors, see Table 3.2.1 for an overview of the number of participants and research sites per vendor, and scan parameters. In case diffusion-weighted images consisted of multiple acquisitions, NifTI files were merged within the FMRIB Software Library (FSL, v5.0.4) [27]; bvec and bval files were

concatenated within MATLAB (v2012a). Diffusion-weighted images were then pre-processed and analysed using a combination of tools from DTI-TK (http://dti-tk.sourceforge.net) and NiftyPipe (http://cmictig.cs.ucl.ac.uk/wiki/index.php/NiftyPipe) software packages [28]. In short, diffusion images were corrected for motion and eddy-current via an affine co-registration between the diffusion-weighted image to the average b0 image, and corrected for susceptibility via phase unwrapping [29]. Diffusion tensor volumes were spatially normalised to a population-specific tensor template with DTI-TK [30-31]. The structural T1-weighted image was used for reference space. To restrict analyses to brain matter and improve registration, we applied a subject specific binary T1 brain mask image, created by means of the Neuromorphometrics protocol [32-33]. We extracted diffusion parameters (fractional anisotropy [FA], mean [MD], radial [DR] and axial diffusivity [AxD]) in WM regions-of-interest (ROI) from the John Hopkins University (JHU) atlas [34] using FSL [27], and selected the following tracts: uncinate fasciculus (UF), superior longitudinal fasciculus (SLF), cingulum, sagittal stratum, posterior thalamic radiation (PTR), anterior (ACR), posterior (PCR) and superior (SCR) corona radiata, external capsule (EC), anterior (ALIC) and posterior limb (PLIC) and retrolenticular part (RPIC) of the internal capsule, and genu, body and splenium of the corpus callosum (respectively gCC, bCC and sCC). Left and right values were averaged to obtain one value per tract.

Table 3.2.1 | **Overview of MRI scanners and scan parameters**

Vendor	Philips	GE	Siemens	Siemens	Siemens
Type	Achieva	Discovery MR750	Trio	Allegra	Skyra
Scans in study	138	20	88	3	6
Research sites	3	1	5	1	1
FM echo time difference (ms)	2.46	2.60	2.46	2.46	2.46
Diffusion EPI readout time (ms)	32.57	28.42	34.56	35.52	34.56
PE direction	AP	AP	AP	AP	AP
FOV (mm)	240 x 240	240 x 240	240 x 240	240 x 240	240 x 240
TE (ms)	69	91	91	83	91
TR (ms)	7000	6900	6900	6900	6900
Acquisition matrix	96x96	96x96	96x96	96x96	96x96
Slice number	55	48	55	55	55
Slice thickness (mm)	2.5	2.9	2.5	3	3
Number of different directions	64	64	64	64	64
B value	1000	1000	1000	1000	1000
Repeats	2	3	4	5	6

Abbreviations: GE, General Electric; FM, field map; EPI, echo-planar imaging; PE, phase-encoding; AP, anterior-posterior; FOV, field of view; TE, echo time; TR, repetition time.

Statistical analysis

Data analysis was carried out using STATA (version 14.2; College Station, TX: StataCorp LP), with the significance level set at $p<0.05$ (two-tailed) across all comparisons. Each participant's age at baseline was subtracted from the average age at onset of symptoms in their family to estimate the years to estimated

symptom onset (EYO) [6]. EYO, and not actual onset age was also used in symptomatic mutation carriers, to provide a common time scale for the analysis. Age at baseline, estimated age at symptom onset, years from estimated symptom onset, and years of education were compared between groups by means of linear regression. Logistic regression was used to investigate differences in sex, and scores on the CBI-R and MMSE. Robust standard errors were used to account for clustering by family. We used linear mixed effects models to examine whether the association between diffusion parameters and EYO differed between each mutation carrier group (*C9orf72*, *MAPT* and *GRN*) and non-carriers. A random intercept for family was included, allowing diffusion parameters to be correlated between members of the same family rather than assuming independence. All analyses were adjusted for sex and research site. To allow for non-linear change in each diffusion parameter we used a restricted cubic spline [35] for EYO relative to expected symptom onset. The spline terms for EYO were included as predictors in the model, along with the interactions between each spline term for EYO and indicator variables for mutation carrier group (*C9orf72*, *MAPT* and *GRN*). The spline modelling approach was chosen to allow a complex pattern of association with EYO, e.g. FA might increase and then later on become lower. The knots were placed at -20, -5 and 7 years relative to expected onset to ensure that each group had a least five participants before the last knot point and after the final knot point, with the middle point splitting the remaining participants into groups of approximately equal sizes. We reran the abovementioned analyses post-hoc in presymptomatic mutation carriers and non-carriers only (with knots at -20, -10 and 0 EYO), to exclude the potential influence of symptomatic mutation carriers. We also investigated left-right differences in *GRN* by calculating the asymmetry in each WM tract as absolute diffusion parameter (left – right)/mean diffusion parameter. As asymmetry values were skewed, we modelled them as a natural log (ln(Asymmetry) – but for easier interpretation we presented the results after exponentiation. This ratio of geometric means can be interpreted as follows: a ratio of 1.1 for *GRN* mutation carriers vs. non-carriers indicates 10% higher asymmetry in mutation carriers than non-carriers. The statistical model was the same as for the other mutation carrier vs. non-carrier analyses – mixed effect model allowing for clustering by family and with spline terms for years to estimated symptom onset.

For each model, we conducted a hypothesis test of whether the mean value of the diffusion parameter differed between each mutation carrier group (*C9orf72*, *MAPT* and *GRN*) compared to non-carriers. This was a joint Wald test of the indicator variable for the mutation carrier group of interest and its interactions with the spline terms for EYO. Therefore, there were 60 tests conducted to compare each mutation carrier group to non-carriers (15 tracts * 4 diffusion parameters). No formal correction has been made for multiple comparisons, as diffusion measures were not independent. From each model we also predicted the mean value of the diffusion parameter for each group, and the differences between each mutation carrier group (*C9orf72*, *MAPT* and *GRN*) and non-carriers every year between 30 years before estimated onset and 10 years after estimated onset. We conducted a sensitivity analysis to examine the impact of outliers on the findings on association between diffusion parameters and EYO. The linear mixed effects model described above was repeated for each diffusion parameter in each tract after excluding any participants with model residuals more than three standard deviations away from the predicted mean in the initial analysis.

Results

Demographic and clinical data

Demographic and clinical data are shown in Table 3.2.2. DNA genotyping assigned participants either to the mutation carrier (n=140; 54 from *C9orf72* families, 30 from *MAPT* families, and 56 from *GRN* families) or non-carrier (n=115; 37 *C9orf72*, 14 *MAPT*, 64 *GRN*) group. 104 participants were presymptomatic (17 *MAPT*, 52 *GRN*, 35 *C9orf72*), and 36 were symptomatic (19 *C9orf72*, 13 *MAPT*, 4 *GRN*). The estimated age at onset was lower in *MAPT* mutation carriers than both *GRN* and *C9orf72* mutation carriers (both $p<0.001$). All three mutation carrier groups had significantly lower MMSE scores than non-carriers (*C9orf72* $p<0.001$, *GRN* $p=0.006$, *MAPT* $p=0.004$). CBI-R scores were significantly higher in *MAPT* and *C9orf72* mutation carriers compared to non-carriers (both $p<0.001$), and compared to *GRN* mutation carriers (*MAPT* $p=0.002$, *C9orf72* $p=0.003$). There were no significant differences regarding sex, age, years from estimated symptom onset, or education. Table 3.2.3 provides an overview of the distribution of symptomatic and presymptomatic mutation carriers and non-carriers across EYO. There was one mutation carrier (*C9orf72*) who became symptomatic before their estimated onset age (between -10 and -5 EYO). There were respectively 4 *C9orf72*, 3 *MAPT* and 12 *GRN* presymptomatic mutation carriers past their estimated onset age (Table 3.2.3).

C9orf72 mutation carriers

Analyses of all (symptomatic and presymptomatic) *C9orf72* repeat expansion carriers demonstrated significant presymptomatic differences across all WM tracts and diffusion metrics (Table 3.2.4, Figure 3.2.2A). The earliest presymptomatic changes – between 30 and 20 years before estimated onset – were seen in the PTR, PCR and RPIC, sCC and gCC, followed by the UF and cingulum. In the last decade prior to estimated onset, significant differences were also found in the bCC, PLIC, EC, SCR, sagittal stratum, and SLF. Surprisingly, in the ALIC the diffusivity values in repeat expansion carriers became more similar to those of non-carriers, and did not differ significantly during an intermediate period from respectively 20 to 10 years before estimated symptom onset. Post-hoc analyses on only presymptomatic expansion carriers demonstrated similar – albeit less extensive – patterns of WM integrity loss, with the earliest and most consistent differences found in the posterior WM tracts, e.g. PTR, sCC, PCR (Figure 3.2.3A). In the late presymptomatic stage also the internal capsule (RPIC, ALIC, PLIC) also became involved (Figure 3.2.3A).

MAPT mutation carriers

Analyses of all (symptomatic and presymptomatic) *MAPT* mutation carriers had significant differences from non-carriers across several WM tracts (Table 3.2.4, Figure 3.2.2B). There was very early involvement of the UF: higher diffusivity was found between 30 and 20 years before estimated symptom onset, and again from 3 years before estimated symptom onset. Somewhat inconsistent findings were demonstrated for the SLF, cingulum and SCR: all three tracts had a presymptomatic time-window in which FA was increased, while diffusivity values were decreased. After estimated symptom onset, mutation carriers also had changes in the PCR, ACR, sagittal stratum, PTR, EC, and corpus callosum (gCC, bCC and sCC). There was weaker evidence for differences in the RPIC, PLIC and ALIC, and even 10 years post-onset values did not show consistent differences compared to non-carriers. Post-hoc analyses on

presymptomatic mutation carriers only confirm the early involvement of the UF: AxD changes are found between -30 and -24 years before estimated symptom onset, followed by changes in FA, MD and RD shortly before or around estimated symptom onset (Figure 3.2.3B). Furthermore, early presymptomatic changes were also found in the cingulum, SLF and SCR. After estimated symptom onset, the internal capsule (ALIC and PLIC) also demonstrated diffusivity changes (Figure 3.2.3B).

Table 3.2.2 | Demographic and clinical data

	mutation carriers (n=140)		non-carriers (n=115)	*p*-value
Female	75 (53.6)		73 (63.5)	0.100
Age (years)	50.1 ± 12.9		49.4 ± 13.3	0.682
Mutated gene				
C9orf72	54 (38.6)		37 (32.3)	–
MAPT	30 (21.4)		14 (12.2)	–
GRN	56 (40.0)		64 (55.7)	–
Clinical status				
presymptomatic	104 (74.3)		115 (100)	–
symptomatic	36 (25.7)		0 (0)	–
Estimated age at onset	57.2 ± 6.5		59.3 ± 7.1	0.066
Years from estimated onset	-7.1 ± 12.6		-9.9 ± 14.4	0.193
Education (years)	13.8 ± 3.2		14.0 ± 3.2	0.637
MMSE	28.1 ± 2.8		29.3 ± 1.0	<0.001
CBI-R	19.7 ± 33.0		3.1 ± 5.4	<0.001
Mutation carriers	*C9orf72*	*MAPT*	*GRN*	*p*-value*
Female	27 (50)	14 (46.7)	34 (60.7)	0.254
Age	50.6 ± 14.0	47.4 ± 12.7	51.0 ± 11.8	0.549
Clinical status				
presymptomatic	35 (33.7)	17 (16.3)	52 (50)	–
symptomatic	19 (52.8)	13 (36.1)	4 (11.1)	–
Estimated age at onset	58.3 ± 6.9	51.0 ± 6.0	59.5 ± 3.9	<0.001
Years from estimated onset	-7.7 ± 13.7	-3.6 ± 12.0	-8.5 ± 11.6	0.244
Education (years)	14.0 ± 3.1	13.0 ± 4.0	14.2 ± 2.9	0.668
MMSE	27.8 ± 2.9	27.8 ± 3.7	28.6 ± 2.0	<0.001
CBI-R	26.3 ± 36.5	33.2 ± 40.0	6.1 ± 16.8	<0.001

Values indicate: count (percentage) or mean ± standard deviation. *Abbreviations: C9orf72*, chromosome 9 open reading frame 72; *MAPT*, microtubule-associated protein tau; *GRN*, progranulin; MMSE, Mini-Mental State Examination; CBI-R, Cambridge Behavioural Inventory – Revised. *represents overall p-value for comparison of non-carriers, *C9orf72*, *MAPT* and *GRN* mutation carriers.

Table 3.2.3 | Distribution of *C9orf72*, *GRN* and *MAPT* symptomatic mutation carriers, presymptomatic mutation carriers, and non-carriers across estimated years to onset

Mutation	EYO								
	-30	-25	-20	-15	-10	-5	0	+5	+10
C9orf72									
Symptomatic	0	0	0	0	1	0	5	11	2
Presymptomatic	6	4	8	8	2	3	1	2	1
Non-carriers	7	4	4	5	4	4	2	4	3
MAPT									
Symptomatic	0	0	0	0	0	0	4	7	2
Presymptomatic	1	3	4	2	3	1	2	1	0
Non-carriers	0	1	2	4	2	0	1	2	2
GRN									
Symptomatic	0	0	0	0	0	0	4	0	0
Presymptomatic	6	4	5	7	9	9	4	8	0
Non-carriers	10	5	8	1	9	12	12	5	2

Abbreviations: EYO, estimated years to symptom onset; *C9orf72*, chromosome 9 open reading frame 72; *MAPT*, microtubule-associated protein tau; *GRN*, progranulin.

GRN mutation carriers

Analyses of all (symptomatic and presymptomatic) *GRN* mutation carriers had significant differences from non-carriers across a relatively limited number of WM tracts (Table 3.2.4, Figure 3.2.2C). The strongest evidence for differences were in the PLIC, ALIC, PCR, SCR, sCC, SLF and cingulum. The most consistent presymptomatic WM integrity changes were in the ALIC and PLIC, which showed significant differences from non-carriers from 10 years before estimated onset. Early presymptomatic changes were also found in the sCC, but differences only remained significant up to 4 years post-onset. The SLF and SCR showed differences from 1 to 2 years before estimated onset, followed by the cingulum and PCR only after estimated onset. The overall test comparing *GRN* mutation carriers to non-carriers did not show evidence for WM integrity changes in UF, sagittal stratum, PTR, ACR, RPIC, bCC and gCC. It was particularly notable that even 10 years after estimated onset, the diffusivity values of the sagittal stratum, RPIC, ACR and PTR were not significantly different between mutation carriers and non-carriers. Post-hoc analyses on only presymptomatic mutation carriers showed consistent diffusivity changes in the internal capsule (ALIC and PLIC) alone (Figure 3.2.3C).

Table 3.2.4 | *P*-values for difference in diffusion parameter between mutation carriers and non-carriers

Tract	parameter	mutation carrier vs. non-carrier	*C9orf72* vs. non-carrier	*MAPT* vs. non-carrier	*GRN* vs. non-carrier
UF	FA	<0.001	0.003	<0.001	0.138
	MD	<0.001	0.002	<0.001	0.515
	RD	<0.001	0.002	<0.001	0.532
	AxD	<0.001	0.010	<0.001	0.155
SLF	FA	0.222	0.005	<0.001	0.433
	MD	<0.001	<0.001	<0.001	0.048
	RD	0.020	0.001	<0.001	0.078
	AxD	<0.001	<0.001	<0.001	0.008
Cingulum	FA	0.011	0.038	<0.001	0.321
	MD	<0.001	<0.001	0.057	0.021
	RD	<0.001	<0.001	0.009	0.051
	AxD	0.015	<0.001	0.027	0.073
Sagittal Stratum	FA	0.131	0.035	0.043	0.727
	MD	<0.001	<0.001	0.001	0.341
	RD	<0.001	0.001	0.003	0.401
	AxD	<0.001	<0.001	<0.001	0.303
PTR	FA	0.058	0.004	0.059	0.056
	MD	<0.001	<0.001	0.193	0.344
	RD	<0.001	<0.001	0.191	0.389
	AxD	<0.001	<0.001	0.081	0.324
PCR	FA	0.871	0.379	0.145	0.470
	MD	<0.001	<0.001	0.015	0.005
	RD	<0.001	<0.001	0.021	0.015
	AxD	<0.001	<0.001	0.007	0.012
SCR	FA	0.847	0.581	0.055	0.279
	MD	<0.001	0.002	<0.001	0.058
	RD	0.001	0.011	<0.001	0.074
	AxD	<0.001	0.001	0.006	0.065
ACR	FA	0.011	<0.001	0.011	0.565
	MD	<0.001	<0.001	0.006	0.314
	RD	<0.001	<0.001	0.005	0.367
	AxD	<0.001	0.001	0.015	0.088

Abbreviations: C9orf72, chromosome 9 open reading frame 72; *MAPT*, microtubule-associated protein tau; *GRN*, progranulin; UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; PTR, posterior thalamic radiation; PCR, posterior corona radiata; SCR, superior corona radiata; ACR, anterior corona radiata; EC, external capsule, RPIC, retrolenticular part of the internal capsule; PLIC, posterior limb of the internal capsule; ALIC, anterior limb of the internal capsule; sCC, splenium of the corpus callosum; bCC, body of the corpus callosum; gCC, genu of the corpus callosum.

Table 3.2.4 | Continued

Tract	parameter	mutation carrier vs. non-carrier	*C9orf72* vs. non-carrier	*MAPT* vs. non-carrier	*GRN* vs. non-carrier
EC	FA	0.139	0.014	0.087	0.146
	MD	<0.001	0.001	0.002	0.059
	RD	0.002	0.001	0.004	0.063
	AxD	<0.001	0.001	0.006	0.053
RPIC	FA	0.413	0.725	0.245	0.356
	MD	<0.001	<0.001	0.277	0.387
	RD	0.004	<0.001	0.565	0.318
	AxD	<0.001	<0.001	0.045	0.610
PLIC	FA	0.136	0.366	0.555	0.002
	MD	0.038	0.001	0.286	0.056
	RD	0.076	0.025	0.448	0.022
	AxD	0.014	0.006	0.656	0.112
ALIC	FA	<0.001	<0.001	<0.001	<0.001
	MD	<0.001	<0.001	0.148	0.049
	RD	<0.001	<0.001	0.068	0.021
	AxD	0.028	0.001	0.240	0.106
sCC	FA	<0.001	<0.001	0.012	0.021
	MD	<0.001	<0.001	0.037	0.020
	RD	<0.001	<0.001	0.033	0.006
	AxD	<0.001	<0.001	0.058	0.165
bCC	FA	0.001	<0.001	0.025	0.149
	MD	<0.001	<0.001	0.002	0.109
	RD	<0.001	<0.001	0.006	0.130
	AxD	<0.001	0.001	<0.001	0.117
gCC	FA	<0.001	<0.001	<0.001	0.194
	MD	<0.001	<0.001	0.005	0.161
	RD	<0.001	<0.001	0.001	0.141
	AxD	<0.001	0.001	0.048	0.261

Abbreviations: C9orf72, chromosome 9 open reading frame 72; *MAPT*, microtubule-associated protein tau; *GRN*, progranulin; UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; PTR, posterior thalamic radiation; PCR, posterior corona radiata; SCR, superior corona radiata; ACR, anterior corona radiata; EC, external capsule, RPIC, retrolenticular part of the internal capsule; PLIC, posterior limb of the internal capsule; ALIC, anterior limb of the internal capsule; sCC, splenium of the corpus callosum; bCC, body of the corpus callosum; gCC, genu of the corpus callosum.

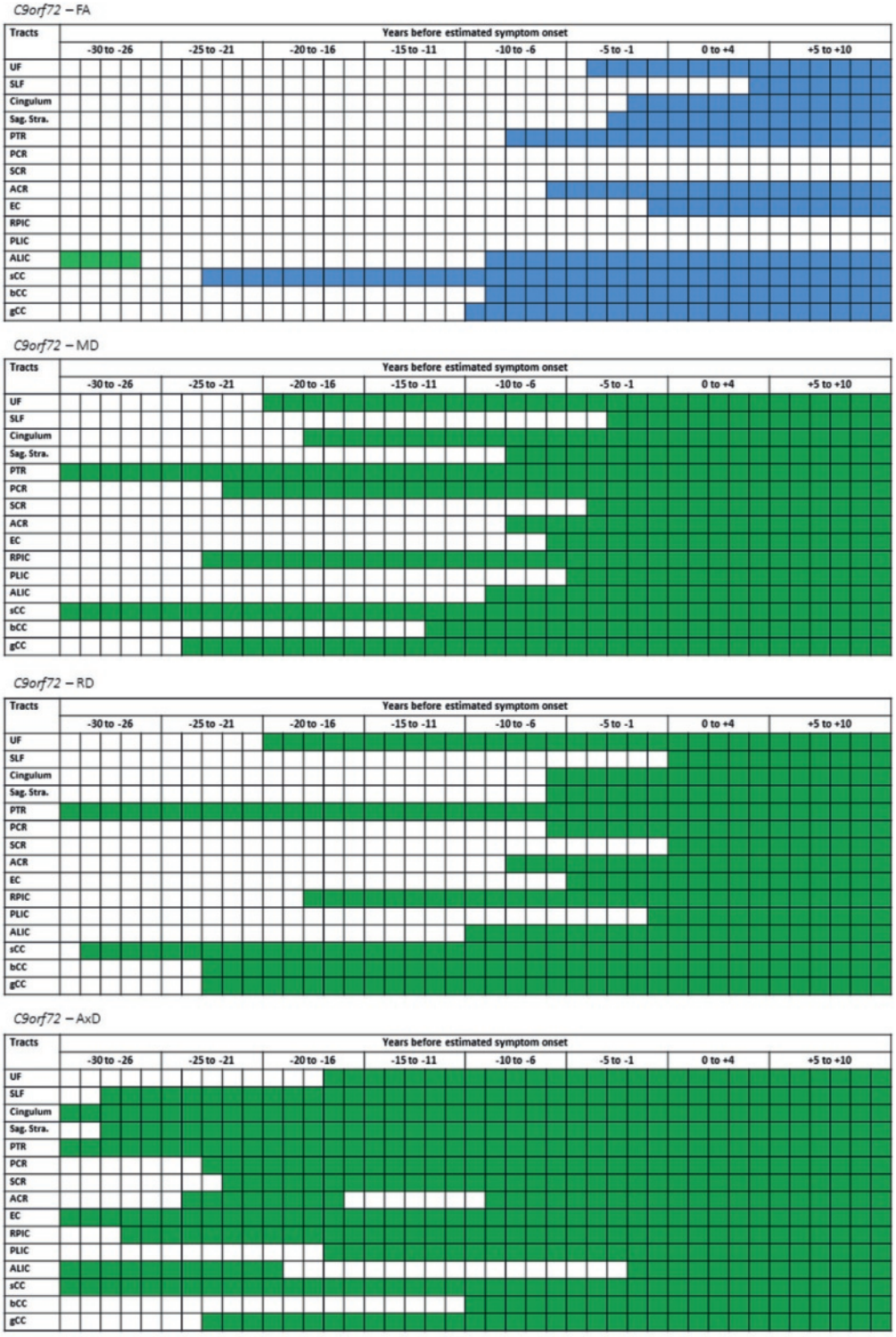
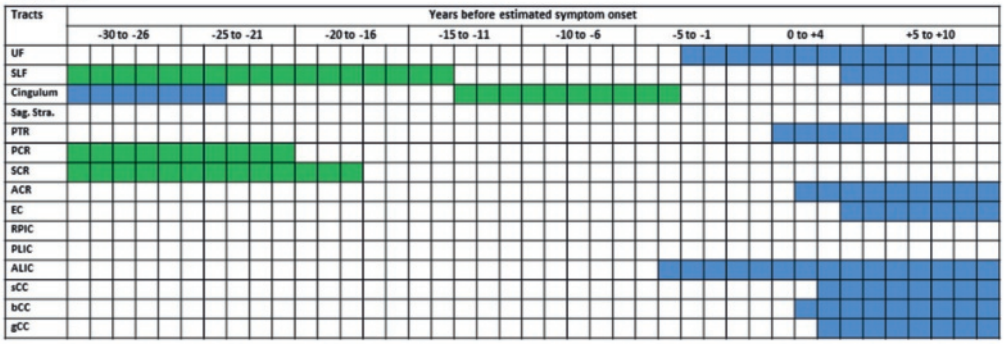
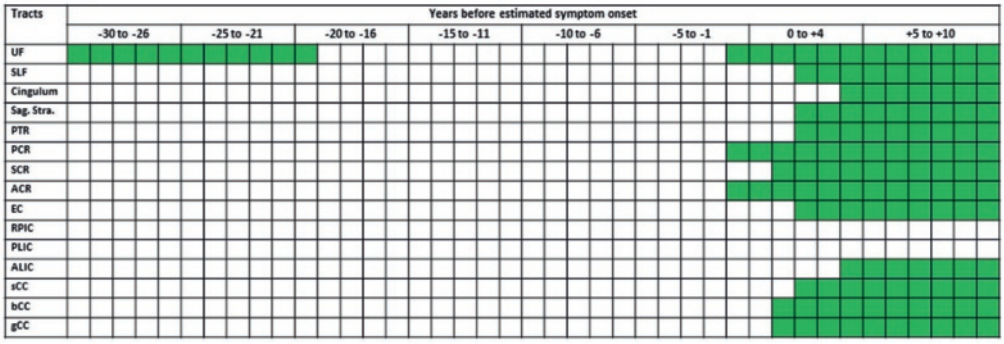

C9orf72 – FA
C9orf72 – MD
C9orf72 – RD
C9orf72 – AxD
Tracts
Years before estimated symptom onset
-30 to -26
-25 to -21
-20 to -16
-15 to -11
-10 to -6
-5 to -1
0 to +4
+5 to +10
UF
SLF
Cingulum
Sag. Stra.
PTR
PCR
SCR
ACR
EC
RPIC
PLIC
ALIC
sCC
bCC
gCC

Figure 3.2.2A

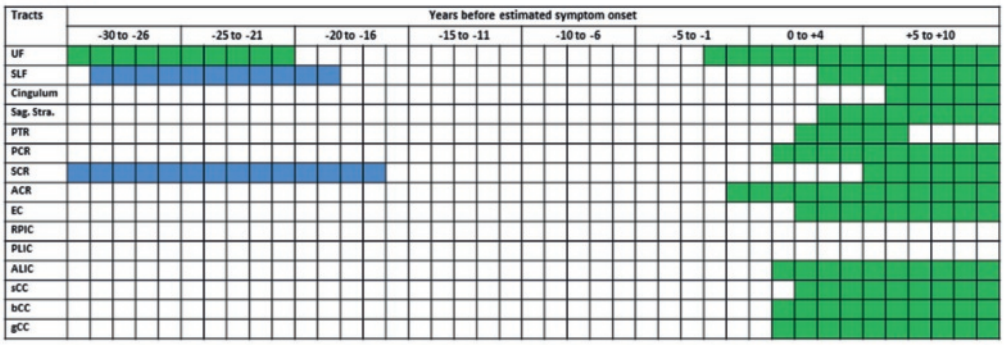
MAPT – FA



MAPT – MD



MAPT – RD



MAPT – AxD

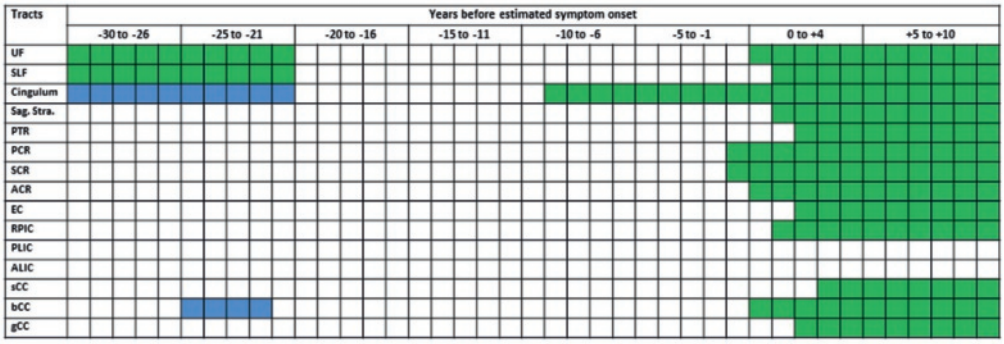
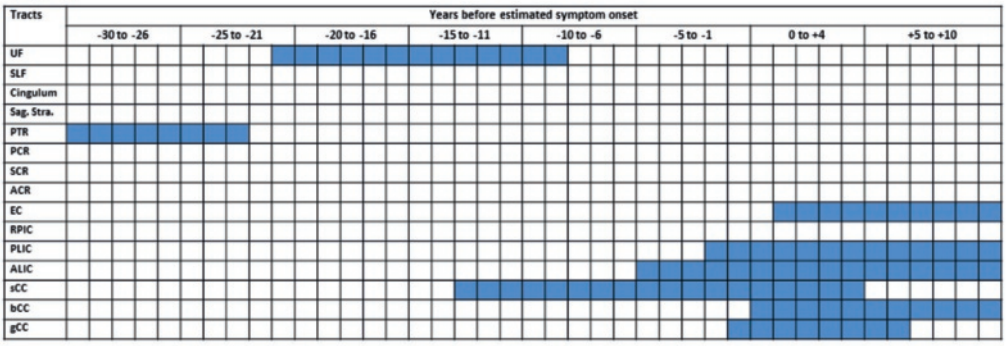
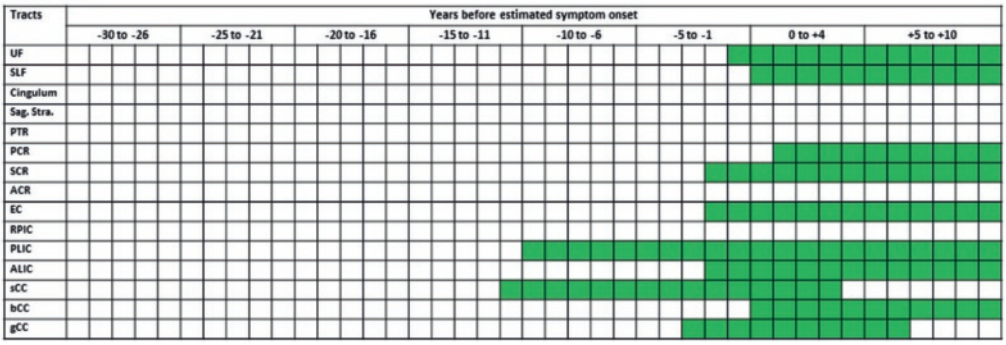


Figure 3.2.2B

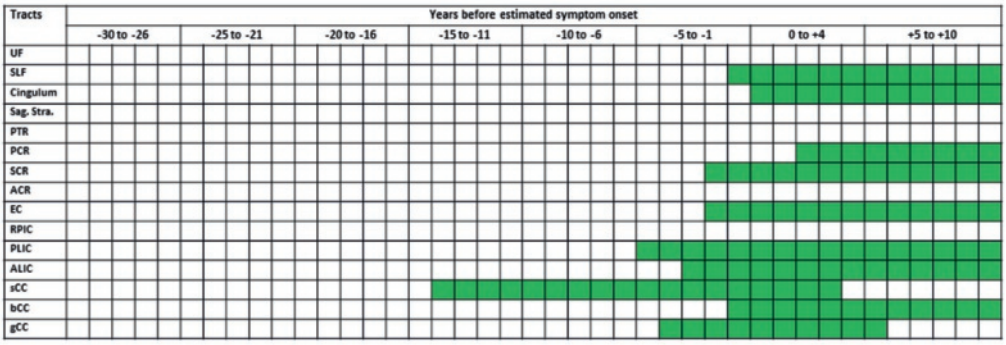
GRN – FA



GRN – MD



GRN – RD



GRN – AxD

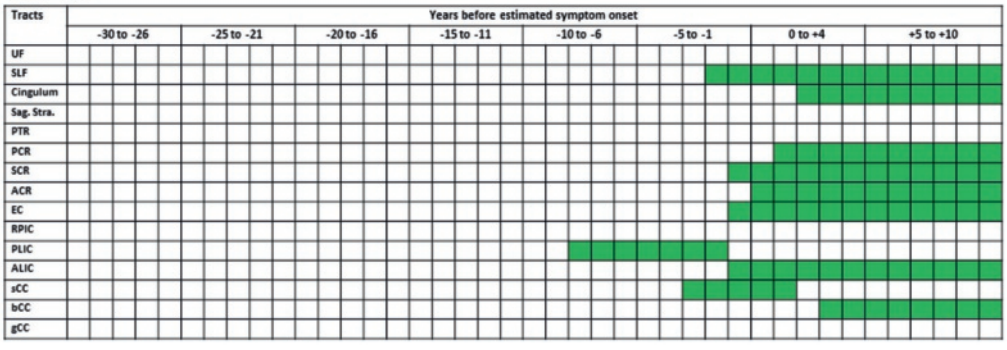


Figure 3.2.2B

Figure 3.2.2 (previous pages) | **Gene-specific differences in WM integrity between mutation carriers and non-carriers between minus 30 years before estimated onset until 10 years post-estimated onset.** Schematic overview of mean diffusion differences between non-carriers and *C9orf72* A), *MAPT* B) and *GRN* mutation carriers C) between minus 30 years before estimated symptom onset and plus 10 years after estimated onset (x-axis), each row represents a different WM tract (y-axis). Blue=where the difference between mutation carriers and non-carriers is negative; green=where the difference between mutation carriers and non-carriers is positive. *NB:* for FA, blue represents lower FA (=lower WM integrity) in mutation carriers than in non-carriers; for MD, RD and AxD, green represents higher parameters (=lower WM integrity) in mutation carriers than in non-carriers. *Abbreviations:* UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; Sag.Stra., sagittal stratum; PTR, posterior thalamic radiation; PCR, posterior corona radiata; SCR, superior corona radiata; ACR, anterior corona radiata; EC, external capsule; RPIC, retrolenticular part of the internal capsule; PLIC, posterior limb of the internal capsule; ALIC, anterior limb of the internal capsule; sCC, splenium of the corpus callosum; bCC, body of the corpus callosum; gCC, genu of the corpus callosum.

Figure 3.2.3 (next pages) | **Gene-specific differences in WM integrity in presymptomatic mutation carriers only.** Schematic overview of mean diffusion differences between non-carriers and *C9orf72* A), *MAPT* B) and *GRN* mutation carriers C) between minus 30 years before estimated symptom onset and plus 10 years after estimated onset (x-axis), each row represents a different WM tract (y-axis). Blue=where the difference between mutation carriers and non-carriers is negative; green=where the difference between mutation carriers and non-carriers is positive. *NB:* for FA, blue represents lower FA (=lower WM integrity) in mutation carriers than in non-carriers; for MD, RD and AxD, green represents higher parameters (=lower WM integrity) in mutation carriers than in non-carriers. *Abbreviations:* UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; Sag.Stra., sagittal stratum; PTR, posterior thalamic radiation; PCR, posterior corona radiata; SCR, superior corona radiata; ACR, anterior corona radiata; EC, external capsule; RPIC, retrolenticular part of the internal capsule; PLIC, posterior limb of the internal capsule; ALIC, anterior limb of the internal capsule; sCC, splenium of the corpus callosum; bCC, body of the corpus callosum; gCC, genu of the corpus callosum.

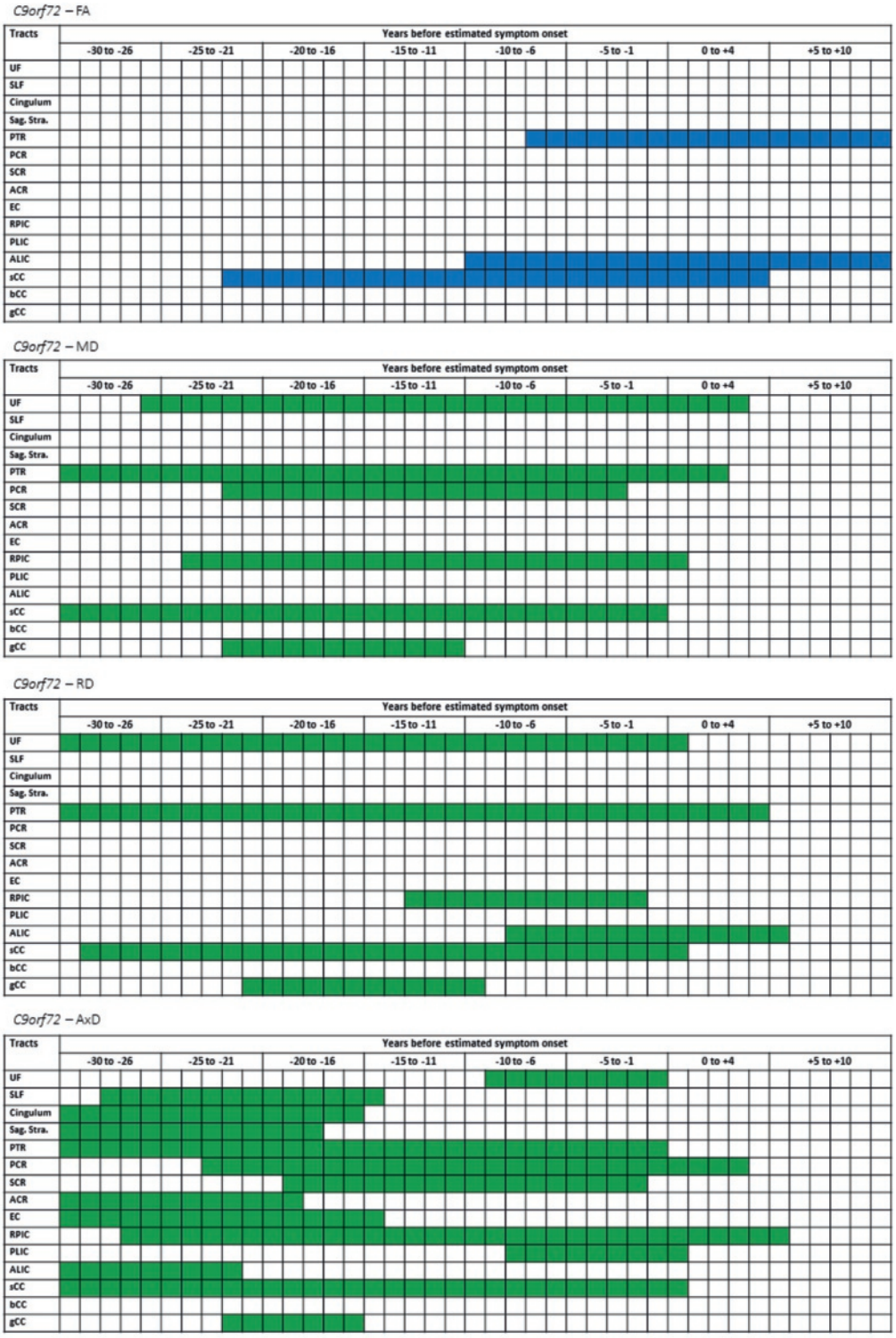
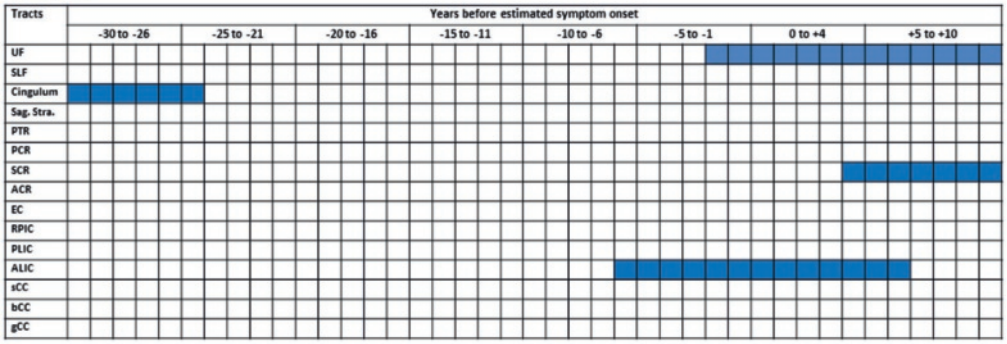
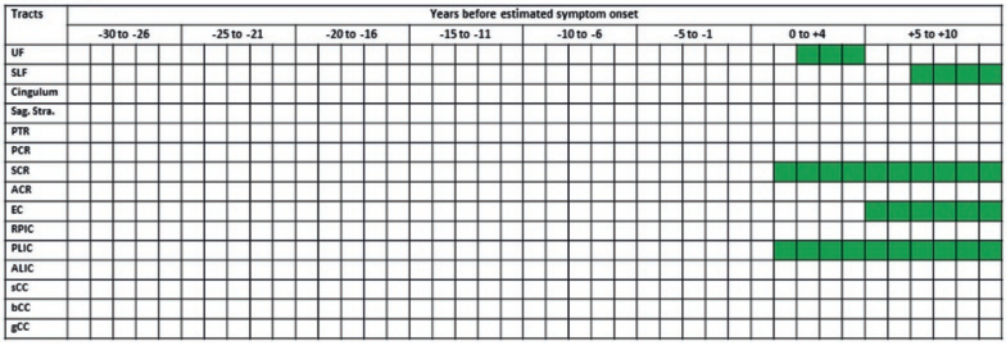

C9orf72 – FA
C9orf72 – MD
C9orf72 – RD
C9orf72 – AxD
Tracts
Years before estimated symptom onset
-30 to -26
-25 to -21
-20 to -16
-15 to -11
-10 to -6
-5 to -1
0 to +4
+5 to +10
UF
SLF
Cingulum
Sag. Stra.
PTR
PCR
SCR
ACR
EC
RPIC
PLIC
ALIC
sCC
bCC
gCC

Figure 3.2.3A

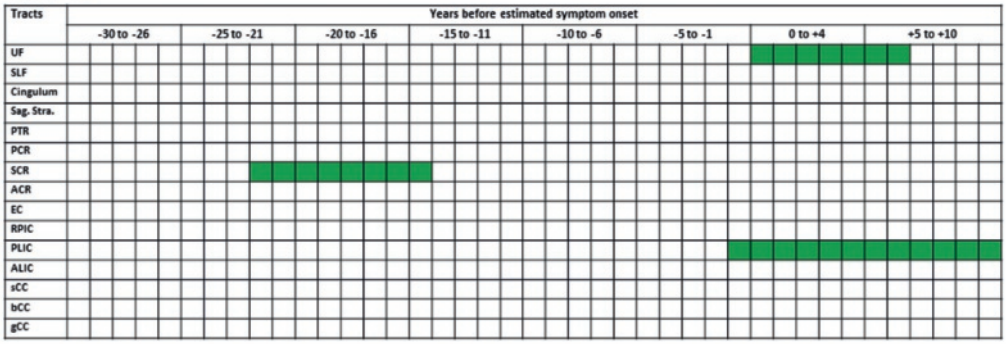
MAPT – FA



MAPT – MD



MAPT – RD



MAPT – AxD

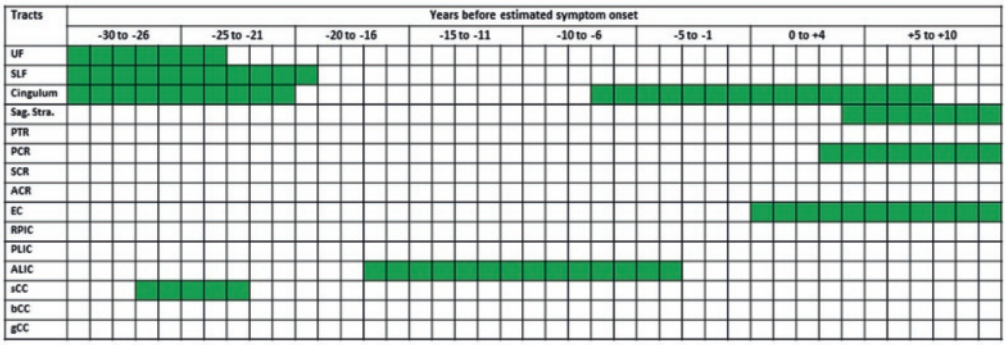
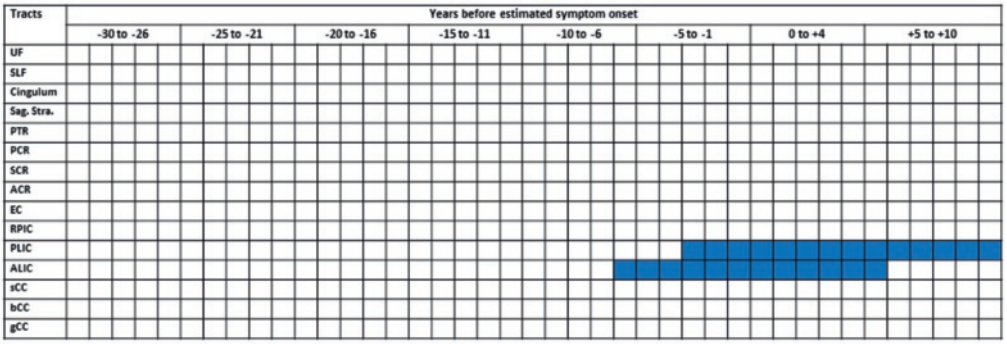
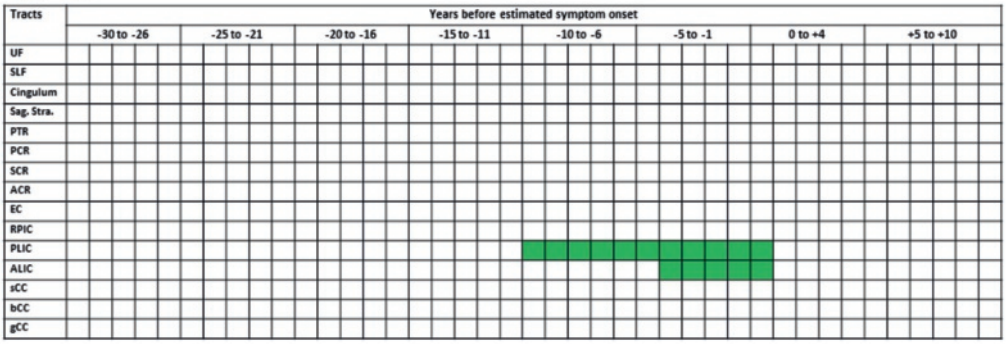


Figure 3.2.3B

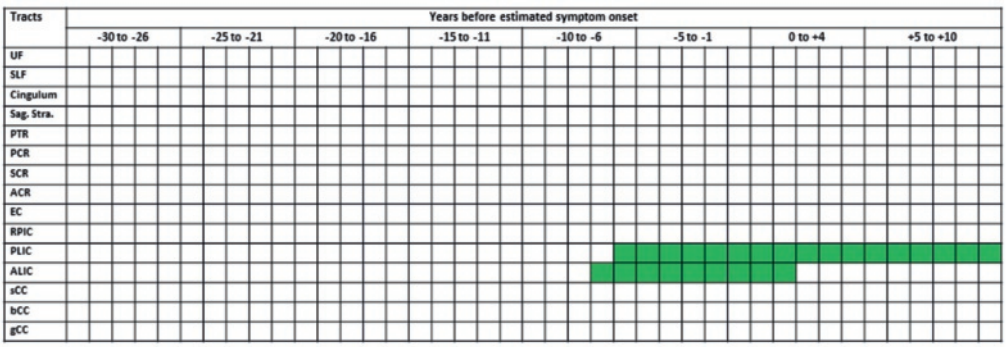
GRN – FA



GRN – MD



GRN – RD



GRN – AxD

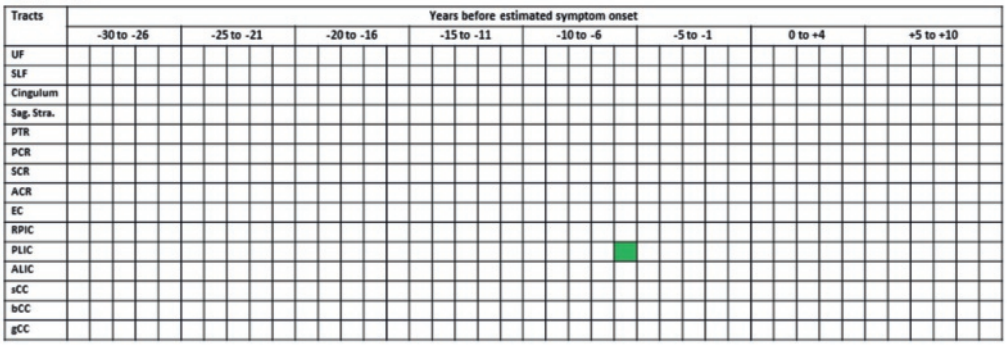


Figure 3.2.3C

We additionally investigated left-right differences between *GRN* mutation carriers and non-carriers. In most tracts significant left-right differences were found between groups in one or more diffusion parameters (Table 3.2.5). The most consistent results were found in the UF, EC, RPIC and ALIC. Asymmetry in the UF was mostly present in the early presymptomatic stage (-30 to +1 EYO), while the EC, RPIC and ALIC demonstrated asymmetry across the entire EYO range for different diffusion parameters (Figure 3.2.4). Interestingly, the 4 tracts demonstrated different patterns over time (Figure 3.2.4). The UF (Figure 3.2.4A) showed less asymmetry with disease progression, while a sharp post-onset increase was seen for the ALIC (Figure 3.2.4D). In the EC a U-shape pattern was visible, with first a decrease in asymmetry in the early presymptomatic stage, followed by an increase from around -5 EYO (Figure 3.2.4B). The RPIC demonstrated an inverse U-shape, with first more asymmetry in the early presymptomatic stage, followed by a decrease from around -5 EYO (Figure 3.2.4C).

Sensitivity analysis

The number of outliers that were excluded for the sensitivity analysis depended on the tract and DTI parameter, with a maximum of five outliers. Findings were very similar once these outliers were excluded. For the *C9orf72* mutation carriers significant differences with non-carriers were apparent in all WM tracts and significant differences remained apparent up to 30 years before estimated onset in the same WM tracts as were identified previously. In *MAPT* mutation carriers there remained differences in the WM tracts that were previously identified and the same pattern remained with early involvement of the UF. For *GRN* mutation carriers consistent differences were still detected in the same WM tracts with the earliest differences seen in the ALIC and PLIC.

Table 3.2.5 | Left-right asymmetry *p*-values for *GRN* mutation carriers vs. non-carriers.

	FA	MD	RD	DA
UF	**0.028**	**0.016**	**0.028**	0.186
SLF	0.656	0.294	0.656	**0.009**
Cingulum	**0.004**	0.689	**0.004**	**0.045**
Sagittal stratum	0.013	0.018	0.013	0.007
PTR	0.747	0.174	0.747	0.948
PCR	0.253	**0.004**	0.253	0.115
SCR	0.948	0.587	0.948	0.470
ACR	**0.049**	0.112	**0.049**	0.080
EC	0.135	**0.011**	0.135	**0.029**
RPIC	0.499	0.075	0.499	**<0.001**
PLIC	0.154	**0.001**	0.154	0.049
ALIC	**0.003**	**0.005**	**0.003**	0.440

Values indicate: p-values for *GRN* mutation carriers vs. non-carriers. *Abbreviations: GRN*, progranulin; UF, uncinate fasciculus; SLF, superior longitudinal fasciculus; PTR, posterior thalamic radiation; PCR, posterior corona radiata; SCR, superior corona radiata; ACR, anterior corona radiata; EC, external capsule; RPIC, retrolenticular part of the internal capsule; PLIC, posterior limb of the internal capsule; ALIC, anterior limb of the internal capsule.

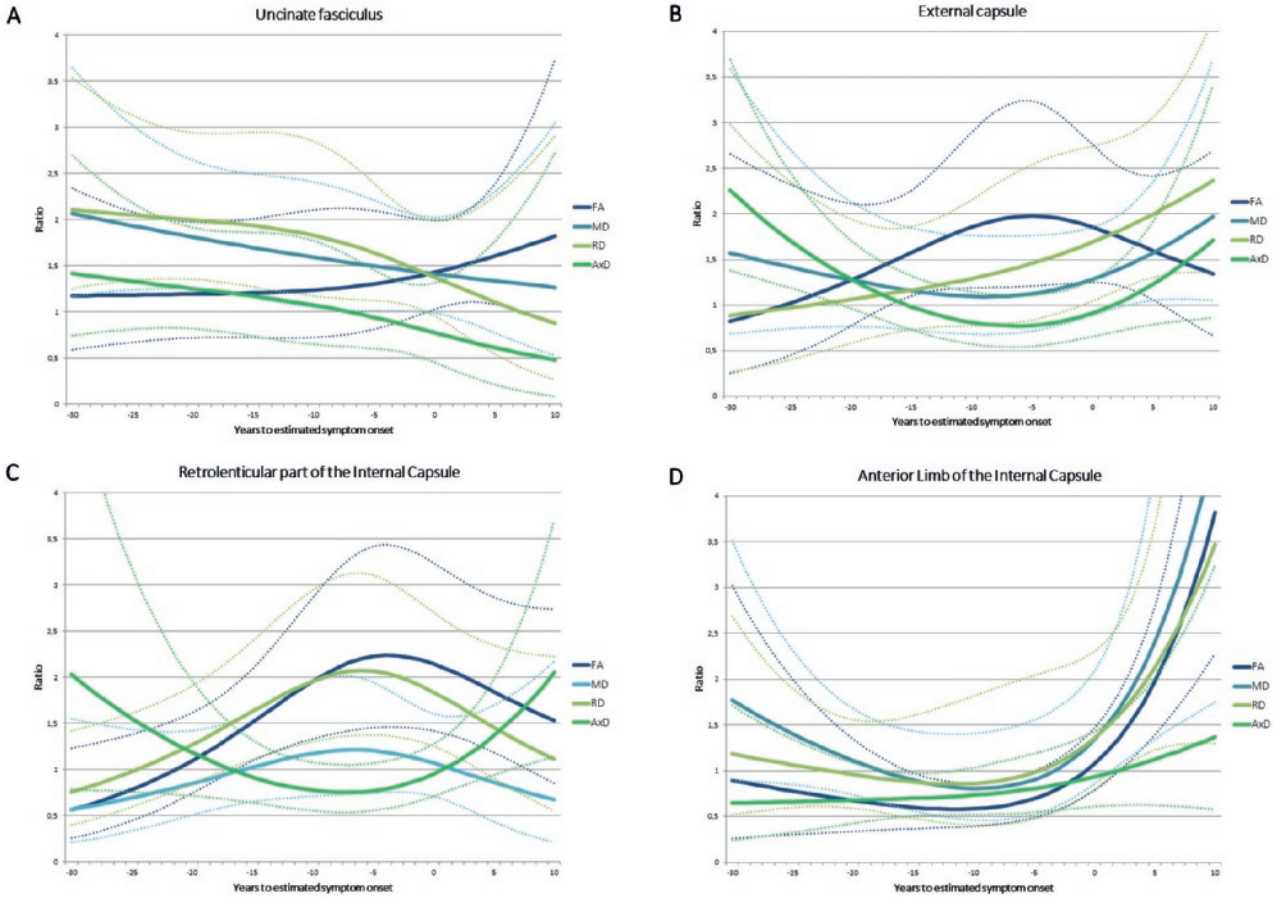


Figure 3.2.4 | **Ratio values across estimated years to symptom onset in *GRN* mutation carriers vs. non-carriers.** [§] The x-axis represents the years to estimated symptom onset (-30 to +10), the y-axis represents the ratio asymmetry in *GRN* mutation carriers vs. non-carriers. A value higher than 1 signifies more asymmetry in mutation carriers (e.g. ratio of 1.10 means 10% more asymmetry in mutation carriers than non-carriers). Ratios are depicted for A) uncinate fasciculus (UF), B) external capsule (EC), C) retrolenticular part of the internal capsule (RPIC), and D) anterior limb of the internal capsule (ALIC). *Abbreviations:* fractional anisotropy (FA; in dark blue), mean diffusivity (MD; in light blue), radial diffusivity (RD; in light green), and axial diffusivity (AxD; in dark green).

Discussion

This study describes WM integrity changes by means of DTI in mutation carriers and non-carriers from families with autosomal dominant FTD due to mutations in *C9orf72*, *MAPT* and *GRN,* within the GENFI consortium. Early WM involvement was found in mutation carriers, with specific genetic patterns for the *C9orf72*, *MAPT* and *GRN* mutations. Our study suggests spreading WM integrity loss towards symptom onset, highlighting the value of DTI as disease tracking and staging biomarker in familial FTD.

The pattern of WM integrity changes in the early presymptomatic stage shows large resemblance to the regions known to be affected in both familial [7,12,15-16] and sporadic [36-40] symptomatic FTD. Furthermore, although the cohort was somewhat different, the damage to the WM seems to be earlier and more widespread than the GM volume loss found earlier in GENFI [6], a finding consistent with previous work in presymptomatic familial [17-18] and sporadic FTD [36-40]. More WM tracts appear to be involved in the present study compared to previous studies of presymptomatic familial FTD [17-21]. An explanation for this more extensive involvement may be sought in our larger sample size (more power to detect small differences, and covering a broader presymptomatic period) and the use of all four diffusion parameters, compared to FA only in previous studies. The additional three diffusivity parameters appeared to be more sensitive than FA, and may provide more accurate measures of the effect and extent of the WM integrity changes in the presymptomatic phase.

The most interesting findings are the gene-specific 'fingerprints' of WM integrity loss in *C9orf72*, *MAPT* and *GRN* mutation carriers. Restricting our analyses to presymptomatic mutation carriers confirmed these findings. In *C9orf72*, specifically the more posteriorly located tracts, such as the PTR, PCR and sCC, are affected. The PTR demonstrates the earliest changes already 30 years before estimated onset – suggesting that damage might be present even before that. This is in line with earlier findings in the GENFI cohort showing GM volume loss of the thalamus and posterior cortical areas from 25 years before estimated onset [6]. The similar pattern and timing of WM pathology seems consistent with the longstanding and slowly progressive symptomatic changes often seen in this mutation [41-42], and coherent with the hypothesis of a developmental origin in *C9orf72*-associated FTD [6]. In both *MAPT* and *GRN*, WM changes have been consistently found later than in *C9orf72*. The observation of presymptomatic changes in the UF and cingulum in *MAPT* mutation carriers is consistent with smaller series of presymptomatic [18] and symptomatic carriers [43-44], and congruent with tracts affected in bvFTD, the most common clinical phenotype of *MAPT* [45]. We could not confirm greater WM damage in the SLF in symptomatic cases with underlying FTD-tau than FTD-TDP (e.g. *GRN* or *C9orf72*) found in a previous study [14], suggesting that this difference might occur later in the disease process or resembles a phenotypic rather than genotypic origin [13-14]. We could not explain the remarkable finding of DTI changes into the opposite direction in the SLF, SCR, cingulum between -30 and -16 years before EYO, and this has to be investigated in larger samples. Recent literature does provide evidence of WM involvement in *GRN*-related FTD [46-47], though interestingly in our *GRN* mutation carriers few tracts were affected, and integrity loss was generally closer to estimated symptom onset than early presymptomatic. Previous studies demonstrated lower FA in the UF of presymptomatic *GRN* mutation carriers [17-18], and we did

find lower FA in the presymptomatic period, but no differences in the symptomatic stage or in other diffusion parameters. One potential explanation for this discrepancy could be the large variation in age at onset within *GRN* families [48], making the estimated age at onset less reliable than in the other mutations. Another point for consideration here is the potential masking of effects by taking the mean value per WM tract, given the asymmetric neuroimaging phenotype of *GRN* [49].

Left-right asymmetry was present in most WM tracts of *GRN* mutation carriers, with the most consistent asymmetry being found in the UF, EC, RPIC and ALIC. These results not only demonstrate that some tracts are more vulnerable to disproportional WM integrity loss than others (e.g. the corona radiata does not show asymmetry), but also that the development of asymmetry has a different timing and pattern in various WM tracts. In line with previous neuroimaging research, showing more asymmetry with disease progression in symptomatic *GRN* mutation carriers [50], we found a sharp increase in asymmetry after estimated symptom onset in the ALIC, whereas the inverse was seen in the UF. Rohrer et al. [6] found greater asymmetry in presymptomatic *GRN* mutation carriers than non-carriers starting 5 years before estimated symptom onset. Also in our study the -5 EYO seems to be a critical time point in the development of asymmetry, with the EC demonstrating more asymmetry and the RPIC showing less asymmetry after -5 EYO. More research using longitudinal data is needed in order to investigate the development of asymmetry over time in more detail.

The development of sensitive biomarkers for diagnosis, e.g. differentiation between clinical, genetic or pathological subtypes, and staging purposes is one of the main challenges in presymptomatic FTD, as future therapeutic interventions ideally start in the unique time-window of minimal pathological damage. Although the identification of "upstream" biomarkers is essential for the development of therapeutic trials, the connectivity correlates of FTD molecular pathology were thus far unknown for the presymptomatic stage [13]. Our results demonstrate the potential application of DTI as a future diagnostic and staging biomarker – providing evidence of very early presymptomatic alterations as well as consistent WM integrity loss when moving from the late presymptomatic into the early symptomatic stage. Also, mutation-specific profiles for *C9orf72*, *MAPT* and *GRN* suggest the potential of DTI in pathology-specific clinical trials. In contrast to FA reductions as a measure of WM integrity loss in previous studies [51], diffusivity measures (MD, RD, AxD) reflected early WM alterations much more sensitively. This is consistent with a previous study into the clinical subtypes of FTD [52], supporting the notion that FA does not capture the full extent of WM pathology, and the four metrics signify different underlying processes with disease progression. As a next step, post-mortem studies are needed to increase our understanding of the histopathological representation of WM changes in relationship to markers of demyelination, neuroinflammation, neuronal loss and underlying pathology. Furthermore, to use DTI in clinical practice, more research is needed on the translation of our group-based results to the individual patient level. Larger studies are also needed to differentiate pathological subtypes in individual patients [53]. Lastly, as neurofilament light chain is thought to be a sensitive marker of axonal damage, and therefore could be associated with DTI [54], it would be interesting to investigate this biomarker further in this cohort.

Key strengths of our study constitute the large sample of FTD mutation carriers and non-carriers. Our study describes the presymptomatic to early symptomatic stage of familial FTD in a long time trajectory of 40 years, with only a single symptomatic mutation carrier (*C9orf72*) before their estimated onset age. Therefore the influence of this symptomatic mutation carrier is most likely very minimal. With respect to pre-processing, registration was improved by computing the image similarity on the basis of full tensor images rather than scalar features, in which the algorithm incorporates local fibre orientations as features driving the alignment of individual WM tracts. The use of only 3T images, extensive data control after each pre-processing step and our sensitivity analysis further ascertained data homogeneity. In the pilot phase of GENFI, more variable DTI acquisition parameters and protocols (e.g. use of field and phase maps) were used, introducing a source of bias to the data. Now in the second phase of GENFI, scan protocols have been fully harmonized, so that from 2015 onwards we are building on a much more consistent dataset. Exploring the involvement of corticospinal tracts, as recent research demonstrated early damage in *C9orf72*-associated ALS [19], bvFTD and PPA [52], would be a very informative next step. Other future directions include the investigation of DTI as a longitudinal neuroimaging biomarker and its potential role in multimodal and composite scores in presymptomatic FTD.

Our study provides evidence of global and gene-specific WM integrity loss as an early pathological feature of presymptomatic familial FTD, making DTI a promising diagnostic and staging neuroimaging biomarker that in the future could be used in upcoming clinical trials for familial FTD.

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Chapter 4

Neuropsychological biomarkers

4.1

Presymptomatic cognitive decline in familial frontotemporal dementia: a longitudinal study

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Abstract

In this prospective cohort study we performed a two-year follow-up study with neuropsychological assessment in the presymptomatic phase of familial FTD due to *GRN* and *MAPT* mutations to explore the prognostic value of neuropsychological assessment in the earliest FTD disease stages. Healthy at-risk first-degree relatives of FTD patients with a *MAPT* (n=13) or *GRN* mutation (n=30) and healthy controls (n=39) underwent neuropsychological assessment at baseline and two-year follow-up. We investigated baseline and longitudinal differences, as well as relationship with age and estimated years before symptom onset. At baseline, *GRN* mutation carriers showed lower scores on mental processing speed than healthy controls (p=0.043). Two years later, *MAPT* mutation carriers showed a steeper decline than *GRN* mutation carriers on social cognition (p=0.002). Higher age was related with cognitive decline in visuoconstruction (p=0.005) and social cognition (p=0.026) in *MAPT*. Memory significantly declined from 8 to 6 years before estimated onset in respectively *MAPT* and *GRN* mutation carriers, and language and social cognition declined only in *MAPT* mutation carriers from respectively 7 to 5 years before estimated onset (p<0.05). Using longitudinal neuropsychological assessment, we detected gene-specific neuropsychological patterns of decline in e.g. social cognition, memory and visuoconstruction. Our results confirm the prognostic value of neuropsychological assessment as potential clinical biomarker in the presymptomatic phase of familial FTD.

Introduction

Frontotemporal dementia (FTD) is a young onset type of dementia, with a clinically heterogeneous presentation of either behavioural disturbances (behavioural-variant, bvFTD) and/or language deterioration [1]. The neuropsychological profile is characterized by deficits in language, executive function and social cognition, while memory and visuoconstruction are relatively spared [2-4]. As FTD has an autosomal dominant inheritance pattern in up to 40% (mutations in *microtubule-associated protein tau* (*MAPT*), *progranulin* (*GRN*) and Chromosome 9 open reading frame 72 (*C9orf72*) genes [5] we can define mutation carriers in the presymptomatic phase [6]. Studying this phase by means of longitudinal neuropsychological assessment could enable us to recognize cognitive patterns towards disease onset, which may serve as sensitive biomarkers for symptomatic onset in clinical practice and upcoming therapeutic trials.

Neuropsychological assessments in the presymptomatic stage of familial FTD are scarcely reported [7], with most studies being case [8-10] or small family-based studies [7,11-16]. A large multicenter cross-sectional study of presymptomatic FTD [17] demonstrated the earliest neuropsychometric changes in mutation carriers around five years before expected symptom onset, showing naming and executive function decline.

In the present study we explored the prognostic value of neuropsychological assessment in the presymptomatic phase of familial FTD due to *GRN* and *MAPT* mutations [18]. We performed a two-year follow-up study, in which we investigated baseline and longitudinal differences, and the relationship with age (i.e. approaching symptom onset). By means of an exploratory analysis we estimated how many years before symptom onset mutation carriers start to cognitively decline compared to controls.

Methods

Participants

We recruited 84 healthy 50 percent at-risk family members from Dutch pathologically confirmed genetic FTD families (either *GRN* or *MAPT*) for our prospective cohort study between December 2009 and March 2011, as previously described [18]. As the *C9orf72* repeat expansion was not yet discovered at the start of our study, we did not include families with this mutation in this paper. All participants underwent standardized neuropsychological assessment at baseline and two-year follow-up. The majority of the participants (>75%) came to the study visits with a knowledgeable informant (e.g. siblings, spouses); they were interviewed on possible cognitive and/or behavioural changes. We defined participants as presymptomatic when established criteria for FTD were not fulfilled [2], i.e. no cognitive disorders (≥2 standard deviations (SD) below normative data mean) on neuropsychological testing, no progressive behaviour deterioration or functional decline. We excluded participants with a history of other neurological or severe psychiatric illness. We excluded two non-mutation carriers from two *GRN* families, as they had cognitive disorders (≥2 SD below mean) on multiple domains. We defined the expected

symptom onset for each participant as the mean onset age per family. We then calculated years from estimated symptom onset by subtracting the estimated onset age from the actual age per participant.

Standard Protocol Approvals, Registrations, and Patient Consents

We obtained written informed consent from all participants. The study has been approved by the Medical and Ethical Review Committee of the Erasmus Medical Center. All clinical investigators and participants were blind for the participants' genetic status.

DNA sequencing

We performed venapunction for DNA sequencing at baseline. We sequenced DNA of both strands of exon 2-13 of *GRN* (NM_002087.2) and strands of exons 2 and 11-15 of *MAPT* (NM_005910.3). We assigned participants either to the mutation carrier (n=43; 13 *MAPT*, 30 *GRN*) or healthy control group (n=39; 9 *MAPT*, 30 *GRN*) [14]. See Appendix 4.1.1 for specific *MAPT* and *GRN* mutations, sample size, carriers' age and mean family onset per mutation.

Neuropsychological assessment

We selected neuropsychological tests to assess global cognitive functioning, as well as six cognitive domains: 1) language, 2) attention & mental processing speed, 3) executive functioning (EF), 4) social cognition, 5) memory, 6) visuoconstruction. We assessed global cognitive functioning by means of Mini-Mental State Examination (MMSE) [19]. We assessed language by means of 60-item Boston Naming Test (BNT) [20], verbal Semantic Association Test (SAT) [21], categorical (animals) and letter fluency [22] and ScreeLing phonology [23]. We rated attention and mental processing speed with Trailmaking Test (TMT) part A [24], Stroop colour-word test card I and II [25] and Letter Digit Substitution Test (LDST) [26]. We assessed EF using Trailmaking Test (TMT) part B [24], Stroop colour-word test card III [25] and modified Wisconsin Card Sorting Test (WCST) concepts [27]. We evaluated memory using the Dutch Rey Auditory Verbal Learning Test (RAVLT) [28], short Visual Association Test (VAT) [29], and WAIS-III digit span [30]. Clock drawing [31] and WAIS-III block design [30] measured visuoconstruction. We evaluated social cognition by means of Happé cartoons (Theory of Mind; ToM, non-Theory of Mind; non-ToM) [32] and Ekman Faces [33]. We rated depressive symptoms using Beck's Depression Inventory (BDI) [34]. At follow-up we assessed neuropsychiatric symptoms using Neuropsychiatric Inventory Questionnaire (NPI) [35] and Cambridge Behavioural Inventory – Revised (CBI-R) [36]. Alternate test forms were used at follow-up, when applicable. An experienced neuropsychologist administered and scored all tests.

Statistical analysis

Statistical analyses were performed using SPSS Statistics 21.0 (SPSS Inc., Chicago, IL, USA). We set the significance level at $p<0.05$ (two-tailed) across all comparisons, uncorrected for multiple comparisons due to the explorative nature of our study. For ease of interpretation, we standardized all raw neuropsychological test scores by converting them into *z*-scores (i.e. individual test score minus the mean of controls, divided by the SD of controls). We calculated composite z-scores for the respective six cognitive domains by averaging the z-scores of the individual tests per time point. We considered the composite z-score missing if more than half of the test scores in that domain were missing. We

compared demographic data, cross-sectional baseline and follow-up z-scores between groups by means of one-way ANCOVAs. We analysed differences in gender between *GRN* mutation carriers, *MAPT* mutation carriers and controls using Pearson's chi-square tests. We performed longitudinal comparisons by means of repeated measures ANCOVA, with z-scores at baseline and follow-up as within-subject variable and carriership and gene as between-subject variables. We used age, gender and education level as covariates in both cross-sectional and longitudinal comparisons. We calculated correlations per gene in order to relate cognitive decline per domain or individual test performance (Δ baseline minus follow-up z-score) with age at baseline – a positive correlation therefore represented cognitive decline with higher age. We used multilevel linear regression modelling to calculate how many years before estimated symptom onset domain and individual test performance deteriorated significantly between baseline and follow-up. We excluded the two converters from this model. We postulated separate models per gene and each outcome. There were two levels in the models: the participants constituted the upper level, their repeated measures the lower level. We entered time (Δ baseline minus follow-up), mutation status, estimated years to symptom onset and (first and second order) interactions as covariates. We used contrasts at various levels of the years before estimated onset for the time*mutation status*years to onset interaction to determine when the time difference became significant.

Results

Demographics

Demographic data for the mutation carriers and controls are shown in Table 4.1.1. *MAPT* mutation carriers were younger than *GRN* mutation carriers (p=0.024). The mean onset age of families carrying *GRN* mutations was higher than those with *MAPT* mutations (p<0.001). There were no significant differences in follow-up duration or behavioural measures between mutation carriers and controls.

Converters

Two presymptomatic mutation carriers (1 *MAPT* and 1 *GRN*) converted to symptomatic bvFTD between baseline and follow-up, according to follow-up neuropsychological assessment and MRI scanning of the brain. Together with an in-depth interview with knowledgeable informants regarding functional and behavioural decline and confirmation of the presence of the pathogenic mutation, formal diagnostic criteria for bvFTD with definite FTLD pathology were met [2]. The *MAPT* (P301L) converter presented with disinhibition and the *GRN* (S82fs) converter with apathy and loss of initiative. The *MAPT* converter declined significantly on tests for divided attention, emotion recognition (all ≥2 SD below group mean), executive function, ToM, and fluency (all ≥1 SD). The *GRN* converter showed a significant decline concerning tests for divided attention, executive function, emotion recognition (all ≥2 SD), fluency and perceptual organization (all ≥1 SD) (Appendix 4.1.2 and 4.1.3).

Table 4.1.1 | Demographic data

	MAPT carriers (n=13)	*GRN* carriers (n=30)	controls (n=39)	*p*-value
Age (years) at baseline	42.8 ± 10.8	52.9 ± 8.5	49.6 ± 12.3	**0.027**
Gender, female (%)	5 (38.5)	19 (6.3)	22 (56.4)	0.488
Education (Verhage[1])	5.4 ± 1.2	5.7 ± 0.9	5.2 ± 1.0	0.113
Onset age family (years)	49.8 ± 4.7	61.4 ± 2.5	59.0 ± 5.8	**<0.001**
Years from estimated onset at baseline	7.0 ± 9.6	8.5 ± 8.2	N/A	0.824
Duration between assessments (months) [range]	30.3 ± 4.3 [24-40]	28.3 ± 2.2 [24-33]	28.5 ± 3.0 [21-39]	0.113
MMSE				
baseline	29.5 ± 0.5	29.0 ± 1.6	29.1 ± 1.3	0.449
follow-up	28.6 ± 2.2	29.1 ± 1.1	29.3 ± 1.3	0.398
BDI				
baseline	3.1 ± 5.3	3.4 ± 3.9	3.7 ± 3.9	0.703
follow-up	3.2 ± 4.3	3.0 ± 4.0	4.1 ± 4.5	0.814
NPI-Q (follow-up*)	0.3 ± 0.7	1.5 ± 5.7	0.5 ± 1.1	0.512
CBI-R (follow-up*)	3.0 ± 3.6	3.1 ± 9.1	1.8 ± 2.9	0.695

Values indicate: mean ± standard deviation, number (percentage). *Abbreviations: MAPT, microtubule-associated protein tau*; *GRN, progranulin*; controls, healthy control; MMSE, Mini-Mental State Examination; BDI, Beck Depression Inventory; NPI-Q, Neuropsychiatric Inventory Questionnaire; CBI-R, Cambridge Behavioural Inventory-Revised. [1]Dutch educational system categorized into levels from 1=less than 6 years of primary education to 7=academic schooling [25]. *data only available on follow-up visit; data is available in 10/13 (76.9%) *MAPT* mutation carriers, 26/30 (86.7%) *GRN* mutation carriers and 32/39 (82.1%) controls.

Baseline neuropsychological assessment

Table 4.1.2 shows the baseline and follow-up z-scores of neuropsychological test performance in *GRN* and *MAPT* mutation carriers – controls have been left out as they had means of zero and SD of one by definition. None of the participants performed at disorder level at baseline or follow-up (i.e. ≥2 SD below normative data mean). *GRN* mutation carriers showed lower scores on LDST than controls. There were no significant differences between *MAPT* mutation carriers and controls, and between *GRN* and *MAPT* mutation carriers, regarding any of the neuropsychological tests. See Appendix 4.1.4 and 4.1.5 for baseline neuropsychological test performance per specific *MAPT* and *GRN* mutation.

Longitudinal neuropsychological assessment

From baseline to follow-up, *MAPT* mutation carriers significantly worsened with respect to LDST, categorical fluency and Happé non-ToM compared to controls (Table 4.1.2), whereas no significant deterioration over time was found in *GRN* mutation carriers compared to controls. *MAPT* mutation carriers showed a steeper decline in social cognition than *GRN* mutation carriers (domain score p=0.046; Happé non-Tom p=0.002). Furthermore, *MAPT* mutation carriers worsened regarding categorical fluency in comparison to *GRN* mutation carriers (p=0.011). By excluding the converter with the *MAPT* mutation, Happé non-ToM remained significant (p=0.039 compared to controls and p=0.032 compared to *GRN* mutation carriers), whereas LDST and categorical fluency were no longer significant (respectively

p=0.082 and *p*=0.098). See Appendix 4.1.4 and 4.1.5 for follow-up neuropsychological test performance per specific *MAPT* and *GRN* mutation.

Table 4.1.2 | Neuropsychological baseline and follow-up data (z-scores) of *MAPT* and *GRN* carriers

Domain (test)	*MAPT* mutation carriers (n=13)			*GRN* mutation carriers (n=30)		
	baseline	follow-up	*p*-value	baseline	follow-up	*p*-value
Language	0.30 ± 0.65	-0.01 ± 0.62	**0.027**	0.12 ± 0.74	0.08 ± 0.52	0.957
BNT	-0.03 ± 1.01	-0.48 ± 1.76	0.105	0.41 ± 0.79	0.31 ± 0.67	0.617
SAT verbal	0.13 ± 1.09	0.13 ± 1.49	0.815	-0.31 ± 1.45	-0.32 ± 1.03	0.799
ScreeLing phonology	0.43 ± 0.37	0.47 ± 0.00	0.844	0.26 ± 0.56	0.16 ± 0.55	0.681
Categorical fluency (animals)	0.52 ± 1.28	-0.05 ± 0.86	**0.038**	-0.20 ± 1.11	-0.05 ± 0.83	0.357
Letter fluency	0.26 ± 1.44	-0.09 ± 1.13	0.108	0.62 ± 1.22	0.31 ± 1.13	0.217
Attention & mental speed	-0.30 ± 0.46	-0.41 ± 0.42	0.260	-0.05 ± 0.88	-0.06 ± 0.84	0.804
TMT A	-0.31 ± 0.67	-0.33 ± 0.68	0.962	0.00 ± 0.81	-0.09 ± 0.94	0.224
Stroop card I	-0.61 ± 1.08	-0.63 ± 0.71	0.918	0.22 ± 1.06	0.18 ± 1.01	0.791
Stroop card II	-0.33 ± 0.80	-0.38 ± 0.69	0.891	-0.19 ± 1.25	-0.13 ± 1.19	0.102
LDST	0.06 ± 0.65	-0.28 ± 0.79	**0.028**	-0.24 ± 1.07	-0.22 ± 0.85	0.674
Executive function	-0.13 ± 0.40	-0.06 ± 0.47	0.385	0.08 ± 0.82	0.10 ± 0.74	0.348
TMT B	-0.29 ±0.95	0.04 ± 1.19	0.098	-0.18 ± 1.46	0.00 ± 1.06	0.942
Stroop card III	-0.47 ± 0.64	-0.19 ± 1.03	0.117	-0.19 ± 1.18	-0.03 ± 1.02	0.583
WCST concepts	0.06 ± 1.32	0.02 ± 0.98	0.938	0.36 ± 0.65	0.05 ± 0.74	0.408
WAIS similarities	0.18 ± 0.90	-0.09 ± 1.14	0.289	0.32 ± 1.03	0.37 ± 0.78	0.631
Social cognition	0.25 ± 0.71	-0.06 ± 0.96	0.225	0.32 ± 0.70	0.24 ± 0.86	0.406
Ekman faces	0.17 ± 0.86	-0.05 ± 1.24	0.883	0.29 ± 0.90	0.30 ± 0.80	0.922
Happé TOM	0.26 ± 1.05	0.13 ± 1.01	0.643	0.27 ± 0.95	0.26 ± 1.12	0.467
Happé non-TOM	0.32 ± 0.87	-0.33 ± 1.12	0.013	0.41 ± 0.97	0.15 ± 1.02	0.373
Memory	0.06 ± 1.06	0.15 ± 0.79	0.173	-0.18 ± 1.27	-0.07 ± 0.82	0.073
RAVLT – learning	0.38 ± 0.88	0.11 ± 1.29	0.222	0.34 ± 1.09	0.11 ± 1.08	0.085
RAVLT – recall	0.25 ± 1.17	0.05 ± 1.30	0.372	0.29 ± 1.05	0.20 ± 1.18	0.550
RAVLT – recognition	0.11 ± 0.98	-0.16 ± 0.28	0.533	0.26 ± 0.56	-0.12 ± 0.24	0.260
VAT	-0.71 ± 2.73	-1.43 ± 4.53	0.344	-0.51 ± 1.58	-0.65 ± 2.44	0.658
WAIS Digit Span	0.29 ± 1.11	0.51 ± 1.43	0.698	0.36 ± 1.21	0.12 ± 1.39	0.338
Visuoconstruction	-0.27 ± 0.65	-0.11 ± 0.77	0.761	-0.06 ± 0.99	-0.05 ± 0.79	0.557
WAIS Block Design	-0.41 ± 1.00	-0.19 ± 1.16	0.732	0.06 ± 1.16	-0.05 ± 1.09	0.391
Clock drawing	-0.28 ± 0.90	-0.03 ± 0.71	0.573	-0.16 ± 1.22	-0.05 ± 0.82	0.851

Values indicate: mean ± standard deviation. *P*-values constitute interaction terms of repeated measures ANCOVA (corrected for age, gender and education level). *Abbreviations: MAPT, microtubule-associated protein tau*; *GRN*, *progranulin*; BNT, Boston Naming Test; SAT, Semantic Association Test; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; TOM, theory of mind; non-TOM, non-theory of mind; RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test.

Cognitive decline in relationship to age

In *MAPT* mutation carriers, higher age was significantly correlated with cognitive decline in the domains visuoconstruction and social cognition, and on the following individual tests: RAVLT recall, clock drawing and Happé non-ToM (Table 4.1.3). In *GRN* mutation carriers, higher age related to decline in RAVLT recognition, WCST and Happé non-ToM (Table 4.1.3). By excluding the *MAPT* converter, the correlations regarding the visuoconstruction domain as well as all individual tests results remained significant. The social cognition domain was no longer significant (r=0.586, p=0.058). Excluding the *GRN* converter did not alter the significance of age correlations with domain and individual test scores. No relationship between age and cognitive decline was found in controls (Table 4.1.3).

Cognitive decline in relationship to years from estimated symptom onset

In *MAPT* mutation carriers, the domains language, social cognition and memory significantly started to decline (negative Δ) between assessments respectively from 7, 5 and 6 years before estimated onset (Figure 4.1.1A, D and E). Visuoconstruction improved between assessments in *MAPT* mutation carriers until 13 years before estimated onset, with a tendency towards decline with approaching estimated onset from then onwards (Figure 4.1.1F). With regards to individual tests, decline between assessments was found in RAVLT immediate and delayed recall (immediate recall from 3 years before estimated onset; delayed recall from 4 years before), Ekman faces (1 year before), BNT (from 3 years before) and categorical fluency (from 6 years before). Additionally, LDST declined between assessments in *MAPT* mutation carriers from 7 years before estimated onset. In *GRN* mutation carriers, the memory domain declined from 8 years before estimated onset (Figure 4.1.1E). With regards to individual tests, Happé non-ToM declined from 5 years before estimated onset.

Discussion

This study examined a large cohort of at-risk participants from *GRN* and *MAPT* families by means of longitudinal neuropsychological assessment. We demonstrated a significant decline over time in social cognition, and a relationship between higher age and decline in social cognition and memory in mutation carriers. Our exploratory model furthermore suggests cognitive decline in mutation carriers up to 8 years before estimated symptom onset. These data confirm the prognostic value of neuropsychological assessment as potential clinical biomarker in the presymptomatic phase of familial FTD.

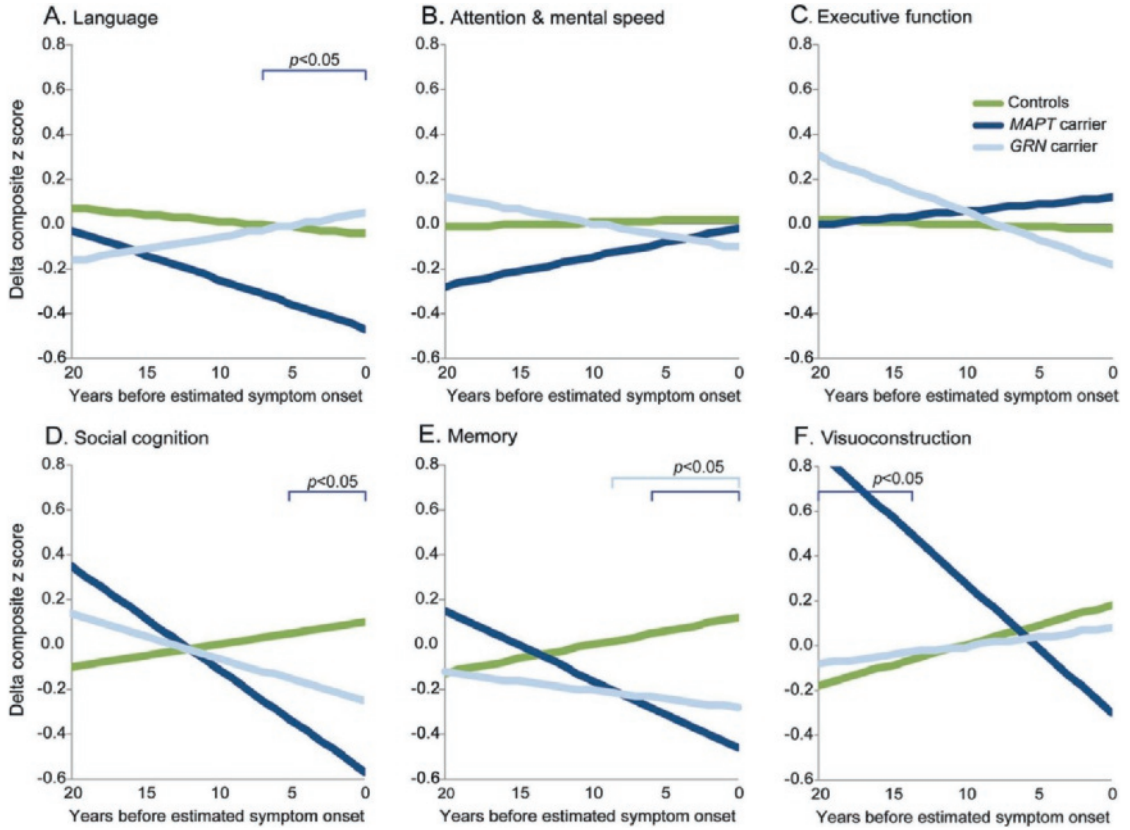

Figure 4.1.1 | **Cognitive decline in relationship to years from estimated symptom onset.** Multilevel linear regression model displaying how many years before estimated symptom onset composite domain scores decline significantly between baseline and follow-up assessments in *MAPT* mutation carriers (dark blue), *GRN* mutation carriers (light blue), and healthy controls (green). Models are displayed for each cognitive domain: A) language, B) attention and mental processing speed, C) executive function, D) social cognition, E) memory, and F) visuoconstruction. A negative delta represents a decline in performance; a positive delta represents better performance. Brackets with $p<0.05$ represent the years before estimated symptom onset in which there is a significant decline in mutation carriers compared to healthy controls. Abbreviation: *GRN*, progranulin; *MAPT*, microtubule-associated protein tau.

Table 4.1.3 | Correlations between age and cognitive decline in *MAPT* carriers, *GRN* carriers and HC

Domain (test)	*MAPT* mutation carriers		*GRN* mutation carriers		HC	
	correlation	*p*-value	correlation	*p*-value	correlation	*p*-value
Language	0.362	0.224	0.268	0.153	0.212	0.194
BNT	0.172	0.573	0.053	0.780	0.034	0.837
SAT verbal	0.043	0.888	0.219	0.246	0.053	0.748
ScreeLing phonology	0.208	0.496	0.201	0.287	0.020	0.906
Categorical fluency (animals)	0.551	0.051	0.121	0.525	0.196	0.232
Letter fluency	0.476	0.100	0.098	0.608	0.059	0.723
Attention & mental speed	0.448	0.124	0.205	0.277	0.010	0.953
TMT A	0.296	0.327	0.188	0.320	0.010	0.950
Stroop card I	0.206	0.500	0.083	0.661	0.093	0.573
Stroop card II	0.312	0.299	0.200	0.288	0.006	0.971
LDST	0.116	0.707	0.034	0.858	0.043	0.794
Executive function	0.144	0.640	0.260	0.165	0.040	0.808
TMT B	0.221	0.468	0.185	0.327	0.053	0.750
Stroop card III	0.278	0.358	0.048	0.802	0.146	0.377
WCST concepts	0.031	0.920	0.418	**0.022**	0.013	0.936
WAIS similarities	0.402	0.173	0.012	0.950	0.054	0.742
Social cognition	0.635	**0.026**	0.237	0.206	0.128	0.438
Ekman faces	0.571	0.052	0.028	0.883	0.264	0.105
Happé TOM	0.170	0.578	0.149	0.431	0.052	0.752
Happé non-TOM	0.645	**0.017**	0.399	**0.029**	0.058	0.726
Memory	0.459	0.115	0.123	0.518	0.132	0.423
RAVLT – learning	0.485	0.093	0.099	0.603	0.038	0.817
RAVLT – recall	0.610	0.027	0.029	0.879	0.042	0.798
RAVLT – recognition	0.130	0.672	0.438	**0.015**	0.051	0.757
VAT	0.038	0.901	0.140	0.461	0.186	0.257
WAIS Digit Span	0.485	0.093	0.225	0.232	0.080	0.627
Visuoconstruction	0.780	0.005	0.092	0.635	0.232	0.155
WAIS Block Design	0.513	0.107	0.077	0.690	0.201	0.220
Clock drawing	0.734	0.004	0.156	0.410	0.173	0.292

Abbreviations: MAPT, microtubule-associated protein tau; *GRN, progranulin*; HC, healthy control; BNT, Boston Naming Test; SAT, Semantic Association Test; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; TOM, theory of mind; non-TOM, non-theory of mind; RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test.

Mutation carriers demonstrated gene-specific cognitive decline, with lower language and mental processing speed scores in *MAPT* mutation carriers and a steeper decline on social cognition tests in *MAPT* than in *GRN* mutation carriers. This is in line with a previous study, in which *MAPT* mutation carriers showed lower scores on these tests three decades prior to predicted symptom onset [12]. In contrast, presymptomatic *GRN* mutation carriers demonstrated lower scores regarding attention, mental flexibility and naming [13], visuospatial function and working memory [14]. These findings could be explained by partly overlapping but also distinct frontal and temporal atrophy patterns in *MAPT* and *GRN* mutations, resulting in different clinical presentations [37]. Lower visuoconstruction scores before symptom onset in our *MAPT* mutation carriers is unexpected, given evidence of early parietal involvement due to *GRN* but not *MAPT* mutations [3]. However, visuospatial dysfunction was also found in Pick disease, another FTD-tauopathy, later in the disease course [38] – follow-up studies of our cohort of presymptomatic carriers will enable us to determine the robustness of this finding. The unexpected trajectories in other domains did not reach significance, but are probably to be explained by task-familiarity at follow-up. Early executive dysfunction is widely recognized in *MAPT* mutations [37]. Although we did not find longitudinal differences in executive function tests, we have found significant decline in categorical fluency in *MAPT* compared to *GRN* mutation carriers and controls. One could argue the underlying construct of such language tasks, as they are verbally-mediated but also require executive functions as self-monitoring and cognitive flexibility [39]. With the temporal cortex mediating category fluency [39], predominant temporal lobe atrophy in *MAPT* mutations [38] could provide a well-grounded explanation for the verbal fluency decline in our cohort.

Our finding of marked decline of ToM corresponds to the changes in social cognition and behaviour characteristic for the symptomatic stage of bvFTD [4]. Neuroimaging studies investigating its neural basis suggest a distributed brain network mediating different aspects of ToM processing, including the prefrontal cortex, temporal poles and amygdala – areas particularly known for early FTD pathology [4]. Consistent with this, the baseline MRI study of our cohort demonstrated lower integrity of the right uncinate fasciculus and lower prefrontal cortex connectivity in presymptomatic carriers [18]. Overall, our results underline the importance of a systematic use of ToM tasks during diagnostic assessment in early FTD [4], and constitute a strong argument to implement social cognition measurements in the standard diagnostic work-up.

Apparent episodic memory decline over time in relation to age and estimated symptom onset is an interesting finding, as marked memory deficits have been considered an exclusion criterion for FTD [2]. Increasing evidence however suggests that memory deficits can be seen in FTD [40] and neuroimaging studies have shown the contributing role of prefrontal atrophy [40]. Within this line of reasoning, it is suggested that FTD patients do not display a 'true' amnesia, but memory dysfunction results from defective, frontal lobe-dependent, retrieval strategies [41]. Interestingly, we found different profiles of memory decline in *GRN* and *MAPT* mutation carriers, with deficits in RAVLT recall in *GRN* and recognition deficits in *MAPT* mutation carriers. It is possible that the multifactorial nature of this test places different demands on prefrontal versus medial temporal lobe functioning [40] – i.e. the clinical presentation of episodic memory deficits in FTD depends on the mutation involved [9,40].

Estimated age at onset has also been used in other studies of dementia, as individual age at symptom onset is often strongly associated with parental and family onset age in autosomal dominant AD and FTD [17,42]. The use of estimated age at onset in FTD-*GRN* may be a matter of debate, as age at onset in our families with *GRN* mutations varies between 45 and 76 years [42] – whereas the variability is smaller for *MAPT* mutations [17]. Both converters in our cohort developed symptoms close to their predicted age at onset. Within our whole cohort we have found a rather comparable pattern of cognitive decline in estimated age at onset as in the analyses with to current age. Furthermore, a previous study using mean age of onset within FTD families [17] has demonstrated that the carriers' age at symptom onset significantly correlates with both median and mean age at onset within the family, and that age at symptom onset of symptomatic carriers does not significantly differ from mean family onset age. Although estimated age at onset has limitations, in our view its use in an exploratory analysis is justified. With the conversion of more presymptomatic carriers to the symptomatic stage within our long-term follow-up we will obtain more robust information about the level of congruence between estimated and actual onset age.

Key strengths of our study are the large number of at-risk participants – allowing not only gene-specific analyses, but also the use of a well-defined and matched control group of family members. Moreover, the comparison of baseline and follow-up neuropsychological assessments reflects a true longitudinal study, whereas previous studies were cross-sectional in nature. Exploring our findings with and without the two converters has confirmed the existence of a 'pure' presymptomatic cognitive profile, as results were not merely driven by cognitive decline due to clinical onset. The addition of social cognition tasks lastly adds great value to our neuropsychological battery, detecting deficits in the ToM domain that would otherwise be largely unrecognized [4]. Although we applied a well-validated test protocol, it is possible that the cognitive changes may be so subtle in the presymptomatic phase that the tests employed lack adequate sensitivity to small magnitudes of change or are not robust to practice effects -- aspects that could have negatively influenced our results. Our large neuropsychological protocol might have increased the family-wise error rate in our data – however, we emphasize the exploratory nature of our study and therefore lack of correction for multiple comparisons. In retrospect, in light of conversion to the symptomatic phase, it would have been informative to monitor functional changes in addition to cognitive decline.

Conclusions

This exploratory study investigates longitudinal cognitive performance in a large cohort of individuals at risk for FTD. We provide evidence that in the absence of apparent cognitive disorders, follow-up neuropsychological assessment is able to identify gene-specific decline with approaching symptom onset in *GRN* and *MAPT* mutation carriers. These results underline the potential value of neuropsychometric testing as biomarker for monitoring FTD disease progression in clinical practice as well as endpoints in future disease-modifying medication trials. Longer follow-up as part of our longitudinal study, in which more presymptomatic mutation carriers will convert to the clinical stage, should allow us to explore the possibility of cognitive and functional prediction models.

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Appendix 4.1.1 | *MAPT* and *GRN* mutations – overview of count, carriers' age and mean onset in family

		mutation carriers (n=43)	HC (n=39)		
gene	mutation	count (%)	count (%)	onset age in family	age carriers at baseline
MAPT					
	P301L	7 (16.3)	5 (12.8)	53.5 ± 4.9 [43.8–64.8]	42.9 ± 9.4 [29.0–55.2]
	G272V	4 (9.3)	3 (7.7)	43.6 ± 3.1 [39.0–47.1]	38.6 ± 2.7 [36.1–42.0]
	L315R	1 (2.3)	1 (2.6)	54.1 ± 8.3 [36.4–65.1]	68.6
	S320F	1 (2.3)	0 (0)	42.7 [–]	32.8
GRN					
	S82fs	20 (46.5)	17 (43.6)	59.8 ± 8.4 [45.2–75.4]	50.9 ± 7.3 [37.5–65.6]
	Q125X	8 (18.6)	11 (28.2)	62.8 ± 10.0 [48.9–79.0]	58.3 ± 10.3 [37.3–67.6]
	V411fs	2 (4.7)	1 (2.6)	61.8 ± 5.4 [58.0–65.6]	51.8 ± 3.8 [49.1–54.5]

Values indicate: count (percentage), mean ± standard deviation [range]. *Abbreviations: MAPT*, microtubule-associated protein tau; *GRN*, progranulin; HC, healthy controls.

Appendix 4.1.2 | Converter 1 – raw neuropsychological test scores

Female, 62 years old, carrying a P301L mutation in the *MAPT* gene, developed symptoms between first neuropsychological assessment (September 2010) and follow-up neuropsychological assessment 2 years later (January 2013). There was a high level of congruence between the expected onset age within the family and the actual onset age, respectively 53.2 years and 55.6 years. The results of these two assessments, raw scores and clinical evaluation, as well as the comparison between the two assessments is provided below..

Cognitive domains and test	Baseline assessment	Clinical evaluation	2 year follow-up assessment	Clinical evaluation	Comparison baseline- follow-up
Global cognition					↔/↓/↑
MMSE	30/30	Normal	30/30	Normal	↔
FAB	–	N/A	16/18	Normal	N/A
Attention, executive functioning & psychomotor speed					
TMT					
– Part A	39″	Average	46″	Average	↔
– Part B	66″	Average	168″	Impaired	↓
Stroop					
– Card 1	39″	Average Average	42″	Average	↔
– Card 2	57″	Average	68″	Below average	↓
– Card 3	79″		117″	Average	↓
LDST (items in 60 seconds)	39	(above) average	31	Average	↓
WCST concepts	6	Average	2	Impaired	↓
WAIS-III Similarities	26/33	Average	18/33	Below average	↓
Memory					
RAVLT					
– Learning	46/75	Average Average	51/75	Average	↔
– Recall	10/15	Average	10/15	Average	↔
– Recognition	30/30		29/30	Average	↔
VAT (12 items)	12/12	Average	12/12	Average	↔
WAIS–III Digit Span	13/30	Average	12/30	Average	↔
Language					
Boston Naming Test	58/60	Average	55/60	Average	↔
Fluency					
– Categorical (animals)	28	Average	17	Below average	↓
– Letter	27	Average	11	Impaired	↓
SAT	28/30	Average	29/30	Average	↔
ScreeLing – phonology	23.5/24	Average	24/24	Average	↔

Values indicate: raw score/total score. *Abbreviations:* MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test; BNT, Boston Naming Test; SAT, Semantic Association Test. Comparison signs indicate: ↔ no changes in performance, ↓ lower performance, ↑ better performance.

Cognitive domains and test	Baseline assessment	Clinical evaluation	2 year follow-up assessment	Clinical evaluation	Comparison baseline-follow-up
Construction					
Clock draw (Royall)	12/14	Average	13/14	Average	↔
WAIS-III Block Design	26/68	Average	12/68	Below average	↓
Social cognition					
Happé cartoons	11/36	Impaired	15/36	Impaired	↔
Ekman 60 faces	58/60	Above average	46/60	Average	↓

Values indicate: raw score/total score. *Abbreviations:* MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test; BNT, Boston Naming Test; SAT, Semantic Association Test. Comparison signs indicate: ↔ no changes in performance, ↓ lower performance, ↑ better performance.

Appendix 4.1.3 | Converter 2 – raw neuropsychological test scores

Female, 67 years old, carrying a frameshift mutation Ser82ValfX174 in the *GRN* gene, developed symptoms between first neuropsychological assessment (February 2011) and follow-up neuropsychological assessment 2 years later (May 2013). There was a low level of congruence between the expected onset age within the family and actual onset age, respectively 59.7 years and 67.6 years. The results of these two assessments, raw scores and clinical evaluation, as well as the comparison between the two assessments is provided below.

Cognitive domains and test	Baseline assessment	Clinical evaluation	2 year follow-up assessment	Clinical evaluation	Comparison baseline- follow-up
Global cognition					↔/↓/↑
MMSE	29/30	Normal	28/30	Normal	↔
FAB	–	N/A	16/18	Normal	N/A
Attention, executive functioning & psychomotor speed					
TMT					
– Part A	44″	Average	47″	Average	↔
– Part B	84″	Average	204″	Impaired	↓
Stroop					
– Card 1	53″	Below average	59″	Impaired	↓
– Card 2	64″	Average	67″	Below average	↓
– Card 3	129″	Below average	132″	Below average	↔
LDST (items in 60 seconds)	31	Average	29	Average	↔
WCST concepts	6	Average	2	Impaired	↓
WAIS-III similarities	25/33	Average	19/33	Average	↓

Values indicate: raw score/total score. *Abbreviations:* MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test; BNT, Boston Naming Test; SAT, Semantic Association Test. Comparison signs indicate: ↔ no changes in performance, ↓ lower performance, ↑ better performance.

Appendix 4.1.3 | Continued

Cognitive domains and test	Baseline assessment	Clinical evaluation	2 year follow-up assessment	Clinical evaluation	Comparison baseline- follow-up
Memory					
RAVLT					
– Learning	39/75	Below average	53/75	Average	↑
– Recall	9/15	Average	11/15	Average	↔
– Recognition	30/30		30/30	Average	↔
VAT (12 items)	11/12	Average	12/12	Average	↔
WAIS-III Digit Span	14/30	Average	12/30	Average	↔
Language					
Boston Naming Test	52/60	Average	53/60	Average	↔
Fluency					
– Categorical (animals)	18	Average	17	Below average	↓
– Letter	29	Average	21	Impaired	↓
SAT	27/30	Average	29/30	Average	↔
ScreeLing – phonology	23/24	Average	23.5/24	Average	↔
Construction					
Clock draw (Royall)	12/14	Average	13/14	Average	↔
WAIS-III Block Design	26/68	Average	12/68	Below average	↓
Social cognition					
Happé cartoons	11/36	Impaired	15/36	Impaired	↔
Ekman 60 faces	58/60	Above average	46/60	Average	↓

Values indicate: raw score/total score. *Abbreviations:* MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test; BNT, Boston Naming Test; SAT, Semantic Association Test. Comparison signs indicate: ↔ no changes in performance, ↓ lower performance, ↑ better performance.

Appendix 4.1.4 | Neuropsychological baseline and follow-up data (z-scores) per *MAPT* mutation (mutation carrier data only)

Domain (test)	*P301L* (n=7)		*G272V* (n=4)		*L315R* (n=1)		*S320F* (n=1)	
	baseline	follow-up	baseline	follow-up	baseline	follow-up	baseline	follow-up
Language	0.24 ± 0.40	0.04 ± 0.38	0.56 ± 0.89	0.01 ± 1.05	0.84	0.16	-0.75	-0.61
BNT	-0.05 ± 1.24	-0.34 ± 1.37	0.47 ± 0.98	-1.15 ± 3.66	0.15	0.65	-0.46	-2.58
SAT verbal	0.31 ± 0.79	0.73 ± 0.70	0.10 ± 1.11	-0.70 ± 1.77	0.23	-0.08	0.23	1.18
ScreeLing phonology	0.00 ± 0.95	0.45 ± 0.00	0.52 ± 0.00	0.45 ± 0.00	0.52	0.45	0.52	0.45
Categorical fluency (animals)	0.06 ± 0.84	-0.10 ± 1.10	0.70 ± 1.33	-0.08 ± 1.14	2.10	0.60	-1.00	-0.40
Letter fluency	-0.63 ± 1.44	-0.56 ± 1.65	0.03 ± 0.97	0.88 ± 1.03	1.00	0.40	-1.30	-1.00
Attention & mental speed	-0.09 ± 0.49	-0.26 ± 0.44	-0.46 ± 0.28	-0.49 ± 0.21	-0.46	-0.29	-0.91	-1.19
TMT A	-0.11 ± 1.03	0.07 ± 0.87	0.60 ± 1.44	0.40 ± 0.73	-0.10	0.40	1.20	2.60
Stroop card I	-0.67 ± 1.31	-0.64 ± 1.09	-0.20 ± 0.50	-0.35 ± 1.04	0.70	0.40	0.80	0.60
Stroop card II	-0.77 ± 1.12	-0.29 ± 1.25	0.15 ± 1.00	-0.15 ± 0.99	0.10	-0.40	1.20	0.50
LDST	0.00 ± 0.72	-0.27 ± 0.60	0.58 ± 1.35	-0.41 ± 1.07	0.00	0.00	-1.28	-1.99
Executive function	-0.06 ± 0.48	-0.06 ± 0.61	-0.15 ± 0.15	-0.02 ± 0.35	-0.74	-0.24	0.02	-0.02
TMT B	0.31 ± 0.92	-0.29 ± 1.32	0.83 ± 1.04	0.88 ± 1.43	-0.10	-0.10	-1.50	-0.80
Stroop card III	-0.21 ± 0.90	-0.14 ± 1.39	0.43 ± 0.92	0.28 ± 1.15	-0.20	-0.40	0.80	0.80
WCST concepts	0.26 ± 0.11	-0.03 ± 0.97	-0.13 ± 0.29	0.05 ± 0.17	-1.20	-1.10	0.00	0.70
WAIS similarities	-0.24 ± 0.98	-0.38 ± 1.15	0.50 ± 0.80	0.50 ± 0.34	0.67	0.67	-1.00	-1.00
Social cognition	0.11 ± 0.61	-0.26 ± 0.93	0.54 ± 1.02	0.31 ± 1.15	0.54	-0.90	-0.21	0.51
Ekman faces	-0.42 ± 1.02	-0.56 ± 1.46	0.32 ± 1.04	0.08 ± 1.47	0.14	-0.64	0.49	0.72
Happé TOM	0.43 ± 0.79	0.22 ± 0.87	0.71 ± 1.25	0.52 ± 1.37	-0.12	-0.38	-1.21	-1.59
Happé non-TOM	0.25 ± 0.75	-0.12 ± 0.88	0.53 ± 0.78	0.22 ± 0.92	1.40	1.24	0.25	-0.12
Memory	0.10 ± 0.72	0.06 ± 0.84	-0.07 ± 1.84	-0.41 ± 2.09	0.33	-1.29	0.09	0.13
RAVLT – learning	-0.59 ± 0.98	0.36 ± 1.34	-0.73 ± 1.62	0.33 ± 1.53	-1.20	-0.90	0.50	1.40
RAVLT – recall	-0.39 ± 1.23	0.57 ± 1.63	-0.43 ± 2.10	-0.05 ± 1.19	-1.00	-1.40	0.70	1.70
RAVLT – recognition	0.16 ± 0.74	0.44 ± 0.43	-1.04 ± 2.22	-0.62 ± 1.52	0.63	-1.94	0.63	-0.18
VAT	0.08 ± 1.00	0.24 ± 0.38	-0.65 ± 2.21	-0.88 ± 2.53	0.46	-0.63	0.46	0.39
WAIS Digit Span	-0.19 ± 0.90	0.33 ± 1.30	1.25 ± 0.88	1.42 ± 1.26	1.33	0.67	-1.33	0.67
Visuoconstruction	-0.16 ± 0.69	-0.22 ± 0.64	-0.24 ± 0.75	0.49 ± 0.61	-0.29	-1.52	-1.10	-0.30
WAIS Block Design	-0.48 ± 1.10	0.05 ± 1.13	0.34 ± 0.47	0.92 ± 1.20	0.00	0.00	-1.99	-0.67
Clock drawing	0.30 ± 0.69	0.32 ± 0.83	-0.77 ± 0.72	0.14 ± 0.00	0.47	-2.26	-0.15	0.14

Values indicate: z-score ± standard deviation. In case of n=1, only mean z-scores are listed. *Abbreviations: MAPT, microtubule-associated protein tau*; BNT, Boston Naming Test; SAT, Semantic Association Test; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; TOM; theory of mind, RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test.

Appendix 4.1.5 | Neuropsychological baseline and follow-up data (z-scores) per *GRN* mutation (mutation carrier data only)

Domain (test)	*Q125X* (n=8)		*S82fs* (n=20)		*V411fs* (n=2)	
	baseline	follow-up	baseline	follow-up	baseline	follow-up
Language	-0.48 ± 0.59	-0.35 ± 0.34	0.34 ± 0.71	0.22 ± 0.51	0.30 ± 0.20	0.37 ± 0.44
BNT	-0.33 ± 1.01	0.25 ± 0.58	0.17 ± 0.78	0.48 ± 0.52	0.55 ± 0.21	0.58 ± 0.18
SAT verbal	-0.51 ± 1.08	-0.70 ± 0.58	0.02 ± 1.07	0.08 ± 0.88	0.50 ± 0.38	0.24 ± 0.44
ScreeLing phonology	-0.69 ± 1.29	-0.53 ± 1.87	0.09 ± 0.98	-0.10 ± 0.77	0.52 ± 0.00	0.45 ± 0.00
Categorical fluency (animals)	-0.85 ± 0.78	-0.19 ± 0.65	-0.03 ± 1.04	0.08 ± 1.14	-0.80 ± 0.00	-0.70 ± 0.42
Letter fluency	-0.81 ± 1.02	-0.56 ± 1.16	0.41 ± 1.07	0.76 ± 1.67	-0.20 ± 1.27	0.75 ± 0.78
Attention & mental speed	-0.65 ± 0.81	-0.62 ± 0.80	0.19 ± 0.83	0.16 ± 0.82	-0.10 ± 0.75	0.00 ± 0.11
TMT A	-0.59 ± 0.73	-0.64 ± 0.78	0.12 ± 1.20	0.33 ± 1.05	-0.15 ± 1.63	-0.40 ± 0.85
Stroop card I	-0.94 ± 0.97	-1.03 ± 0.75	-0.46 ± 1.15	-0.53 ± 1.19	-1.40 ± 1.27	-0.90 ± 0.42
Stroop card II	-0.99 ± 1.11	-0.96 ± 1.05	-0.48 ± 1.26	-0.37 ± 1.31	-1.50 ± 0.42	-1.20 ± 0.14
LDST	-0.88 ± 1.18	-0.45 ± 1.25	0.08 ± 0.75	0.30 ± 1.05	0.00 ± 0.00	-0.42 ± 0.00
Executive function	-0.79 ± 0.91	-0.43 ± 0.63	0.40 ± 0.52	0.28 ± 0.72	0.35 ± 0.35	0.37 ± 0.04
TMT B	-0.84 ± 1.46	-0.46 ± 0.87	0.30 ± 1.16	0.45 ± 1.12	-0.15 ± 0.07	-0.50 ± 0.57
Stroop card III	-0.98 ± 0.63	-0.78 ± 0.60	-0.13 ± 1.20	0.26 ± 1.27	-0.85 ± 0.64	-0.65 ± 0.35
WCST concepts	-0.03 ± 0.80	-0.33 ± 0.87	0.29 ± 0.25	-0.16 ± 1.09	0.00 ± 0.14	-0.05 ± 0.21
WAIS similarities	-0.33 ± 1.15	0.17 ± 0.89	0.57 ± 0.76	0.65 ± 0.82	0.67 ± 0.47	0.83 ± 0.71
Social cognition	-0.11 ± 0.72	-0.43 ± 0.87	0.43 ± 0.63	0.43 ± 0.75	0.95 ± 0.73	1.00 ± 0.01
Ekman faces	-0.68 ± 1.08	-0.58 ± 0.67	0.28 ± 0.89	0.34 ± 0.78	0.85 ± 0.75	0.98 ± 0.12
Happé TOM	0.16 ± 1.00	-0.08 ± 1.10	0.35 ± 0.85	0.22 ± 0.99	1.12 ± 0.97	0.97 ± 1.06
Happé non-TOM	0.14 ± 0.71	-0.25 ± 0.83	0.61 ± 0.86	0.27 ± 1.01	0.82 ± 0.41	0.56 ± 0.48
Memory	-0.78 ± 0.66	-0.92 ± 0.82	0.43 ± 0.49	0.18 ± 0.56	1.04 ± 0.11	0.88 ± 0.76
RAVLT – learning	-1.64 ± 0.69	-0.33 ± 0.87	-0.541.19	0.55 ± 0.87	0.10 ± 0.00	1.30 ± 0.00
RAVLT – recall	-1.39 ± 0.97	-0.16 ± 0.92	-0.210.99	0.47 ± 1.02	0.85 ± 0.07	1.10 ± 0.14
RAVLT – recognition	-0.70 ± 0.94	-0.29 ± 1.10	0.330.51	0.17 ± 0.92	0.63 ± 0.00	0.69 ± 0.00
VAT	-0.76 ± 1.15	-0.50 ± 1.26	0.280.36	0.28 ± 0.31	0.46 ± 0.00	0.39 ± 0.00
WAIS Digit Span	-0.04 ± 1.17	0.04 ± 0.79	0.501.08	0.53 ± 1.17	0.83 ± 0.71	1.67 ± 0.47
Visuoconstruction	-0.75 ± 0.79	-0.80 ± 0.58	0.30 ± 0.90	0.20 ± 0.70	-0.65 ± 1.41	0.43 ± 0.05
WAIS Block Design	-0.29 ± 0.95	-0.21 ± 0.85	0.601.15	0.77 ± 1.01	0.34 ± 0.47	1.17 ± 0.23
Clock drawing	-0.46 ± 1.10	-0.76 ± 1.07	0.380.86	0.32 ± 0.98	-1.08 ± 2.20	0.14 ± 0.00

Values indicate: z-score ± standard deviation. In case of n=1, only mean z-scores are listed. *Abbreviations: MAPT, microtubule-associated protein tau*; BNT, Boston Naming Test; SAT, Semantic Association Test; TMT, Trail Making Test; LDST, Letter Digit Substitution Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; TOM; theory of mind, RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test.

4.2

Longitudinal cognitive biomarkers predicting symptom onset in presymptomatic familial frontotemporal dementia

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Abstract

In our prospective cohort, we performed four-year follow-up neuropsychological assessment to investigate cognitive decline and the prognostic abilities from presymptomatic to symptomatic familial frontotemporal dementia (FTD). Presymptomatic *MAPT* (n=15) and *GRN* mutation carriers (n=31), and healthy controls (n=39) underwent neuropsychological assessment every 2 years. Eight mutation carriers (5 *MAPT*, 3 *GRN*) became symptomatic. We investigated cognitive decline with multilevel regression modeling; the prognostic performance was assessed with ROC analyses and stepwise logistic regression. *MAPT* converters declined on language, attention, executive function, social cognition, and memory, and *GRN* converters declined on attention and executive function ($p<0.05$). Cognitive decline in ScreeLing phonology ($p=0.046$) and letter fluency ($p=0.046$) were predictive for conversion to non-fluent variant PPA, and decline on categorical fluency ($p=0.025$) for an underlying *MAPT* mutation. Using longitudinal neuropsychological assessment, we detected a mutation-specific pattern of cognitive decline, potentially suggesting prognostic value of neuropsychological trajectories in conversion to symptomatic FTD.

Introduction

Frontotemporal dementia (FTD) is a presenile neurodegenerative disorder, leading to a heterogeneous clinical presentation, involving behavioural (behavioural variant FTD; bvFTD) and/or language deterioration (primary progressive aphasia; PPA) [1]. FTD has an autosomal dominant pattern of inheritance in 30 percent of cases, with mutations in the progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*) genes as its two main causes [2]. The cognitive profile of FTD varies depending on the clinical phenotype and the underlying genotype. Patients with bvFTD are characterized by deficits in executive function, social cognition and language, whereas memory and visuoconstruction are initially spared [3-5]. Non-fluent variant PPA (nfvPPA) patients have agrammatism and speech sound errors/distortions, while semantic variant PPA (svPPA) patients experience deficits in confrontation naming and word comprehension [6]. *GRN* mutations often lead to a clinical diagnosis of bvFTD, nfvPPA or parkinsonism. In *MAPT*, bvFTD is the main phenotype, and semantic and memory impairments can be prominent neuropsychological symptoms [7].

Research in familial FTD has demonstrated the presence of a presymptomatic stage in which subtle cognitive changes have been identified [8-12]. More specifically, cognitive decline can start as early as 8 years prior to estimated symptom onset and shows mutation-specific patterns, with *GRN* mutation carriers declining in memory, and *MAPT* mutation carriers declining in language, social cognition *and* memory [8,10]. This suggests that cognitive measures could function as disease-tracking biomarkers in the presymptomatic stage. However, it is currently unknown what the long-term cognitive profiles of presymptomatic FTD mutations are, whether neuropsychological assessment can be used to track disease progression to the symptomatic stage, and what the prognostic value is of cognitive trajectories in the presymptomatic and early symptomatic stage of FTD.

In this study, we investigated longitudinal cognitive decline on neuropsychological assessment in presymptomatic mutation carriers (*MAPT* or *GRN*) and controls from the same families within our longitudinal presymptomatic Dutch familial FTD Risk Cohort (FTD-RisC). Secondly, we assessed the difference in cognitive course between converters' genotypes (i.e. *MAPT* vs. *GRN*) and phenotypes (i.e. bvFTD vs. nfvPPA) versus non-converters. Lastly, we investigated the prognostic value of neuropsychological trajectories in predicting symptom onset within 2 to 4 years.

Methods

Participants

In FTD-RisC, we follow healthy 50% at-risk family members from genetic FTD families on a two-year basis. In the current study, we included 87 participants from *MAPT* or *GRN* families with data entries between December 2009 and January 2013 [8-9,13]. The follow-up period was 4 years, in which we acquired neuropsychological assessments at study entry, follow-up after 2 years and follow-up after 4 years. DNA genotyping (see *Procedure*) assigned participants either to the presymptomatic mutation carrier

(n=46; 31 *GRN*, 15 *MAPT*), or control group (n=39; 29 *GRN*, 10 *MAPT* family members). We excluded two controls as they had cognitive disorders (≥2 SD below mean) on multiple domains, ultimately including 85 participants (46 mutation carriers, 37 controls; Figure 4.2.1).

Standard Protocol Approvals, Registrations, and Patient Consents

Clinical investigators were blind for participants' genetic status if they had not undergone predictive testing. In case of conversion to clinical FTD, we offered the patient and family members genetic counselling and unblinding of genetic status, in order to confirm the presence of the pathogenic mutation. At study entry, all participants gave written informed consent. The study was approved by the Medical and Ethical Review Committee of the Erasmus Medical Center.

Procedure

Every 2 years, participants underwent a standardised assessment consisting of a neuropsychological test battery, neurological examination, and MR imaging of the brain. DNA sequencing was performed at study entry. All participants were asymptomatic according to established diagnostic criteria for bvFTD [3] or PPA [6] at baseline. Knowledgeable informants were asked about cognitive and/or behavioural deterioration at each study visit by means of a structured interview and a well-validated questionnaire (Neuropsychiatric Inventory; NPI) [14].

Converters

Eight mutation carriers became symptomatic within the study time window ("converters"). Symptom onset was determined by means of the above mentioned assessment (anamnesis, MR imaging of the brain, neuropsychological assessment, heteroanamnestic information and unblinding of genetic status). Conversion was determined in a multidisciplinary consensus meeting of the Erasmus MC FTD Expertise Centre, involving neurologists (LDK, JCvsS), neuropsychologists (LCJ, JLP, SF, EvdB, JMP), medical doctors (LHM, ELvdE), as well as neuroradiologists, geriatricians, a clinical geneticist (RvM), and a care consultant. Six converters (5 *MAPT*, 1 *GRN*) presented with progressive behaviour deterioration, functional decline, and frontal and/or temporal lobe atrophy on MRI, fulfilling the international diagnostic consensus criteria of Rascovsky et al. [3] for bvFTD with definite FTLD pathology. Two converters (both *GRN*) presented with isolated language difficulties and no impairments of daily living activities, thereby fulfilling the diagnostic criteria for PPA of Gorno-Tempini et al. [6]. Both developed nfvPPA, as they showed a non-fluent, halting speech, with sound errors and agrammatism. See Supplementary Table 4.2.1 for demographic, clinical and neuropsychological data of the converters. We defined mutation carriers remaining without FTD symptoms as non-converters (n=38; 28 *GRN*, 10 *MAPT*).

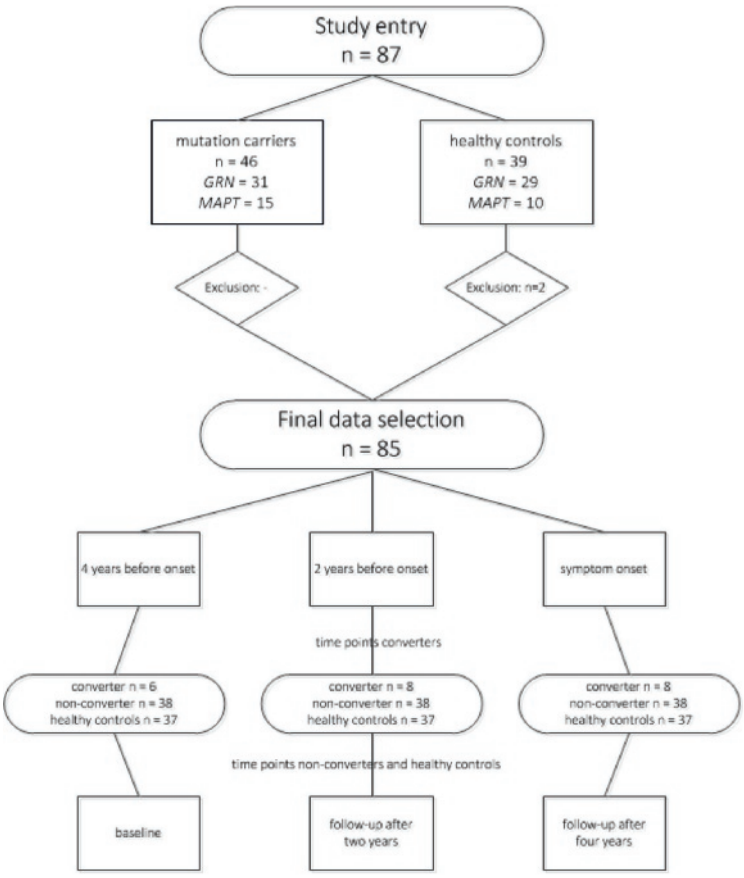


Figure 4.2.1 | **Participant in- and exclusion and sample size per time point.** Two controls were excluded as they had multiple cognitive disorders (≤2 standard deviations below reference mean) on neuropsychological testing. Eight mutation carriers converted to clinical frontotemporal dementia within the study window. Their data were restructured, so that there were three time points: four years before symptom onset, two years before symptom onset and symptom onset. Four years before symptom onset, only data of six converters was available, as two mutation carriers converted between baseline and first follow-up. The data of converters was compared to respectively baseline, follow-up after two years and follow-up after four years in non-converters and healthy controls.

Neuropsychological assessment

We screened global cognitive functioning by means of the Mini-Mental State Examination [15] (MMSE) and Frontal Assessment Battery [16] (FAB). Experienced neuropsychologists (LCJ, JLP, SF) administered neuropsychological tests within six cognitive domains: language, attention and mental processing speed, executive functioning, social cognition, memory, and visuoconstruction. We rated language with the 60-item Boston Naming Test (BNT) [17], verbal Semantic Association Test (SAT) [18], ScreeLing phonology

[19], and categorical fluency [20]. We assessed attention and mental processing speed by means of Trailmaking Test (TMT)-A [21], Stroop Color-Word Test I and II [22], Wechsler Adult Intelligence Scale III (WAIS-III) Digit Span forwards [23], and Letter Digit Substitution Test (LDST) [24]. Executive functioning was evaluated using TMT-B [21], Stroop Color-Word Test III [22], WAIS-III Digit Span backwards [23], modified Wisconsin Card Sorting Test (WCST) concepts [25], letter fluency [20], and WAIS-III Similarities [23]. Happé cartoons [26] and Ekman Faces [27] measured social cognition. We assessed memory using the Dutch Rey Auditory Verbal Learning Test (RAVLT) [28] and Visual Association Test (VAT [29]. We evaluated visuoconstruction by means of clock drawing [30] and WAIS-III Block Design [23]. Alternate forms were used at follow-up visits, when applicable (letter fluency, RAVLT, VAT). Depressive symptoms were rated with the Beck's Depression Inventory (BDI) [31].

Study design

In converters, we restructured the three original time points within our study window (baseline, follow-up after 2 years, follow-up after 4 years) into the following three new time points (Figure 4.2.1):

- *4 years before symptom onset* – in converters, we used the data of the study visit 4 years before diagnosis. Analyses could were performed in six converters, as two (1 *GRN*, 1 *MAPT* – 2 bvFTD) developed symptoms between baseline and first follow-up (i.e. at 2 years follow-up), and therefore no data 4 years prior to symptom onset were available.
- *2 years before symptom onset* – in converters, we used the data of the study visit 2 years before diagnosis. Analyses included all eight converters.
- *after symptom onset* – in converters, we used the data of the diagnosis visit. Analyses included all eight converters.

In non-converters and controls we used the original time points: baseline (data were compared to "4 years before symptom onset" data of converters), follow-up after 2 years (data were compared to "2 years before symptom onset" data of converters) and follow-up after 4 years (data were compared to "after symptom onset" data of converters).

Statistical analysis

Statistical analyses were performed using SPSS Statistics 21.0 (IBM Corp., Armonk, NY) and GraphPad Prism 7 (La Jolla, California, USA), with the significance level at $p<0.05$ (two-tailed) across all comparisons. We compared demographic data between *MAPT* mutation carriers, *GRN* mutation carriers and controls, and between converters, non-converters and controls by means of one-way ANOVAs. We performed Pearson χ^2 tests to investigate differences in sex. Longitudinal comparisons of clinical data were performed with repeated measures ANOVAs. We standardized all raw neuropsychological test scores by converting them into z-scores (i.e. individual test score minus the baseline mean of the controls, divided by the baseline SD of the controls) per time point, after which we calculated composite z-scores for the respective six cognitive domains by averaging the z-scores of the individual tests per domain. For the longitudinal comparisons we used multilevel linear regression modeling. This analysis corrects for bias when data absence is dependent on characteristics present in the model, and can therefore efficiently handle

missing and unbalanced time points. There were two levels in the models: the participants constituted the upper level; their repeated measures the lower level. We ran two analyses to assess cognitive decline per mutation (1 and clinical status (2:

- We entered **mutation status** (*MAPT* mutation carrier, *GRN* mutation carrier or control), **time** (4 years before symptom onset, 2 years before symptom onset, and after symptom onset), and **first-order interactions**, with age, gender and educational level as covariates. We reran the analyses excluding the converters, to exclude converters driving the cognitive decline in the mutation carrier groups;
- We split the converter group according to genotype (*MAPT* or *GRN*) and phenotype (bvFTD or nfvPPA) in order to investigate specific profiles of cognitive decline over time. We then entered **clinical status** (converter, non-converter or control), time, and first-order interactions, with age, gender and educational level as covariates.

Thirdly, to investigate the prognostic abilities of cognitive decline in discriminating between converters and non-converters, we determined the area under the curve (AUC) by receiver operating characteristic (ROC) analyses on the neuropsychological trajectories between visits. For this, we calculated deltas between test scores; one between 4 and 2 years before symptom onset and one between 2 years before symptom onset and symptom onset. Optimal cut-off levels were given by the highest Youden's index [32]. Again, we split the converter group according to genotype (*MAPT* or *GRN*) and phenotype (bvFTD or nfvPPA). Next, we performed logistic regression analyses, taking group (converter vs. non-converter) as the dependent variable and the deltas (tests with significant diagnostic performance in abovementioned ROC analyses) as the independent variables. The models were selected with a forward stepwise method according to the likelihood ratio test and applying the standard *p*-values for variable inclusion (0.05) and exclusion (0.10), with age, sex and education as covariates. Goodness of fit was evaluated with the HL χ^2 test. Nagelkerke R^2 is reported as measure of effect size. We checked predictor variables for multicollinearity. All models were corrected for multiple comparisons (Bonferroni).

Results

Demographics

MAPT mutation carriers were significantly younger than *GRN* mutation carriers (p=0.012; Table 4.2.2). The mean familial symptom onset age was lower in *MAPT* than in *GRN* mutation carriers and controls (both p<0.001). There were no significant differences between groups regarding estimated years to symptom onset (p>0.05). Longitudinal analyses demonstrated that *MAPT* mutation carriers declined significantly more than *GRN* mutation carriers and controls with regards to the MMSE (p=0.014), and also developed more depressive symptoms (p=0.028). FAB and NPI scores did not significantly change over time (p>0.05). Converters, non-converters and controls did not differ regarding demographic variables, apart from a younger family onset in *MAPT* converters than *GRN* converters (p=0.043) and non-converters (p=0.001; Table 4.2.2). Both *MAPT* and *GRN* converters declined significantly with respect to MMSE score

(p<0.001) and they developed more neuropsychiatric symptoms in the form of higher BDI (p=0.001) and NPI (p=0.021) scores in comparison to non-converters and controls. FAB scores did not significantly change over time (p>0.05).

Longitudinal cognitive decline in *MAPT* and *GRN* mutation carriers

The whole group of *MAPT* mutation carriers declined significantly within the domains language, social cognition and memory compared with controls (Table 4.2.3; Figure 4.2.2). This was reflected in lower scores on the BNT and categorical fluency, Happé cartoons, VAT and RAVLT delayed recall (Table 4.2.3). In the whole group of *GRN* mutation carriers, no longitudinal decline was found in comparison to controls. In comparison to *GRN* mutation carriers, *MAPT* mutation carriers declined significantly on the domains language (β=-0.015, p<0.001) and memory (β=-0.016, p=0.008), reflected in lower BNT (β=-0.085, p=0.01), SAT (β=-0.027, p=0.015), category fluency (β=-0.107, p=0.002), and RAVLT delayed recall (β=-0.047, p=0.001) scores. There were no cognitive domains or tests on which *GRN* mutation carriers declined more than *MAPT* mutation carriers (Table 4.2.3). By excluding the five *MAPT* converters from the analyses, none of the domain scores in *MAPT* mutation carriers continued to show significant decline over time in comparison to controls. Regarding individual tests, however, the decline on the RAVLT delayed recall remained significant (β=-0.032, p=0.023). The results did not change by excluding the three *GRN* converters from the analyses. In comparison to *GRN, MAPT* mutation carriers still declined more on language (β=-0.010, p=0.004), reflected in lower ScreeLing phonology (β=-0.008, p=0.024) and category fluency (β=-0.007, p=0.041). There was no cognitive decline in controls – but significant improvement was found on social cognition (Happé non-ToM and Ekman Faces) and memory (RAVLT immediate and delayed recall) (Table 4.2.3). The raw neuropsychological test scores per time point can be found in Supplementary Table 4.2.1.

Longitudinal cognitive decline in converters and non-converters

Converters with a *MAPT* mutation deteriorated significantly on all domains but visuoconstruction (Figure 4.2.2 A-D, F; Table 4.2.4). Within these domains, performances declined on BNT (p<0.001), LDST (p=0.035), Stroop I, II and III (I: p=0.017; II: p<0.001; III: p=0.021), categorical fluency (p=0.001), WAIS similarities (p<0.001), Happé ToM (p=0.011), and RAVLT immediate (p=0.004) and delayed recall (p=0.030). Converters with a *GRN* mutation deteriorated significantly on attention and mental processing speed, and executive function (Figure 4.2.2 B-C; Table 4.2.4). Within these domains, performances on TMT-B (p<0.001), Stroop III (p<0.001), WCST (p=0.005), letter fluency (p=0.012) and WAIS similarities (p<0.001) deteriorated significantly over time. Converters with bvFTD had a similar pattern of cognitive decline as *MAPT* converters, with lower scores on social cognition, memory, language, attention and executive function (Table 4.2.4). Comparably, converters with nfvPPA had a similar pattern of cognitive decline as *GRN* converters, with lower scores on attention and executive function (Table 4.2.4). There were no differences in decline between converters with bvFTD and nfvPPA (Table 4.2.4). The raw neuropsychological test scores per time point can be found in Supplementary Table 4.2.2.

Table 4.2.1 | Demographic, clinical and neuropsychological data of the converters at symptom onset

Demographics	Converter							
	1	2	3	4	5	6	7	8
Clinical diagnosis	bvFTD	bvFTD	bvFTD	nfvPPA	nfvPPA	bvFTD	bvFTD	bvFTD
Age at onset	67	56	57	51	57	42	45	43
Mean onset age family	59.7	53.2	53.2	59.7	59.7	44.5	44.5	44.5
Gene	*GRN*	*MAPT*	*MAPT*	*GRN*	*GRN*	*MAPT*	*MAPT*	*MAPT*
Mutation	Ser82fs	P301L	P301L	Ser82fs	Ser82fs	G272V	G272V	G272V
Gender	Female	Female	Male	Female	Female	Male	Male	Male
Study visit on which diagnosis was set	Follow-up 1	Follow-up 1	Follow-up 2	Follow-up 2	Follow-up 2	Follow-up 2	Follow-up 2	Follow-up 2
Global cognition and questionnaires								
MMSE (/30)	28	30	27	29	26	26	26	27
FAB (/18)	16	16	13	18	15	15	16	17
NPI (/144)	29	0	23	2	1	15	1	39
CBI-R (/180)	46	0	32	4	0	42	25	55
Neuropsychological test								
Social cognition								
Happé Cartoon Test ToM	-1.3	-0.7	-2.2	1.0	-1.0	-2.2	-0.7	-0.4
Happé Cartoon Test non-ToM	-2.1	-2.1	-1.8	1.2	-1.4	-2.5	-1.4	0.8
Ekman Faces Test	-0.3	-2.4	-1.1	1.0	-1.9	-2.1	-0.6	0.3
Language								
Boston Naming Test 60-item	-0.4	0.0	-0.4	0.7	0.3	-7.1	-3.1	0.5
ScreeLing phonology	-0.1	0.5	0.5	-0.6	-0.6	0.5	0.5	0.5
SAT	0.9	0.9	-1.0	0.3	0.9	-4.1	0.3	0.3
Categorical fluency (animals)	-1.3	-1.3	-1.8	-0.1	-1.3	-2.0	-1.2	-1.3

Table 4.2.1 | Continued

Demographics	Converter							
	1	2	3	4	5	6	7	8
Executive function								
Letter fluency	-1.7	-2.4	-1.2	-0.7	-0.9	-0.8	0.0	-0.3
TMT part B	-3.6	-2.7	-1.1	-0.5	>-3.0	0.3	0.9	0.1
Stroop card III	-2.5	-1.7	-3.1	-2.4	-1.7	0.3	0.4	-1.1
WCST	-3.2	-3.2	-2.3	-1.4	-1.4	0.3	0.3	0.3
Similarities WAIS-III	-1.0	-1.2	-1.2	0.1	-1.8	-1.0	0.9	-0.7
Digit Span backwards WAIS-III	-1.3	-1.3	-0.3	-0.8	-1.8	1.3	1.8	-0.8
Attention & mental processing speed								
TMT part A	-1.8	-1.7	-1.5	0.6	-1.2	1.3	1.1	0.3
Stroop card I	-1.1	0.6	-0.6	-0.2	-0.2	0.0	0.6	-0.9
Stroop card II	-0.8	-0.9	-3.6	-0.8	-0.6	-0.7	-0.3	-1.2
LDST	-0.9	-0.6	-1.4	0.0	-0.9	0.0	0.7	-2.0
Digit Span forwards WAIS-III	-0.6	-0.6	-1.3	-1.3	-2.6	0.1	2.2	0.1
Memory								
RAVLT immediate recall	0.2	0.0	-1.9	1.7	-1.4	-1.7	-0.1	-1.5
RAVLT delayed recall	-0.1	-0.4	-2.1	1.3	-0.4	-3.8	-0.4	-1.8
RAVLT recognition	0.6	-0.2	-0.2	0.6	-0.2	-8.2	-0.2	-1.8
Visual Association Test	0.4	0.4	-2.3	0.4	0.4	-2.9	-2.3	0.4
Visuoconstruction								
Clock drawing	0.2	0.2	0.2	0.2	-0.9	-1.9	-0.9	0.2
Block Design WAIS-III	-2.0	-1.6	-0.4	-0.2	-1.6	-0.4	1.7	-0.4

Values indicate: z-scores (i.e. individual test score minus the mean of healthy controls, divided by the standard deviation of healthy controls). *Abbreviations:* bvFTD, behavioural variant frontotemporal dementia; nfvPPA, nonfluent variant primary progressive aphasia; *GRN*, progranulin; *MAPT*, microtubule-associated protein tau; MMSE, Mini-Mental State Examination; FAB, frontal assessment battery; NPI-Q, Neuropsychiatric Inventory; CBI-R, Cambridge Behavioural Inventory-Revised; ToM, theory of mind; SAT, Semantic Association Test; TMT, Trailmaking Test; WCST, Wisconsin Card Sorting Test; WAIS, Wechsler Adult Intelligence Scale; LDST, Letter Digit Substitution Test; RAVLT, Rey Auditory Verbal Learning Test. Cognitive disorders (≥2 SD below mean) are highlighted in red; values below average (-2 ≤ SD ≥ -1) are highlighted in orange. Follow-up 1 = visit 2 years after study entry; follow-up 2 = visit 4 years after study entry.

Table 4.2.2 | Demographics and clinical data

Demographics		HC (n=39)	*MAPT* carriers (n=15)	*GRN* carriers (n=31)	*p*-value*	*MAPT* converters (n=5)	*GRN* converters (n=3)	non-converters (n=38)	*p*-value**
Age at study entry, y		49.1 ± 12.2	41.9 ± 10.0	52.1 ± 8.2	0.012[a]	45.3 ± 8.5	54.9 ± 9.0	48.8 ± 10.3	0.704
Sex, female (%)		20 (56%)	7 (47%)	20 (65%)	0.506	1 (20%)	3 (100%)	23 (60.5%)	0.154
Education (Verhage)[1]		5.2 ± 1.0	5.1 ± 1.6	5.7 ± 0.9	0.102	6.0 ± 0.7	5.7 ± 0.6	5.4 ± 1.3	0.409
Onset age family, y		59.0 ± 5.8	51.3 ± 6.7	61.0 ± 2.4	**<0.001**[a,b]	48.0 ± 4.7	59.7 ± 0.0	58.8 ± 6.1	0.002c,d
Estimated years to onset, y		-10.2 ± 11.2	-7.7 ± 9.6	-9.4 ± 7.9	0.690	-2.7 ± 4.0	-4.8 ± 9.0	-10.0 ± 8.5	0.335
Clinical data	Years to onset								
MMSE	**4**	29.1 ± 1.3	29.6 ± 0.5	29.1 ± 1.6	0.451	29.5 ± 0.6	29.0 ± 1.4	29.2 ± 1.4	0.924
	2	29.2 ± 1.3	28.7 ± 2.2	28.9 ± 1.6	0.513	29.8 ± 0.4	28.0 ± 1.0	27.7 ± 1.5	0.271
	0	29.2 ± 1.0	28.4 ± 1.5	29.2 ± 1.4	0.099	27.2 ± 1.6	27.7 ± 1.5	29.3 ± 1.2	**0.001**[c,d]
FAB***	**4**	–	–	–	–	–	–	–	–
	2	17.4 ± 0.9	17.4 ± 0.8	17.5 ± 0.9	0.883	17.3 ± 1.0	17.5 ± 0.7	17.5 ± 0.9	0.929
	0	16.7 ± 1.7	16.5 ± 1.6	17.0 ± 1.1	0.639	15.4 ± 1.5	16.3 ± 1.5	17.1 ± 1.1	0.120
BDI	**4**	4.1 ± 4.5	4.0 ± 6.3	3.2 ± 3.9	0.693	1.3 ± 1.0	2.0 ± 2.8	3.7 ± 5.0	0.645
	2	3.7 ± 3.9	4.5 ± 5.0	3.2 ± 4.0	0.638	5.0 ± 4.7	2.7 ± 3.8	3.5 ± 4.4	0.866
	0	3.5 ± 4.3	7.6 ± 9.5	3.0 ± 6.7	0.108	11.6 ± 13.0	6.3 ± 5.1	3.1 ± 6.5	**0.042**[c,d]
NPI	**4**	0.1 ± 0.5	4.6 ± 11.2	1.4 ± 3.4	0.180	0.0 ± 0.0	–	3.0 ± 7.5	**0.006**[c-e]
	2	0.6 ± 1.2	6.4 ± 20.7	0.3 ± 0.7	0.095	0.2 ± 0.4	0.0 ± 0.0	2.9 ± 13.3	0.767
	0	0.8 ± 1.5	12.3 ± 18.7	2.1 ± 6.6	**0.001**[a,b]	15.6 ± 16.3	10.7 ± 15.9	3.4 ± 11.4	**0.009**[d]

Values indicate: mean ± standard deviation. *Abbreviations: GRN*, *progranulin*; HC, healthy control; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery; BDI, Beck's Depression Inventory; NPI, Neuropsychiatric Inventory; CBI-R, Cambridge Behavioural Inventory Revised. [1]Dutch educational system categorized into levels from 1 = less than 6 years of primary education to 7 = academic schooling (Verhage, 1964). * *P*-value represents result of overall ANOVA between *MAPT* mutation carriers, *GRN* mutation carriers and healthy controls. ** *P*-value represents result of overall ANOVA between *MAPT* converters, *GRN* converters, non-converters and HC. *** Data only available on follow-up visits. Significant comparisons are displayed in bold. [a] significant post-hoc test between *MAPT* and *GRN* mutation carriers, [b] significant post-hoc test between *MAPT* mutation carriers and healthy controls, [c] significant post-hoc test between converters and non-converters, [d] significant post-hoc test between converters and healthy controls. [e]Only data of *MAPT* converters available, therefore the *p*-value represents the comparison between *MAPT* converters, non-converters and HC.

Table 4.2.3 | Cognitive trajectories in mutation carriers (converters, non-converters) and healthy controls

Domain Test	healthy controls (n=39)			*MAPT* mutation carriers (n=15)			*GRN* mutation carriers (n=31)		
	baseline	β	*p*	baseline	β	*p*	baseline	β	*p*
Language	0.0 ± 0.6	0.000	0.931	0.2 ± 0.6	-0.010	**0.002**	0.1 ± 0.7	0.004	0.121
BNT	53.4 ± 4.5	0.026	0.105	52.6 ± 5.30	-0.080	**0.005**	55.1 ± 3.7	0.006	0.786
SAT	27.8 ± 1.1	-0.003	0.604	27.9 ± 1.50	-0.008	0.604	27.5 ± 2.0	0.019	**0.033**[a]
ScreeLing phonology	23.5 ± 0.8	0.001	0.733	23.9 ± 0.28	-0.005	0.190	23.8 ± 0.5	-0.001	0.863
Categorical fluency	23.9 ± 4.9	0.026	0.141	26.5 ± 6.62	-0.087	**0.006**	23.4 ± 5.7	0.021	0.424
Attention & processing speed	0.0 ± 0.8	-0.001	0.084	0.3 ± 0.6	-0.003	0.096	0.1 ± 0.9	-0.003	0.075
TMT part A*	31.8 ± 15.0	-0.022	0.416	26.1 ± 9.7	0.065	0.192	31.4 ± 12.2	0.060	0.145
Stroop card I*	47.1 ± 8.0	0.039	**0.011**	43.2 ± 8.8	-0.017	0.529	45.0 ± 8.4	-0.001	0.951
Stroop card II*	58.5 ± 10.6	0.012	0.539	54.9 ± 8.5	0.027	0.470	60.2 ± 13.2	0.001	0.969
Digit Span forwards	8.7 ± 1.9	0.001	0.871	9.0 ± 2.6	-0.010	0.294	9.4 ± 2.4	-0.016	0.055
LDST	34.5 ± 6.8	0.001	0.894	34.2 ± 4.7	-0.636	0.699	33.2 ± 7.4	0.005	0.798
Executive function	0.0 ± 0.7	0.001	0.505	0.3 ± 0.6	-0.005	0.065	0.2 ± 0.8	-0.004	0.052
TMT part B*	67.8 ± 29.3	0.052	0.494	61.0 ± 28.5	0.079	0.570	72.2 ± 42.7	-0.099	0.390
Stroop card III*	93.7 ± 22.6	-0.087	**0.021**	83.8 ± 14.7	0.141	**0.042**	96.6 ± 26.2	0.013	0.815
Digit Span backwards	6.1 ± 2.0	0.008	0.194	6.6 ± 1.8	0.002	0.877	6.6 ± 2.1	-0.011	0.222
WCST concepts	5.5 ± 0.9	0.002	0.592	5.6 ± 1.1	-0.009	0.296	5.80 ± 0.6	-0.010	0.144
Letter fluency	32.1 ± 9.9	0.134	**<0.001**[b]	36.1 ± 14.3	-0.108	**0.049**	38.9 ± 12.0	-0.062	0.173
Similarities	24.8 ± 4.7	0.006	0.645	25.5 ± 4.7	-0.034	0.122	26.2 ± 5.0	-0.011	0.556
Social cognition	0.0 ± 0.8	0.000	0.878	0.2 ± 0.7	-0.009	**0.007**	0.3 ± 0.7	-0.003	0.332
Happé ToM	11.8 ± 3.4	0.013	0.172	12.6 ± 3.7	-0.044	**0.011**	12.9 ± 2.9	-0.005	0.707
Happé non-Tom	11.7 ± 2.9	0.020	**0.013**	12.4 ± 2.8	-0.036	**0.017**	13.0 ± 2.6	-0.012	0.331
Ekman Faces	45.7 ± 6.4	0.038	**0.009**	47.0 ± 5.5	-0.028	0.293	47.10 ± 5.5	-0.013	0.548

Table 4.2.3 | Continued

Domain Test	healthy controls (n=39)			*MAPT* mutation carriers (n=15)			*GRN* mutation carriers (n=31)		
	baseline	β	*p*	baseline	β	*p*	baseline	β	*p*
Memory	0.0 ± 0.7	0.000	0.848	0.1 ± 1.3	-0.017	**<0.001**[b]	0.1 ± 0.9	-0.001	0.745
VAT	11.8 ± 0.6	0.001	0.740	11.4 ± 1.6	-0.012	**0.019**	11.5 ± 0.9	0.000	0.926
RAVLT imm. recall	42.6 ± 9.8	0.157	**<0.001**[b]	47.5 ± 9.7	-0.076	0.090	46.3 ± 10.6	-0.015	0.686
RAVLT del. recall	8.4 ± 3.2	0.050	**<0.001**[b]	9.7 ± 3.9	-0.048	**<0.001**[a,b]	9.4 ± 3.3	-0.000	0.983
RAVLT recognition	28.6 ± 2.1	0.014	0.127	29.0 ± 2.0	-0.022	0.176	29.2 ± 1.2	-0.009	0.505
Visuoconstruction	0.0 ± 0.8	-0.001	0.656	-0.2 ± 0.7	-0.005	0.266	0.0 ± 1.0	0.000	0.963
Block Design	36.5 ± 14.0	0.034	0.305	35.5 ± 20.8	-0.006	0.917	39.3 ± 18.5	-1.164	0.246
Clock drawing	12.6 ± 1.4	0.003	0.453	12.2 ± 1.3	-0.009	0.284	12.4 ± 1.8	0.005	0.475

Values indicate: mean ± standard deviation; β represents estimate of change over time. Composite domain scores are z-scores, individual test scores are raw scores. *Abbreviations: MAPT*, microtubule-associated protein tau; *GRN*, *progranulin*; BNT, Boston Naming Test; SAT, semantic association test; TMT, Trailmaking test; WAIS, Wechsler Adult Intelligence Scale; LDST, letter digit substitution test; WCST, Wisconsin Card Sorting Test; ToM, theory of mind; VAT, visual association test; RAVLT, Rey Auditory Verbal Learning Test, imm, immediate; del, delayed. Composite domain scores are expressed as z-scores, the individual test scores are raw scores. *P*-values represent comparisons to healthy controls. *Higher scores and β weights indicate worse performance. [a] remained significant after excluding converters from the analyses. [b] Survived Bonferroni correction for multiple comparisons. Significant comparisons are displayed in bold.

Table 4.2.4 | Cognitive trajectories in *MAPT*, *GRN*, bvFTD and nfvPPA converters, and non-converters

Domain Test	*MAPT* converters (n=5)			*GRN* converters (n=3)			bvFTD converters (n=6)			nfvPPA converters (n=2)			non-converters (n=38)		
	baseline	β	*p*	baseline	β	*p*	baseline	β	*p*	baseline	β	*p*	baseline	β	*p*
Language	0.1 ± 0.7	-0.028	**<0.001**[a]	0.6 ± 0.2	-0.007	0.299	0.1 ± 0.7	-0.025	**<0.001**[a]	0.6 ± 0.2	-0.014	0.061	0.1 ± 0.6	0.002	0.408
BNT	54.3 ± 6.9	-0.239	**<0.001**[a]	57.5 ± 2.1	-0.019	0.604	54.3 ± 6.9	-0.224	**<0.001**[a]	57.5 ± 2.1	-0.033	0.396	54.2 ± 4.2	-0.001	0.960
SAT	27.0 ± 1.4	-0.040	**0.034**	28.0 ± 1.4	0.006	0.805	27.0 ± 1.4	-0.036	0.052	28.0 ± 1.4	0.000	0.993	27.7 ± 2.0	0.013	0.127
ScreeLing phonology	24.0 ± 0.0	0.002	0.617	24.0 ± 0.0	-0.011	0.114	24.0 ± 0.0	0.004	0.358	24.0 ± 0.0	-0.017	**0.018**	23.8 ± 0.4	-0.002	0.551
Categorical fluency	25.8 ± 4.6	-0.250	**<0.001**[a]	28.0 ± 2.8	-0.149	**0.022**	25.8 ± 4.6	-0.237	**<0.001**[a]	28.0 ± 2.8	-0.170	**0.015**	24.0 ± 6.3	0.014	0.546
Attention & mental processing speed	0.3 ± 0.6	-0.010	**0.006**	0.2 ± 0.3	-0.013	**0.005**	0.3 ± 0.6	-0.010	**0.004**	0.2 ± 0.3	-0.013	**0.006**	0.1 ± 0.8	-0.001	0.321
TMT part A*	20.0 ± 6.3	0.067	0.448	25.0 ± 8.5	0.073	0.539	20.0 ± 6.3	0.065	0.449	25.0 ± 8.5	0.090	0.483	31.1 ± 11.8	0.051	0.181
Stroop card I*	44.0 ± 5.2	0.101	**0.030**	46.5 ± 6.4	0.058	0.349	44.0 ± 5.2	0.106	**0.020**	46.5 ± 6.4	0.044	0.503	44.4 ± 8.9	-0.020	0.345
Stroop card II*	58.5 ± 7.6	0.331	**<0.001**[a]	56.5 ± 0.7	0.186	**0.006**	57.5 ± 7.6	0.319	**<0.001**[a]	56.5 ± 0.7	0.194	**0.008**	58.8 ± 12.9	-0.032	0.217
Digit Span forwards	9.5 ± 1.7	0.010	0.609	9.0 ± 0.0	-0.038	0.146	9.5 ± 1.7	0.010	0.601	9.0 ± 0.0	-0.043	0.119	9.3 ± 2.6	-0.013	0.088
LDST	34.8 ± 6.7	-0.100	**0.012**	35.0 ± 0.0	-0.061	0.235	34.8 ± 6.7	-0.098	**0.011**	35.0 ± 0.0	-0.061	0.270	33.3 ± 6.9	0.004	0.809
Executive function	0.6 ± 0.4	-0.018	**<0.001**[a]	0.6 ± 0.1	-0.032	<0.001	0.6 ± 0.4	-0.020	**<0.001**	0.6 ± 0.1	-0.029	**<0.001**[a]	0.2 ± 0.8	-0.001	0.515
TMT part B*	57.0 ± 27.0	0.472	**0.038**	48.0 ± 32.5	1.448	**<0.001**[a]	57.0 ± 27.0	0.684	**0.006**	48.0 ± 32.5	0.921	**0.010**	71.2 ± 40.4	-0.132	0.195
Stroop card III*	87.5 ± 23.4	0.468	**<0.001**[a]	86.5 ± 7.8	0.734	**<0.001**[a]	87.5 ± 23.4	0.449	**<0.001**[a]	86.5 ± 7.8	0.815	**<0.001**[a]	93.7 ± 24.8	-0.026	0.577
Digit Span backwards	8.0 ± 1.4	-0.018	0.284	5.5 ± 0.7	-0.039	0.082	8.0 ± 1.4	-0.022	0.186	5.5 ± 0.7	-0.033	0.172	6.5 ± 2.0	-0.003	0.721
WCST concepts	6.0 ± 0.0	-0.015	0.193	6.0 ± 0.0	-0.040	**0.007**	6.0 ± 0.0	-0.021	0.073	6.0 ± 0.0	-0.032	**0.035**	5.7 ± 0.8	-0.006	0.323
Letter fluency	35.8 ± 7.9	-0.143	0.101	45.5 ± 17.7	-0.328	**0.010**	35.8 ± 7.9	-0.156	0.066	45.5 ± 17.7	-0.339	**0.013**	37.9 ± 13.0	-0.048	0.245
Similarities	29.0 ± 1.2	-0.151	**<0.001**[a]	29.0 ± 1.4	-0.175	**<0.001**[a]	29.0 ± 1.2	-0.155	**<0.001**[a]	29.0 ± 1.4	-0.175	**<0.001**[a]	25.5 ± 4.0	0.004	0.775
Social cognition	0.0 ± 1.0	-0.022	**<0.001**[a]	0.8 ± 0.1	-0.012	0.127	0.0 ± 1.0	-0.021	**<0.001**[a]	0.8 ± 0.1	-0.016	0.071	0.3 ± 0.7	-0.002	0.336
Happé ToM	12.3 ± 5.1	-0.096	**0.002**[a]	13.5 ± 2.1	0.017	0.672	12.3 ± 5.1	-0.078	**0.012**	13.5 ± 2.1	-0.019	0.669	12.8 ± 3.0	-0.012	0.380
Happé non-Tom	12.3 ± 2.4	-0.067	**0.010**	15.5 ± 0.7	-0.041	0.215	12.3 ± 2.4	-0.060	**0.016**	15.5 ± 0.7	-0.062	0.080	12.8 ± 2.7	-0.012	0.267
Ekman Faces	43.5 ± 6.1	-0.089	**0.023**	50.0 ± 0.0	-0.175	**0.001**[a]	43.5 ± 6.1	-0.118	**0.003**	50.0 ± 0.0	-0.127	**0.024**	47.3 ± 5.4	-0.001	0.965

Table 4.2.4 | Continued

Domain Test	*MAPT* converters (n=5)			*GRN* converters (n=3)			bvFTD converters (n=6)			nfvPPA converters (n=2)			non-converters (n=38)		
	baseline	β	*p*	baseline	β	*p*	baseline	β	*p*	baseline	β	*p*	baseline	β	*p*
Memory	-1.0 ± 2.0	-0.050	**<0.001**[a]	0.7 ± 0.8	0.002	0.751	-1.0 ± 2.0	-0.044	**<0.001**[a]	0.7 ± 0.8	-0.005	0.525	0.2 ± 0.8	-0.002	0.473
VAT	10.0 ± 2.4	-0.030	**0.005**	12.0 ± 0.0	0.004	0.675	10.0 ± 2.4	-0.027	**0.011**	12.0 ± 0.0	0.000	0.983	11.6 ± 0.8	-0.002	0.705
RAVLT imm. recall	42.5 ± 9.1	-0.241	**0.001**[a]	54.5 ± 19.1	-0.111	0.226	42.5 ± 9.1	-0.210	**0.003**	54.5 ± 19.1	-0.177	0.067	46.7 ± 10.0	-0.009	0.797
RAVLT del. recall	7.5 ± 5.5	-0.085	**<0.001**[a]	10.5 ± 5.0	0.002	0.951	7.5 ± 5.5	-0.080	**<0.001**[a]	10.5 ± 5.0	-0.002	0.954	9.7 ± 3.2	-0.009	0.359
RAVLT recognition	27.3 ± 3.1	-0.037	**0.005**	30.0 ± 0.0	-0.014	0.266	27.3 ± 3.1	-0.036	**0.004**	30.0 ± 0.0	-0.014	0.308	29.3 ± 1.1	-0.009	0.461
Visuoconstruction	0.2 ± 0.8	-0.009	0.217	0.2 ± 0.2	-0.010	0.312	0.2 ± 0.8	-0.008	0.250	0.2 ± 0.2	-0.013	0.237	-0.1 ± 1.0	0.000	0.895
Block Design	51.0 ± 27.1	-0.222	0.064	32.0 ± 1.4	-0.148	0.333	51.0 ± 27.1	-0.235	**0.042**	32.0 ± 1.4	-0.109	0.503	37.1 ± 18.5	-0.006	0.898
Clock drawing	11.8 ± 2.1	-0.002	0.876	13.5 ± 0.7	-0.014	0.459	11.8 ± 2.1	-0.001	0.966	13.5 ± 0.7	-0.023	0.281	12.3 ± 1.6	0.001	0.888

Values indicate: mean ± standard deviation; β represents estimate of change over time. Composite domain scores are z-scores, individual test scores are raw scores. *Abbreviations: MAPT*, microtubule-associated protein tau; *GRN*, *progranulin*; bvFTD, behavioural variant frontotemporal dementia; nfvPPA, non-fluent variant primary progressive aphasia; BNT, Boston Naming Test; SAT, semantic association test; TMT, Trailmaking test; WAIS, Wechsler Adult Intelligence Scale; LDST, letter digit substitution test; WCST, Wisconsin Card Sorting Test; ToM, theory of mind; VAT, visual association test; RAVLT, Rey Auditory Verbal Learning Test, imm, immediate; del, delayed. Composite domain scores are expressed as z-scores, the individual test scores are raw scores. *P*-values represent comparisons to non-converters. *Higher scores and β weights indicate worse performance. [a] Survived Bonferroni correction for multiple comparisons. Significant comparisons are displayed in bold.

Table 4.2.5 | ROC analyses on neuropsychological decline between 2 years before conversion and symptom onset in converters.

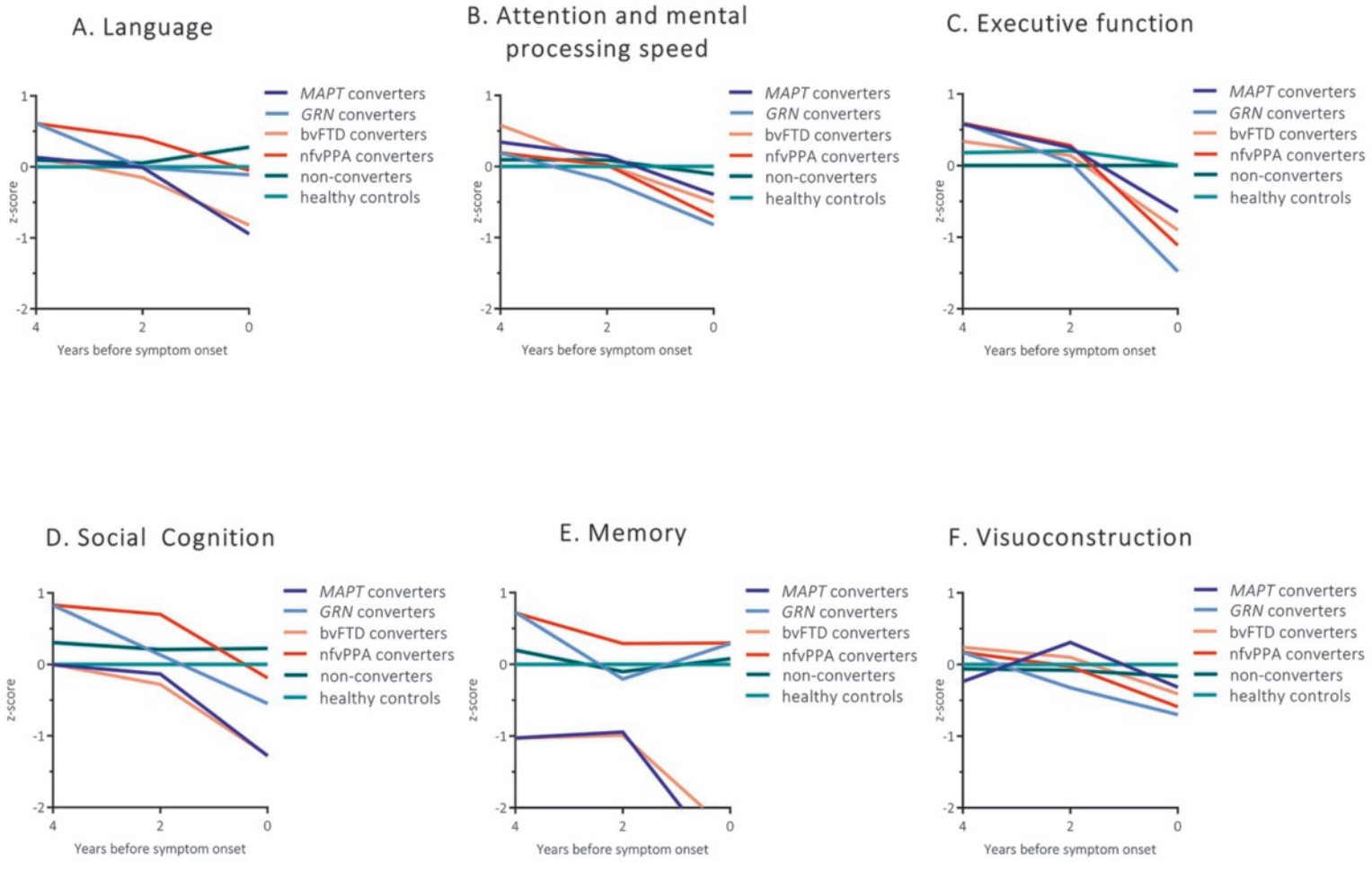
Domain and individual neuropsychological tests	bvFTD vs. nfvPPA converters						*MAPT* vs. *GRN* converters					
	AUC	95% CI	*p*	Optimal Δ*	Sensitivity (%)	Specificity (%)	AUC	95% CI	*p*	Optimal Δ**	Sensitivity (%)	Specificity (%)
Language	0.667	[0.29-1.00]	0.505	–	–	–	0.867	[0.51-1.00]	0.101	–	–	–
BNT	0.708	[0.34-1.00]	0.405	–	–	–	0.90	[0.67-1.00]	0.074	–	–	–
SAT	0.625	[0.24-1.00]	0.617	–	–	–	0.833	[0.54-1.00]	0.136	–	–	–
ScreeLing phonology	1.000	[1.00-1.00]	**0.046**	-0.5	100	100	0.700	[0.21-1.00]	0.371	–	–	–
Categorical fluency	0.833	[0.53-1.00]	0.182	–	–	–	1.000	[1.00-1.00]	**0.025**	-6.5	100	100
Attention & mental processing speed	0.750	[0.41-1.00]	0.317	–	–	–	0.600	[0.19-1.00]	0.655	–	–	–
TMT part A	0.542	[0.00-1.00]	0.868	–	–	–	0.50	[0.05-0.95]	1.000	–	–	–
Stroop card I	0.583	[0.19-0.97]	0.739	–	–	–	0.600	[0.17-1.00]	0.655	–	–	–
Stroop card II	0.583	[0.12-1.00]	0.739	–	–	–	0.667	[0.22-1.00]	0.456	–	–	–
Digit Span forwards WAIS-III	0.750	[0.40-1.00]	0.317	–	–	–	0.633	[0.23-1.00]	0.551	–	–	–
LDST	0.625	[0.23-1.00]	0.617	–	–	–	0.633	[0.22-1.00]	0.551	–	–	–
Executive function	0.583	[0.19-0.98]	0.739	–	–	–	0.733	[0.36-1.00]	0.297	–	–	–
TMT part B	0.667	[0.29-1.00]	0.617	–	–	–	0.900	[0.64-1.00]	0.121	–	–	–
Stroop card III	0.833	[0.51-1.00]	0.182	–	–	–	0.600	[0.15-1.00]	0.655	–	–	–
Digit Span backwards WAIS-III	0.542	[0.09-1.00]	0.868	–	–	–	0.567	[0.14-0.99]	0.766	–	–	–
WCST concepts	0.500	[0.10-0.90]	1.000	–	–	–	0.700	[0.32-1.00]	0.371	–	–	–
Letter fluency	1.000	[1.00-1.00]	**0.046**	-16	100	100	0.767	[0.36-1.00]	0.233	–	–	–
Similarities WAIS-III	0.625	[0.14-1.00]	0.617	–	–	–	0.567	[0.13-1.00]	0.766	–	–	–
Social cognition	0.500	[0.00-1.00]	1.000	–	–	–	0.667	[0.13-1.00]	0.456	–	–	–
Happé ToM	0.458	[0.00-1.00]	0.868	–	–	–	0.700	[0.21-1.00]	0.371	–	–	–
Happé non-Tom	0.500	[0.00-1.00]	1.000	–	–	–	0.667	[0.22-1.00]	0.456	–	–	–
Ekman Faces	0.667	[0.15-1.00]	0.505	–	–	–	0.567	[0.07-1.00]	0.766	–	–	–

Table 4.2.5 | Continued

Domain and individual neuropsychological tests	bvFTD vs. nfvPPA converters						*MAPT* vs. *GRN* converters					
	AUC	95% CI	*p*	Optimal Δ*	Sensitivity (%)	Specificity (%)	AUC	95% CI	*p*	Optimal Δ**	Sensitivity (%)	Specificity (%)
Memory	0.750	[0.41-1.00]	0.317	–	–	–	0.933	[0.75-1.00]	0.053	–	–	–
VAT	0.792	[0.45-1.00]	0.243	–	–	–	0.933	[0.75-1.00]	0.053	–	–	–
RAVLT immediate recall	0.667	[0.15-1.00]	0.505	–	–	–	0.600	[0.09-1.00]	0.655	–	–	–
RAVLT delayed recall	0.667	[0.27-1.00]	0.505	–	–	–	0.867	[0.58-1.00]	0.101	–	–	–
RAVLT recognition	0.750	[0.37-1.00]	0.317	–	–	–	0.900	[0.65-1.00]	0.074	–	–	–
Visuoconstruction	0.583	[0.19-0.98]	0.739	–	–	–	0.600	[0.19-1.00]	0.655	–	–	–
Block Design WAIS-III	0.808	[0.35-1.00]	0.405	–	–	–	0.500	[0.07-0.93]	1.000	–	–	–
Clock drawing	0.667	[0.29-1.00]	0.505	–	–	–	0.600	[0.16-1.00]	0.655	–	–	–

Abbreviations: AUC, area under the curve; CI, confidence interval; bvFTD, behavioural variant frontotemporal dementia; nfvPPA, non-fluent variant frontotemporal dementia; *MAPT,* microtubule-associated protein tau; *GRN*, progranulin; BNT, Boston Naming Test; SAT, semantic association test; TMT, Trailmaking test; WAIS, Wechsler Adult Intelligence Scale; LDST, letter digit substitution test; WCST, Wisconsin Card Sorting Test; ToM, theory of mind; VAT, visual association test; RAVLT, Rey Auditory Verbal Learning Test. *negative delta represents decline in test performance in nfvPPA vs. bvFTD (i.e. when a converter declines on this particular task, he/she is more likely to develop nfvPPA. **negative delta represents decline in test performance in *MAPT* vs *GRN* (i.e. when a converter declines on this particular task, he/she is more likely to have a underlying *MAPT* mutation.

Figure 4.2.2 | **Multilevel linear regression model displaying longitudinal decline (4 years, 2 years and after symptom onset) in composite domain z-score** in *MAPT* converters (dark blue), *GRN* converters (light blue), bvFTD converters (pink), nfvPPA converters (red), non-converters (dark green) and healthy controls (light green). Models are displayed per cognitive domain: A) social cognition, B) attention and mental processing speed, C) executive functioning, D) memory, E) visuoconstruction, and F) language. *NB:* the healthy controls have a mean z-score of zero by default as the z-scores of mutation carriers were based on that (raw score minus mean score of healthy controls, divided by the standard deviation of healthy controls). *Abbreviations*: *MAPT*, microtubule-associated protein tau; *GRN*, progranulin, bvFTD, behavioural variant frontotemporal dementia; nfvPPA, non-fluent variant primary progressive aphasia.


A. Language
B. Attention and mental processing speed
C. Executive function
D. Social Cognition
E. Memory
F. Visuoconstruction
MAPT converters
GRN converters
bvFTD converters
nfvPPA converters
non-converters
healthy controls
z-score
Years before symptom onset

Classification between converters and non-converters

Between 4 and 2 years before symptom onset, the delta domain and individual neuropsychological test scores failed to distinguish significantly between converters and non-converters. Between 2 years before symptom onset and symptom onset decline on categorical fluency was predictive of an underlying *MAPT* mutation (p=0.025; Table 4.2.5). Decline on ScreeLing phonology (p=0.046) and letter fluency (p=0.046) was predictive of conversion to nfvPPA (Table 4.2.5).

Discussion

This study examined a large cohort of at-risk participants from *GRN* and *MAPT* FTD families by means of neuropsychological assessment during a four-year follow-up. Within the study time window, eight mutation carriers became symptomatic. Converters with a *MAPT* and *GRN* mutation had mutual as well as gene-specific profiles of cognitive decline. Cognitive decline on categorical fluency between 2 years before conversion and symptom onset was predictive for an underlying *MAPT* mutation, and decline on ScreeLing phonology and letter fluency was predictive for conversion to nfvPPA. These results suggest that neuropsychological assessment could provide sensitive clinical biomarkers to identify and track FTD mutation carriers at-risk of converting to the symptomatic stage. These findings hold potential for improving early clinical diagnosis by identifying the most sensitive neuropsychological tests for conversion, and use in upcoming disease-modifying clinical trials.

Following the *MAPT* mutation carriers over a four-year period, we found significant decline in language, social cognition and memory. This is consistent with findings from previous presymptomatic familial FTD studies, in which both cross-sectional [9-11,33] and longitudinal [8] decline was found. Specifically, in our first follow-up study [8], we demonstrated decline in the domains language, social cognition and memory 5 to 8 years before estimated symptom onset. It should be taken into account that this study made use of estimated onset as a proxy, instead of actual symptom onset as in the present study – but the similar profile of decline confirms the presence of early changes in these three domains. As in our previous study, the present results are largely driven by the converters. This could suggest that neuropsychological test scores remain static while mutation carriers are presymptomatic, and cognitive decline starts only near or at symptom onset [34-36], suggesting an explosive rather than gradual start of the symptomatic disease stage. Alternatively, we might be unable to pick up subtle cognitive changes in presymptomatic mutation carriers due to lack of power. Also, although well-validated, most of our neuropsychological tests were not developed for repeated administration in a preclinical population [37]. We therefore cannot rule out that familiarity and/or practice effects are obscuring subtle cognitive decline, a notion that seems to be underwritten by improvement in social cognition and memory in controls, but not mutation carriers.

In our exploratory analyses in converters, we discovered both common as well as mutation-specific profiles of cognitive decline in *MAPT* and *GRN*. In both mutations, decline in attention, mental processing speed and executive function was found – while only converters with a *MAPT* mutation demonstrated

decline on language, memory and social cognition. Previous studies in familial FTD also point to distinct profiles for *MAPT* and *GRN* [8,10-12], and are largely consistent with our present findings. Another important aspect is the longitudinal tracking of the different clinical phenotypes. The similar patterns of cognitive decline in bvFTD as *MAPT*, and nfvPPA as *GRN* is related to the dominant genotype in each group (e.g. all nfvPPA converters have a *GRN* mutation). These findings suggest that neuropsychological assessment can be used to track the different mutations and phenotypes from the presymptomatic to the symptomatic stage, which is advantageous considering the need for good clinical endpoints in future disease-modifying trials.

Extending the findings from our first follow-up study [8], we demonstrated significant decline on the RAVLT recall in presymptomatic *MAPT* mutation carriers. The additional finding that lower memory scores over time were also found in *MAPT*, and not *GRN* converters – suggesting a mutation-specific aetiology – corroborates this. Although memory loss has been described in *GRN* [38-39], this is usually a later symptom, while episodic memory impairment has been found as the presenting and most prominent symptom in *MAPT* [7,40-41]. Interestingly, the Genetic Frontotemporal dementia Initiative (GENFI) consortium revealed hippocampal atrophy in presymptomatic *MAPT* from 15 years before estimated symptom onset [10], and as this medial temporal structure is critical for episodic memory processing [42] this offers a good explanation for our findings. In line with earlier studies [42-43], we did find deficits in verbal recall but not visual-associative memory. Semantically loaded tasks such as the RAVLT can be particularly more difficult than visual memory tasks like the VAT, as a result of the prominent semantic impairments seen early in *MAPT*-associated FTD [44]. Our results contribute to the present thinking that memory deficits can be an integral part of the clinical spectrum [42], and comprehensive memory tasks should therefore be incorporated in the standard diagnostic work-up.

Knowing the cognitive profile of decline indicative for conversion is important to get more insight into the timing of clinical changes in the earliest disease stage. We found that conversion can be predicted based on cognitive decline in the 2 years prior to symptom onset, but not earlier. As the cognitive decline was part of the diagnostic process of determining conversion, this is not a surprising finding. However, it does suggest a more explosive disease development with cognitive decline accelerating rapidly in proximity of symptom onset, which is in line with evidence from a large familial Alzheimer's Disease cohort [45]. By selectively choosing tests within the domains that have prognostic abilities, the neuropsychological battery can be shortened, which would benefit patient burden and helps cutting healthcare expenses. Especially fluency tasks seem to be promising candidates, as they were able to distinguish accurately between future phenotype and underlying genotype. The latter is essential for patient stratification in future clinical trials targeting specific pathologies, and ideally these interventions should be applied in the presymptomatic stage [46]. Reliable phenotypic prediction furthermore optimizes the diagnostic process by shortening the current diagnostic delay [47], and is helpful for the patient, caregiver and clinician in knowing what disease presentation and course to expect. Verbal fluency tests are widely used in dementia diagnosis setting [48], and are affected in both presymptomatic [8,11] and symptomatic FTD [9-50]. Future research could additionally investigate the use of qualitative assessment of verbal fluency (e.g. clustering, switching between clusters), as recent research [49] points

to differences between FTD and PPA subtypes – making this a promising application of verbal fluency for a precise clinical differentiation in presymptomatic and early stage FTD.

Key strengths of our study constitute our longitudinal design, spanning a four-year follow-up of at-risk participants from both *MAPT* and *GRN* families. Although our group of converters is currently small, this is the first study tracking FTD mutation carriers from the presymptomatic to symptomatic disease stage. Being aware of the caveats of small sample sizes and administering a large amount of neuropsychological tests with respect to statistical power, our results warrant replication in our cohort as well as larger international cohorts such as GENFI [10], in which with the passing of time more mutation carriers will approach symptom onset and/or convert to clinical FTD. The dropout rate is very low, creating balanced data sets across the three time points. Additionally, use of multilevel linear modelling further handles efficiently with missing data. Directions for future research entail the development of neuropsychological tasks more suited to administer in the presymptomatic phase (robust to ceiling effects) and repeated administration (robust to practice and able to measure small changes). More extensive quantification tools of behavioural functioning are also needed to capture the entire clinical spectrum of (presymptomatic) FTD, as well as assessment methods that rely less on the accuracy of informant report [37]. A disadvantage of the study is the fact that the neuropsychological assessment was part of the clinical assessment with which we determined conversion to the symptomatic stage. This has likely led to a circular reasoning, as we demonstrated that converters declined over time, while cognitive decline was considered a prerequisite for conversion. Ideally, the tests assessed in our study should not have been used in the diagnosis of conversion. However, in our multidisciplinary meeting we followed the international consensus criteria for bvFTD [3] and PPA [6], using all available clinical information – e.g. MR imaging of the brain, anamnestic and heteroanamnestic information, behavioural and neuropsychiatric questionnaires, unblinding of genetic status – so that symptom onset did not solely depend on the neuropsychological assessment. Furthermore, as the multilevel model assumes a linear relationship between genetic status and cognitive decline over time, we could have missed non-linear effects over time. Lastly, the analyses on the non-converters and controls were performed by using the original baseline and follow-up visits, regardless of e.g. age and time to estimated symptom onset. It is possible that these analyses therefore lost some sensitivity to detect cognitive decline over time. However, as between-group analyses on age and estimated years to symptom onset in converters, non-converters, and controls did not show significant differences (respectively p=0.99 and p=0.19), we believe this effect is minimal.

Our study investigates longitudinal neuropsychological performance in a large cohort of at-risk individuals from genetic FTD families. We provide evidence of mutation-specific cognitive decline when moving from the presymptomatic into symptomatic stage, and of neuropsychological trajectories predicting symptom onset. These results suggest the potential biomarker value of neuropsychological assessment in both disease-monitoring and predicting conversion to clinical FTD.

Supplementary Table 4.2.1 | Raw neuropsychological test scores of healthy controls, *MAPT* mutation carriers, and *GRN* mutation carriers at four years before symptom onset (-4), two years before symptom onset (-2) and at symptom onset (0).

Cognitive domains	healthy controls (n=39)			*MAPT* mutation carriers (n=15)			*GRN* mutation carriers (n=31)		
and individual tests	-4	-2	0	-4	-2	0	-4	-2	0
Language	0.0 ± 0.6	0.0 ± 0.5	0.0 ± 0.7	0.2 ± 0.6	0.1 ± 0.6	-0.3 ± 1.0	0.1 ± 0.7	0.0 ± 0.4	0.3 ± 0.4
BNT	53.4 ± 4.5	54.4 ± 8.0	54.8 ± 4.5	52.6 ± 5.3	53.0 ± 7.1	50.9 ± 9.4	55.1 ± 3.7	56.6 ± 2.6	56.6 ± 2.2
SAT	27.8 ± 1.1	28.4 ± 1.3	27.6 ± 1.6	27.9 ± 1.5	28.5 ± 2.0	27.5 ± 2.2	27.5 ± 2.0	27.9 ± 1.4	28.5 ± 1.0
ScreeLing phonology	23.5 ± 0.8	23.7 ± 0.7	23.6 ± 0.9	23.9 ± 0.3	24.0 ± 0.1	23.7 ± 0.6	23.8 ± 0.5	23.8 ± 0.4	23.7 ± 0.5
Categorical fluency	23.9 ± 4.9	24.5 ± 6.4	25.4 ± 6.4	26.5 ± 6.6	25.6 ± 4.9	23.3 ± 7.5	23.4 ± 5.7	24.2 ± 5.3	25.3 ± 5.9
Attention & processing speed	0.0 ± 0.8	0.0 ± 0.8	0.0 ± 0.8	0.3 ± 0.6	0.3 ± 0.5	0.0 ± 0.9	0.1 ± 0.9	0.0 ± 0.9	-0.3 ± 0.9
TMT part A*	31.8 ± 15.0	30.5 ± 12.9	28.7 ± 10.4	26.1 ± 9.7	25.6 ± 7.3	29.1 ± 11.8	31.4 ± 12.2	31.6 ± 12.0	35.5 ± 13.4
Stroop card I*	47.1 ± 8.0	47.6 ± 8.3	48.4 ± 10.1	43.2 ± 8.8	42.3 ± 6.4	44.2 ± 7.8	45.0 ± 8.4	45.9 ± 8.1	47.9 ± 8.4
Stroop card II*	58.5 ± 10.6	58.7 ± 10.9	56.0 ± 11.1	54.9 ± 8.5	53.5 ± 7.0	57.7 ± 15.6	60.2 ± 13.2	60.0 ± 12.9	61.3 ± 13.5
Digit Span forwards	8.7 ± 1.9	9.0 ± 1.8	8.8 ± 1.4	9.0 ± 2.6	9.5 ± 2.2	8.6 ± 2.5	9.4 ± 2.4	9.0 ± 2.4	8.4 ± 1.7
LDST	34.5 ± 6.8	34.8 ± 8.1	35.2 ± 6.7	34.2 ± 4.7	33.1 ± 6.3	33.6 ± 7.7	33.2 ± 7.4	33.1 ± 6.8	33.4 ± 6.6
Executive function	0.0 ± 0.7	0.0 ± 0.6	0.0 ± 0.6	0.3 ± 0.6	0.2 ± 0.6	-0.1 ± 0.9	0.2 ± 0.8	0.2 ± 0.7	-0.2 ± 0.8
TMT part B*	67.8 ± 29.3	69.6 ± 34.4	67.6 ± 37.7	61.0 ± 28.5	61.6 ± 27.7	71.9 ± 36.0	72.2 ± 42.7	65.5 ± 26.4	76.6 ± 45.7
Stroop card III*	93.7 ± 22.6	92.3 ± 24.1	86.4 ± 18.6	83.8 ± 14.7	83.4 ± 22.3	85.6 ± 25.3	96.6 ± 26.2	92.9 ± 24.5	95.1 ± 23.7
Digit Span backwards	6.1 ± 2.0	6.5 ± 2.0	6.5 ± 2.0	6.6 ± 1.8	7.4 ± 2.6	7.3 ± 2.5	6.6 ± 2.1	7.2 ± 2.4	6.0 ± 1.8
WCST concepts	5.5 ± 0.9	5.4 ± 1.5	5.6 ± 1.1	5.6 ± 1.1	5.4 ± 1.6	5.2 ± 1.5	5.8 ± 0.6	5.6 ± 0.9	5.3 ± 1.1
Letter fluency	32.1 ± 9.9	39.5 ± 13.9	40.4 ± 11.3	36.1 ± 14.3	39.0 ± 14.0	35.1 ± 14.3	38.9 ± 12.0	44.1 ± 15.4	40.8 ± 14.2
Similarities	24.8 ± 4.7	25.2 ± 5.2	25.4 ± 4.6	25.5 ± 4.7	24.7 ± 5.3	23.4 ± 5.0	26.2 ± 5.0	27.3 ± 3.8	25.6 ± 5.2
Social cognition	0.0 ± 0.8	0.0 ± 0.8	0.0 ± 0.8	0.2 ± 0.7	0.0 ± 0.8	-0.3 ± 1.1	0.3 ± 0.7	0.2 ± 0.8	0.1 ± 0.8
Happé ToM	11.8 ± 3.4	12.6 ± 3.2	12.5 ± 3.4	12.6 ± 3.7	13.2 ± 3.0	11.0 ± 3.8	12.9 ± 2.9	13.3 ± 3.8	13.2 ± 3.2
Happé non-Tom	11.7 ± 2.9	12.7 ± 2.7	12.8 ± 2.7	12.4 ± 2.8	11.6 ± 3.3	11.5 ± 3.5	13.0 ± 2.6	13.1 ± 2.8	13.2 ± 2.6
Ekman Faces	45.7 ± 6.4	46.7 ± 6.2	48.0 ± 6.2	47.0 ± 5.5	47.8 ± 6.5	47.5 ± 8.4	47.1 ± 5.5	49.0 ± 5.2	48.7 ± 5.6

Supplementary Table 4.2.1 | Continued

Cognitive domains and individual tests	healthy controls (n=39)			*MAPT* mutation carriers (n=15)			*GRN* mutation carriers (n=31)		
	-4	-2	0	-4	-2	0	-4	-2	0
Memory	0.0 ± 0.7	0.0 ± 0.7	0.0 ± 0.8	0.1 ± 1.3	-0.3 ± 1.5	-0.9 ± 3.0	0.1 ± 0.9	-0.2 ± 0.9	0.0 ± 0.9
VAT	11.8 ± 0.6	11.9 ± 0.3	11.8 ± 0.4	11.4 ± 1.6	11.5 ± 1.3	10.9 ± 2.9	11.5 ± 0.9	11.7 ± 0.8	11.6 ± 0.8
RAVLT imm. recall	42.6 ± 9.8	50.5 ± 8.8	51.1 ± 10.7	47.5 ± 9.7	51.7 ± 10.5	51.4 ± 12.2	46.3 ± 10.6	51.0 ± 9.7	53.8 ± 10.2
RAVLT del. recall	8.4 ± 3.2	10.5 ± 2.6	11.2 ± 3.0	9.7 ± 3.9	10.7 ± 3.2	9.7 ± 4.5	9.4 ± 3.3	10.9 ± 3.0	12.1 ± 2.9
RAVLT recognition	28.6 ± 2.1	29.8 ± 4.5	29.3 ± 1.3	29.0 ± 2.0	29.3 ± 1.3	28.6 ± 2.9	29.2 ± 1.2	29.3 ± 1.1	29.5 ± 1.1
Visuoconstruction	0.0 ± 0.8	0.0 ± 0.8	0.0 ± 0.8	-0.2 ± 0.7	-0.1 ± 0.7	-0.4 ± 0.9	0.0 ± 1.0	0.0 ± 0.8	-0.1 ± 1.0
Block Design	36.5 ± 14.0	38.8 ± 13.6	38.9 ± 13.4	35.5 ± 20.8	36.4 ± 14.6	38.3 ± 14.2	39.3 ± 18.5	38.6 ± 14.2	36.0 ± 15.5
Clock drawing	12.6 ± 1.4	13.0 ± 1.1	12.8 ± 0.9	12.2 ± 1.3	13.0 ± 0.8	12.1 ± 1.1	12.4 ± 1.8	12.9 ± 0.9	12.7 ± 1.0

Values indicate: mean ± standard deviation. Composite domain scores are z-scores, individual test scores are raw scores. *Abbreviations: MAPT*, microtubule-associated protein tau; *GRN*, *progranulin*; BNT, Boston Naming Test; SAT, semantic association test; TMT, Trailmaking test; WAIS, Wechsler Adult Intelligence Scale; LDST, letter digit substitution test; WCST, Wisconsin Card Sorting Test; ToM, theory of mind; VAT, visual association test; RAVLT, Rey Auditory Verbal Learning Test, imm, immediate; del, delayed. Composite domain scores are expressed as z-scores, the individual test scores are raw scores. *Higher scores indicate worse performance.

Supplementary Table 4.2.2 | Raw neuropsychological test scores of *MAPT* converters, *GRN* converters, bvFTD converters, nfvPPA converters and non-converters at four years before symptom onset

Cognitive domains and individual tests	*MAPT*/bvFTD converters (n=5)			*GRN* converters (n=3)			nfvPPA converters (n=2)			non-converters (=38)		
	-4	-2	0	-4	-2	0	-4	-2	0	-4	-2	0
Language	0.1 ± 0.7	0.0 ± 0.9	-0.9 ± 1.3	0.6 ± 0.2	0.0 ± 0.7	-0.1 ± 0.2	0.6 ± 0.2	0.1 ± 0.4	-0.1 ± 0.2	0.1 ± 0.6	0.1 ± 0.4	0.3 ± 0.4
BNT	54.3 ± 6.9	53.8 ± 9.4	45.8 ± 14.2	57.5 ± 2.1	56.3 ± 3.8	55.7 ± 2.5	57.5 ± 2.1	55.6 ± 4.1	57.0 ± 1.4	54.2 ± 4.2	55.6 ± 4.1	55.9 ± 3.1
SAT	27.0 ± 1.4	28.0 ± 2.9	26.4 ± 3.2	28.0 ± 1.4	28.3 ± 1.5	28.7 ± 0.6	28.0 ± 1.4	28.1 ± 1.4	28.5 ± 0.7	27.7 ± 2.0	28.1 ± 1.4	28.4 ± 1.1
ScreeLing phonology	24.0 ± 0.0	23.9 ± 0.2	24.0 ± 0.0	24.0 ± 0.0	23.7 ± 0.6	23.2 ± 0.3	24.0 ± 0.0	23.9 ± 0.3	23.0 ± 0.0	23.8 ± 0.4	23.9 ± 0.3	23.7 ± 0.5
Categorical fluency	25.8 ± 4.6	37.4 ± 3.3	15.8 ± 2.2	28.0 ± 2.8	23.0 ± 7.0	19.7 ± 4.6	28.0 ± 2.8	24.8 ± 5.3	21.0 ± 5.7	24.0 ± 6.3	24.8 ± 5.3	26.4 ± 5.7
Attention & mental speed	0.3 ± 0.6	0.1 ± 0.6	-0.4 ± 1.0	0.2 ± 0.3	-0.2 ± 0.5	-0.8 ± 0.4	0.2 ± 0.3	0.1 ± 0.8	-0.7 ± 0.6	0.1 ± 0.8	0.1 ± 0.8	-0.1 ± 0.9
TMT part A*	20.0 ± 6.3	26.6 ± 8.9	29.6 ± 14.7	25.0 ± 8.5	33.7 ± 9.6	36.7 ± 13.1	25.0 ± 8.5	29.8 ± 11.5	31.5 ± 13.4	31.1 ± 11.8	29.8 ± 11.5	33.6 ± 13.1
Stroop card I*	44.0 ± 5.2	43.4 ± 6.2	48.6 ± 6.8	46.5 ± 6.4	47.3 ± 5.1	53.0 ± 5.2	46.5 ± 6.4	44.7 ± 8.2	50.0 ± 0.0	44.4 ± 8.9	44.7 ± 8.2	45.8 ± 8.6
Stroop card II*	58.5 ± 7.6	58.0 ± 3.8	72.8 ± 14.6	56.5 ± 0.7	58.3 ± 6.0	66.3 ± 1.2	56.5 ± 0.7	57.9 ± 12.8	66.0 ± 1.4	58.8 ± 12.9	57.9 ± 12.8	57.6 ± 13.7
Digit Span forwards	9.5 ± 1.7	9.2 ± 2.3	9.0 ± 1.9	9.0 ± 0.0	7.7 ± 0.6	6.7 ± 1.5	9.0 ± 0.0	9.3 ± 2.5	6.0 ± 1.4	9.3 ± 2.6	9.3 ± 2.5	8.5 ± 2.0
LDST	34.8 ± 6.7	32.6 ± 6.9	30.8 ± 7.1	35.0 ± 0.0	34.0 ± 6.1	31.0 ± 3.5	35.0 ± 0.0	33.1 ± 6.8	32.0 ± 4.2	33.3 ± 6.9	33.1 ± 6.8	34.1 ± 7.1
Executive function	0.6 ± 0.4	0.3 ± 0.4	0.6 ± 1.1	0.6 ± 0.1	0.0 ± 0.5	-1.5 ± 0.7	0.6 ± 0.1	0.2 ± 0.7	-1.1 ± 0.2	0.2 ± 0.8	0.2 ± 0.7	0.0 ± 0.7
TMT part B*	57.0 ± 27.0	56.2 ± 20.9	86.6 ± 53.0	48.0 ± 32.5	64.0 ± 21.1	146.0 ± 82.0	48.0 ± 32.5	65.4 ± 28.0	88.0**	71.2 ± 40.4	65.4 ± 28.0	68.9 ± 35.0
Stroop card III*	87.5 ± 23.4	87.2 ± 15.7	105.4 ± 27.2	86.5 ± 7.8	101.0 ± 24.6	127.0± 7.8	86.5 ± 7.8	89.3 ± 25.1	124.5 ± 9.2	93.7 ± 24.8	89.3 ± 25.1	86.6 ± 21.7
Digit Span backwards	8.0 ± 1.4	7.2 ± 1.6	6.8 ± 2.6	5.5 ± 0.7	5.0 ± 1.0	4.0 ± 1.0	5.5 ± 0.7	7.4 ± 2.6	4.0 ± 1.4	6.5 ± 2.0	7.4 ± 2.6	6.6 ± 2.0
WCST concepts	6.0 ± 0.0	6.0 ± 0.0	4.6 ± 1.9	6.0 ± 0.0	6.0 ± 0.0	3.3 ± 1.2	6.0 ± 0.0	5.4 ± 1.3	4.0 ± 0.0	5.7 ± 0.8	5.4 ± 1.3	5.5 ± 0.9
Letter fluency	35.8 ± 7.9	37.4 ± 9.8	29.6 ± 10.6	45.5 ± 17.7	47.0 ± 17.5	28.0 ± 6.2	45.5 ± 17.7	42.8 ± 15.6	31.5 ± 2.1	37.9 ± 13.0	42.8 ± 15.6	41.2 ± 14.5
Similarities	29.0 ± 1.2	26.6 ± 3.0	21.4 ± 5.5	29.0 ± 1.4	26.3 ± 3.2	19.7 ± 6.0	29.0 ± 1.4	26.5 ± 4.7	20.0 ± 8.5	25.5 ± 4.0	26.5 ± 4.7	49.7 ± 4.7
Social cognition	0.0 ± 1.0	-0.1 ± 0.7	-1.3 ± 1.0	0.8 ± 0.1	0.1 ± 1.0	-0.5 ± 1.4	0.8 ± 0.1	0.2 ± 0.8	-0.2 ± 1.8	0.3 ± 0.7	0.2 ± 0.8	0.2 ± 0.7
Happé ToM	12.3 ± 5.1	12.6 ± 2.8	8.2 ± 3.0	13.5 ± 2.1	11.3 ± 6.4	11.0 ± 4.4	13.5 ± 2.1	13.5 ± 3.4	12.5 ± 5.0	12.8 ± 3.0	13.5 ± 3.4	13.2 ± 3.1
Happé non-Tom	12.3 ± 2.4	13.0 ± 2.0	9.0 ± 3.5	15.5 ± 0.7	12.7 ± 4.9	10.7 ± 4.7	15.5 ± 0.7	12.6 ± 3.0	12.5 ± 5.0	12.8 ± 2.7	12.6 ± 3.0	13.3 ± 2.4
Ekman Faces	43.5 ± 6.1	43.4 ± 5.1	40.6 ± 6.9	50.0 ± 0.0	51.7 ± 5.7	45.3 ± 9.0	50.0 ± 0.0	49.1 ± 5.3	45.0 ± 12.7	47.3 ± 5.4	49.1 ± 5.3	49.7 ± 5.6

Supplementary Table 4.2.2 | Continued

Cognitive domains and individual tests	*MAPT*/bvFTD converters (n=5)			*GRN* converters (n=3)			nfvPPA converters (n=2)			non-converters (=38)		
	-4	-2	0	-4	-2	0	-4	-2	0	-4	-2	0
Memory	-1.0 ± 2.0	-0.9 ± 2.1	-2.9 ± 1.0	0.7 ± 0.8	-0.2 ± 1.0	0.3 ± 0.7	0.7 ± 0.8	-0.1 ± 0.9	0.3 ± 1.0	0.2 ± 0.8	-0.1 ± 0.9	0.1 ± 0.9
VAT	10.0 ± 2.4	11.0 ± 2.2	9.4 ± 4.7	12.0 ± 0.0	11.3 ± 0.6	12.0 ± 0.0	12.0 ± 0.0	11.7 ± 0.7	12.0 ± 0.0	11.6 ± 0.8	11.7 ± 0.7	11.6 ± 0.8
RAVLT imm. recall	42.5 ± 9.1	48.0 ± 10.2	40.0 ± 9.7	54.5 ± 19.1	54.0 ± 13.5	52.7 ± 16.5	54.5 ± 19.1	51.4 ± 9.7	52.5 ± 23.3	46.7 ± 10.0	51.4 ± 9.7	54.9 ± 9.4
RAVLT del. recall	7.5 ± 5.5	9.4 ± 3.5	6.2 ± 4.1	10.5 ± 5.0	12.0 ± 2.6	12.0 ± 2.6	10.5 ± 5.0	11.0 ± 3.0	12.5 ± 3.5	9.7 ± 3.2	11.0 ± 3.0	12.0 ± 3.1
RAVLT recognition	27.3 ± 3.1	29.2 ± 1.8	26.6 ± 4.3	30.0 ± 0.0	30.0 ± 0.0	29.7 ± 0.6	30.0 ± 0.0	29.3 ± 1.1	29.5 ± 0.7	29.3 ± 1.1	29.3 ± 1.1	29.6 ± 1.0
Visuoconstruction	0.2 ± 0.8	0.3 ± 0.5	-0.3 ± 0.6	0.2 ± 0.2	-0.3 ± 0.7	-0.7 ± 0.6	0.2 ± 0.2	-0.1 ± 0.8	-0.6 ± 0.9	-0.1 ± 1.0	-0.1 ± 0.8	-0.2 ± 1.0
Block Design	51.0 ± 27.1	44.0 ± 15.2	36.4 ± 15.9	32.0 ± 1.4	29.3 ± 8.5	22.3 ± 13.1	32.0 ± 1.4	37.8 ± 14.4	27.5 ± 13.4	37.1 ± 18.5	37.8 ± 14.4	38.3 ± 14.6
Clock drawing	11.8 ± 2.1	13.2 ± 0.4	12.4 ± 0.9	13.5 ± 0.7	13.0 ± 1.0	12.7 ± 0.6	13.5 ± 0.7	12.9 ± 0.9	12.5 ± 0.7	12.3 ± 1.6	12.9 ± 0.9	12.6 ± 1.1

Values indicate: mean ± standard deviation. Composite domain scores are z-scores, individual test scores are raw scores. *Abbreviations: MAPT*, microtubule-associated protein tau; *GRN*, progranulin; BNT, Boston Naming Test; SAT, semantic association test; TMT, Trailmaking test; WAIS, Wechsler Adult Intelligence Scale; LDST, letter digit substitution test; WCST, Wisconsin Card Sorting Test; ToM, theory of mind; VAT, visual association test; RAVLT, Rey Auditory Verbal Learning Test, imm, immediate; del, delayed. Composite domain scores are expressed as z-scores, the individual test scores are raw scores. *Higher scores indicate worse performance. *NB:* as all *MAPT* converters had a bvFTD phenotype, *MAPT* converters and bvFTD converters are summarized in one column. ** n=1, therefore no mean and SD available.

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4.3

Qualitative assessment of verbal fluency performance in frontotemporal dementia

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Abstract

Verbal fluency is impaired in patients with frontotemporal dementia (FTD) and primary progressive aphasia (PPA). This study explored qualitative differences in verbal fluency (clustering of words, switching between strategies) between FTD and PPA variants. Twenty-nine patients with behavioural variant (bvFTD) and 50 with PPA (13 nonfluent/agrammatic, 14 semantic, 23 logopenic) performed a semantic and letter fluency task. Clustering (number of multiword strings) and switching (number of transitions between clustered and non-clustered words) was recorded by two independent raters. Between-group differences, associations with memory, language and executive functioning and longitudinal change (subsample) in clustering and switching were examined. Interrater reliability was high (median 0.98). PPA patients generated smaller (number of) clusters on semantic and letter fluency compared with bvFTD ($p<0.05$). Semantic variant patients used more switches than nonfluent/agrammatic or logopenic variants ($p<0.05$). Clustering in semantic fluency was significantly associated with memory and language (range standardized regression coefficients 0.24-0.38). Switching in letter fluency was associated with executive functioning (0.32-0.35). Clustering and switching in verbal fluency differed between patients with subtypes of FTD and PPA. Qualitative aspects of verbal fluency provide additional information on verbal ability and executive control which can be used for clinical diagnostic purposes.

Introduction

Frontotemporal dementia (FTD) is an early-onset dementia characterized by a heterogeneous clinical presentation including behavioural changes, frontal executive deficits and/or selective language disorders [1] caused by pathophysiological changes in the frontal and temporal lobes [2-3]. Patients with the behavioural variant FTD (bvFTD) typically present with personality and behavioural changes, such as inappropriate social conduct, apathy or disinhibition [4-5]. The language variants are collectively referred to as primary progressive aphasia (PPA) and include a semantic variant (characterized by multimodal loss of semantic knowledge; svPPA), a nonfluent/agrammatic variant (characterized by agrammatism and apraxia of speech; nfvPPA) and the more recently defined logopenic variant (characterized by a slowed rate of speech and impaired sentence repetition; lvPPA), which is also associated with Alzheimer type pathology [1,6].

The clinical diagnosis of FTD and PPA is aided by detailed neuropsychological examination, including measures of language, executive functioning and memory. Executive control is often evaluated by tests of verbal fluency [7-8]. Verbal fluency refers to the ability to generate words from a semantic category (e.g. animals, groceries, fruits) or a specified letter of the alphabet within a limited time. Verbal fluency tasks are easy to administer and the number of correct responses provides a rich source of information on semantic, lexical and executive cognitive processes [9]. Based on the differences in clinical subtypes of FTD and PPA a disparate pattern of impairment in verbal fluency tasks is expected. Indeed, a previous study showed that patients with sv PPA were more impaired on semantic than letter fluency, whereas patients with bvFTD and nfvPPA were equally impaired on both types of tasks [8].

In this study we aim to examine not only quantitative differences in verbal fluency in FTD and PPA, but focus on potential qualitative differences as well. Qualitative aspects of lexical retrieval, such as the clustering of related words and switching between categories, can offer additional insights into the cognitive processes of fluency-task performance in specific patient groups, especially into the decay of semantic knowledge [10], and executive control [11]. The diagnostic utility of clustering and switching in verbal fluency has been shown for different patient groups, such as traumatic brain injury [12] and schizophrenia [13], but is unknown for FTD. Also, whether measures of clustering and switching provide additional information on related cognitive functions, such as memory, language, processing speed or executive functioning in these patients is unclear. Qualitative verbal fluency measures may have prognostic value, already demonstrated in the prediction of conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) [14], but whether disease progression in FTD could be predicted by clustering and switching measures remains to be evaluated. The present study thus aimed to examine clustering and switching in semantic and letter fluency in patients with bvFTD and PPA. Additionally, associations with other cognitive functions as well as longitudinal changes in fluency measures in a subsample of patients were evaluated.

Methods

Participants

This retrospective study included 79 patients who visited the Alzheimer Centre of the Erasmus University Medical Center, Rotterdam, the Netherlands, between January 2012 and December 2015 and were diagnosed with bvFTD or PPA. The clinical diagnosis was made in a multidisciplinary consensus meeting using international diagnostic consensus criteria. For bvFTD (n=29) the diagnostic criteria of Rascovsky et al. were used [5]. The diagnosis of patients with primary progressive aphasia (14 semantic, 13 nonfluent/agrammatic and 23 logopenic) was based on the diagnostic criteria of Gorno-Tempini et al. [6]. As part of their diagnostic workup, all patients underwent a standardized clinical assessment including medical history, informant-based history, physical and neurological exam, neuropsychological assessment (including Mini Mental-State Examination (MMSE) and Frontal Assessment Battery (FAB)), laboratory tests and brain imaging. Nineteen patients of the present sample (3 bvFTD, 6 semantic, 4 nonfluent/agrammatic, 6 logopenic) performed a second neuropsychological assessment at follow-up after 14.9 ± 6.0 months on average. Duration of illness was defined as the interval between patient and/or informant-reported first symptoms and the first memory clinic evaluation. Level of education was classified according to the system of Verhage ranging from one (less than primary school) to seven (university degree) [15]. The study was approved by the Medical and Ethical Review Committee of the Erasmus MC University Medical Center. Participants gave written informed consent.

Verbal fluency measures

All participants performed a semantic and letter fluency task as part of a standardized neuropsychological assessment (see below). For the semantic fluency task, participants were asked to generate as many exemplars as possible from the category animals in 60 seconds. For the letter fluency task, participants were asked to generate as many different words as possible beginning with the letter D, then A, and then T, with 60 seconds allowed for each letter. The letters DAT are considered the Dutch equivalent to the letters FAS [16]. At follow-up the letters KOM or PGR were used as parallel versions. Participants were instructed not to generate proper names or a previously generated word with only a different suffix. The total number of correct animals and the total number of correct words generated were recorded. Impaired performance for individual patients was defined as a T-score ≤27 compared to age-, sex- and education-adjusted normative data (corresponding to ≤1st percentile). In addition, semantic and letter fluency performance of each participant was re-evaluated by means of the scoring system reported in Ledoux et al. [17] (adaptation of [11]). Table 4.3.1 shows a summary of the scoring guidelines; further details of the scoring procedure for clustering and switching are reported elsewhere [17]. Based on this scoring procedure, the following measures were scored for semantic and letter fluency performance of each participant[1]:

1 The original variable 'percentage of clustered words (including errors)' yielded no meaningful data in our patient sample due to the relatively large number of errors and was therefore omitted from the analysis.

- *Total number of words:* Sum of all words produced, excluding repetitions and rule breaks. For letter fluency the sum of letters D, A and T was used
- *Number of clusters:* Number of multiword strings. Each cluster contains at least two successive words
- *Number of switches:* Number of transitions between clustered or non-Clustered words (i.e. switches from one associative strategy to another or to none at all)
- *Total cluster size:* Sum of all clustered words
- *Mean cluster size:* Total cluster size divided by the number of clusters

Other cognitive functions

The standardized neuropsychological assessment included validated tests covering the major cognitive domains. Memory was assessed with the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT [18]; immediate recall, delayed recall, delayed recognition, subtest Story Recall from the Rivermead Behavioural Memory Test [19] and the Visual Association Test [20]. Language was examined with the 60-item Boston Naming Test [21]. Information processing speed was assessed with the Letter Digit Substitution Test [22], the Trailmaking Test Part A [23] and the Stroop Color-Word Test I and II [24]. Attention & Executive functioning were assessed with the Trailmaking Test B/A ratio, the Stroop Color-Word Test III/II ratio, the modified Wisconsin Card Sorting Test (mWCST [25], number of concepts), the Digit Span subtest of the Wechsler Adult Intelligence Scale 3rd edition (WAIS-III [26]; total score) and the Zoo Map and Key Search subtests of the Behavioural Assessment of Dysexecutive Symptoms (BADS [27]). Raw test scores were converted to standardized z-scores based on the mean and SD of the study population. Z-scores were then averaged per cognitive domain into a composite domain score.

Table 4.3.1 | Scoring guidelines for qualitative fluency variables

Successive words are considered a cluster when:	Example
Semantic fluency	
– words that belong to the same subcategory	dog, cat, hamster
– words that an obviously strong association	lion, tiger, bear
– words that share the same first sound	cat, kangaroo
– items that contain the same word	lion, sea lion
– words that rhyme	dog, frog
Letter fluency	
– words with the same first two letters	snail, snow
– words with the same first and last sound, differing only in a vowel sound	simple, sample
– words that are homophones	see, sea
– words that rhyme	smart, start
– words with semantic/associative relationships	sneaker, sock; salt, shaker; sit, stand

These scoring guidelines are based on Ledoux et al. [17]

Statistical analysis

Statistical analyses were performed using SPSS Statistics 21.0 (IBM Corp., Armonk, NY). Between group differences were analysed with analysis of variance for continuous data, Mann-Whitney U tests for ordinal data and χ^2 tests for dichotomous data. All analyses were adjusted for age and sex. Analysis of the qualitative fluency variables were additionally adjusted for the total number of generated words. Because the number of patients with PPA was limited, the primary analysis of the fluency variables examined the difference between bvFTD and the three PPA groups (semantic, nonfluent/agrammatic and logopenic variants) taken together by means of a one-way univariate analysis of covariance. In case of a significant difference in the primary analysis, post hoc comparisons between the PPA groups were performed. Interrater reliability was calculated by means of intraclass correlation analysis. Change over time for the fluency variables was performed by means of repeated measures analysis of variance, including main effects of Time, Group and the Time x Group interaction. Associations between fluency variables and composite cognitive domains were examined with stepwise regression analysis including age and sex in step 1 and the composite cognitive domain scores (language, memory, processing speed, attention & executive functioning) in step 2. Alpha was set at 0.05 (two-tailed) for all comparisons.

Results

Demographics

The characteristics of the patient sample are presented in Table 4.3.2. The subgroups differed significantly in age ($F\ [3,75]=3.6$, $p<0.05$, $\eta^2=0.13$) and gender ($\chi^2\ [3]=12.4$, $p<0.01$), with higher age and more women in the logopenic group compared to the other groups. The groups did not differ in education level, disease duration or frontal assessment battery score (FAB) (all $p>0.05$), but the logopenic group had a lower MMSE score than the bvFTD and the nonfluent/agrammatic variant patients ($F\ [3,71]=6.5$, $p<0.01$, $\eta^2=0.22$).

Interrater reliability

Two independent raters, blinded for patient status, scored the fluency clustering and switching parameters (see Methods) based on the scoring system described in Ledoux et al. [17]. Table 4.3.3 shows high levels of interrater reliability for both the semantic (range 0.90 to 1.0) and letter fluency variables (range 0.80 and 0.99).

Baseline verbal fluency performance

For semantic fluency, 46% of patients showed impaired performance compared with normative data (i.e. T-score ≤27). Patients with PPA produced a significantly lower total number of words than patients with bvFTD ($F\ [1,75]=5.8$, $p< 0.05$, $\eta^2=0.07$). In addition, PPA patients produced smaller semantic clusters compared with patients with bvFTD (Table 4.3.2; total cluster size: $F\ [1,74]=6.3$, $\eta^2=0.08$; mean cluster size: $F\ [1,74]=6.3$, $p<0.05$, $\eta^2=0.08$). Post hoc comparisons within the PPA group showed no significant differences in the fluency variables between patients the variants (all $p>0.05$). For letter fluency, 29% of patients showed impaired performance compared with normative data (i.e. T-score ≤27). The total

number of generated words did not differ between patients with PPA and bvFTD (F [1,74]=1.5, p=0.22, η^2=0.02). However, patients with PPA produced a lower number of clusters and total cluster size compared with patient with bvFTD (Table 4.3.2; F [1,70]=3.9, p<0.05, η^2=0.05; F [1,70]=4.1, p<0.05, η^2=0.06). Post hoc comparisons within the PPA groups showed that patients with svPPA produced significantly more words (F [2,43]=3.7, p< 0.05, η^2=0.15), but also more switches (F [2,43]=8.3, p<0.01, η^2=0.28, adjusted for total number of words) than patients with nfvPPA (Figure 4.3.1).

Table 4.3.2 | Demographics, disease characteristics and verbal fluency performance

	bvFTD	PPA			Statistics
		SD	PNFA	LPA	
n	29	14	13	23	ns
Age (y)	58.9 ± 9.4	65.8 ± 9.1	64.0 ± 12.0	67.0 ± 8.3	p<0.05
Sex (n, % male)	20 (69%)	8 (57%)	8 (62%)	5 (22%)	p<0.05
Level of education	4.6 ± 1.2	4.9 ± 1.4	4.9 ± 1.6	4.4 ± 1.4	ns
MMSE	25.3 ± 4.0	25.0 ± 2.9	27.7 ± 2.2	21.9 ± 4.3	p<0.05
Frontal Assessment Battery	13.3 ± 3.9	13.7 ± 2.8	13.9 ± 2.8	11.6 ± 3.1	ns
Symptom onset (y)	3.6 ± 3.0	3.6 ± 1.6	2.8 ± 1.0	2.6 ± 1.6	ns
Measures of verbal fluency					bvFTD vs. PPA
Semantic fluency					
Number of words	13.5 ± 6.3	8.2 ± 4.9	10.5 ± 5.7	10.4 ± 5.0	p<0.05
Number of clusters	3.7 ± 1.6	2.9 ± 1.6	2.9 ± 1.6	3.0 ± 1.6	ns
Number of switches	5.8 ± 3.8	4.2 ± 2.4	4.2 ± 2.4	4.3 ± 2.5	ns
Total cluster size	11.8 ± 5.7	6.9 ± 4.3	8.9 ± 5.8	8.6 ± 5.1	p<0.05
Mean cluster size	3.3 ± 1.2	2.2 ± 0.8	2.8 ± 1.0	2.8 ± 1.0	p<0.05
Impaired performance (n, %)[a]	9 (31%)	8 (57%)	7 (54%)	12 (52%)	p<0.05
Letter fluency					
Number of words	19.5 ± 11.6	22.4 ± 11.3	12.0 ± 10.0	14.6 ± 9.7	ns
Number of clusters	5.4 ± 3.8	4.4 ± 3.3	2.9 ± 2.9	3.8 ± 2.9	p<0.05
Number of switches	14.1 ± 9.6	17.9 ± 11.0	6.3 ± 5.0	9.1 ± 6.0	ns
Total cluster size	13.5 ± 10.1	9.7 ± 6.9	8.3 ± 9.4	9.0 ± 7.2	p<0.05
Mean cluster size	5.8 ± 2.7	4.9 ± 2.5	4.7 ± 3.0	5.1 ± 2.4	ns
Impaired performance (n, %)[a]	8 (30%)	3 (23%)	7 (60%)	5 (28%)	ns

Data a mean ± SD unless otherwise specified; *Abbrevations:* ns, not significant; bvFTD, behavioral variant frontotemporal dementia; PPA, primary progressive aphasia; SD, semantic dementia; PNFA, progressive nonfluent aphasia; LPA, logopenic progressive aphasia; MMSE, Mini Mental-State Examination; [a] performance below the 1st percentile (i.e. T-score ≤27) compared to normative data.

Table 4.3.3 | Single measure intraclass correlations for the verbal fluency variables based on 2 raters

	Semantic fluency	Letter fluency
Number of words	1.0	0.99
Number of clusters	0.96	0.98
Number of switches	0.98	0.99
Total cluster size	0.98	0.97
Mean cluster size	0.90	0.80

Table 4.3.4 | Relation between measures of verbal fluency and cognitive domain scores

	Language	Memory	Processing speed	Attention & Executive functioning
Semantic fluency				
Number of words	0.35**	0.24*	0.48**	0.24*
Number of clusters	0.25*	0.25*	0.50**	0.22
Number of switches	0.21	-0.02	0.35*	0.22
Total cluster size	0.26*	0.38**	0.47**	0.17
Mean cluster size	0.07	0.26	0.14	-0.04
Letter fluency				
Number of words	0.14	0.03	0.55**	0.35**
Number of clusters	0.20	0.07	0.53**	0.20
Number of switches	0.05	-0.02	0.50**	0.32*
Total cluster size	0.23	0.08	0.54**	0.20
Mean cluster size	0.33*	-0.04	0.50**	0.11

Data are age- and sex-adjusted standardized regression coefficients beta; * $p<0.05$; ** $p<0.01$.

Change over time in verbal fluency performance

Nineteen patients (3 bvFTD, 6 svPPA, 4 nfvPPA, 6 lvPPA) performed the semantic and letter fluency at follow-up. For semantic fluency, the patient group as a whole showed a significant decline in total number of words ($F [1, 18]=9.8$, $p<0.01$, $\eta^2=0.35$) and cluster size ($F [1, 18]=5.0$, $p<0.05$, $\eta^2=0.32$). For letter fluency, the patient group as a whole showed a significant decline in total number of words ($F [1, 18]=5.7$, $p<0.05$, $\eta^2=0.24$), number of clusters ($F [1, 18]=8.4$, $p<0.05$, $\eta^2=0.32$), number of switches ($F [1, 18]=10.3$, $p<0.01$, $\eta^2=0.37$) and cluster size ($F [1, 18]=7.3$, $p<0.05$, $\eta^2=0.29$). Examination of the Time x Group (bvFTD vs. PPA) interaction for semantic fluency showed that patients with PPA had a greater decline in total number of words ($F [1, 17]=5.3$, $p<0.05$, $\eta^2=0.24$) and number of clusters ($F [1, 17]=4.2$, $p<0.05$, $\eta^2=0.20$) compared with patients with bvFTD. For letter fluency no significant Time x Group interactions were observed.

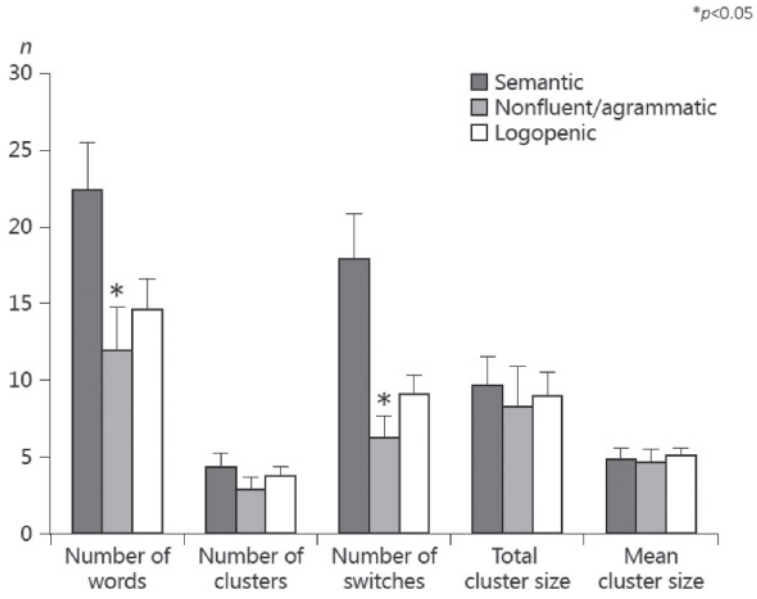

Figure 4.3.1 | Letter fluency performance for the PPA variants

Association with other cognitive functions

The results of regression analysis (Table 4.3.4) showed that all but one measure of semantic and letter fluency correlated significantly with information processing speed (range standardized regression coefficient beta 0.14 to 0.54). Furthermore, for semantic fluency the total number of words, the number of clusters and the cluster size showed significant associations with the domain scores language and memory (range beta 0.24 to 0.38). For letter fluency the total number of words and the number of switches correlated significantly with attention and executive functioning (range beta 0.32 to 0.35).

Discussion

The present study examined clustering and switching in verbal fluency in patients with bvFTD and PPA. We found both quantitative and qualitative differences in verbal fluency between these patient groups. Patients with PPA not only generated fewer words on semantic fluency than patients with bvFTD, but also produced fewer and smaller clusters on semantic and letter fluency. These findings fit well within the theoretical notion that clustering relies on the generation of semantic, associative or letter related words and is thus mainly supported by the integrity of the semantic system. Damage to the left temporal lobe, as is present in PPA, evidently impairs access to lexical information and deterioration of semantic storage [28].

Our results also showed differences between subtypes of PPA. Patients with svPPA produced more words than patients with nfvPPA and lvppa. The number of generated words in letter fluency in svPPA patients was comparable to bvFTD, reflecting the uncompromised fluency of speech in svPPA. However, svPPA patients showed significantly more switches than patients with nfvPPA or lvPPA. This relative increase in the number of switches in svPPA may reflect the combination of both intact fluency of speech and the deterioration of semantic knowledge. Switching is thought to invoke a deliberate, controlled search and is associated with executive functioning [17]. It is mainly supported by frontal lobe functioning, which is relatively spared in svPPA, at least in early stages of the disease.

As would be expected, patients with nfvPPA showed the lowest output on both semantic and letter fluency, which is thought to result primarily from speech apraxia [6,8,29-31]. Cluster sizes in nfvPPA were, however, comparable to those found in patients with svPPA and lvPPA. Whether the PPA subtypes might rely on different strategies to counter degradation of semantic knowledge (e.g. spelling or sound similarities vs. semantic similarities) could not be derived from the present analysis. There were no clear differences in clustering and switching between patients with nfvPPA and lvPPA.

The diagnostic utility of verbal fluency in identifying subtypes of dementia has been examined by several previous studies [7,14,30,32]. Although patients with FTD showed an overall worse fluency performance than patients with AD, the disparity between letter and semantic fluency is particularly effective in differentiating the two patient groups [7]. Moreover, AD can be distinguished from nfvPPA and svPPA based on their profile of verbal fluency (number of words, word frequency, type of errors) [30] and a recent study indicated that measures of lexical similarity in verbal fluency predicts conversion of MCI to AD [14]. In line with these findings, the results of the present study indicate that subtypes of FTD can also be distinguished by qualitative inspection of clustering and switching measures. More specifically, analysis of the clustering and switching variables support the semantic deficit in svPPA in contrast to the agrammatism and motor speech errors in nfvPPA, thereby aiding timely and accurate diagnosis.

The scoring method used in the present study, as described in Ledoux [17], is based on the original scoring by Troyer et al. [11]. The interrater reliability of this method was adequate in the present study (median 0.98) and highly similar to the interrater reliability reported in the original study by Ledoux et al. [17]. Clustering and switching are considered robust theory-based fluency measures, a notion that is supported by data from patients with schizophrenia, HIV, Huntington's disease, Parkinson's disease, multiple sclerosis and traumatic brain [12,13,33-36]. A recent study showed that machine learning in verbal fluency outperformed traditional structural MRI measures in predicting conversion from MCI to AD (AUC MRI measures 0.76 vs. 0.87 for machine learning predictors [14]). Although this machine learning approach may not be easily adapted in standard clinical care, our findings provide further support to the diagnostic value of verbal fluency tests in FTD. Moreover, it might be useful to examine the value of different types of relationships (i.e. phonological, orthographic or semantic) as these are not separately recorded in the Ledoux scoring method. In this regard, inclusion of an AD comparison group could potentially yield additional information on these processes. Longitudinal data on verbal fluency in relation to onset or progression of dementia are scarce. Raoux et al. showed that patients with

Alzheimer's disease already produce fewer words and switches 5 years before their clinical diagnosis [37, 38]. In addition, Pakhomov & Hemmy, using an automated approach, showed that in 239 cognitively intact participants a larger semantic cluster size was associated with a 38% and 26% reduced dementia risk after 6 and 17 years, respectively [39]. In the present study clustering and switching in letter fluency showed a particularly strong decline in PPA patients, regardless of the subtype of PPA. Letter fluency thus appears a sensitive measure of cognitive decline in PPA.

Verbal fluency is supported by both common and distinct cognitive processes. Our results show a general association with measures of processing speed, which is in line with previous studies [40-41] and probably reflects the timed nature of the task. Clustering in semantic fluency was significantly associated with memory and language, whereas in letter fluency switching was associated with executive functioning. These findings fit well within the theoretical model of verbal fluency proposed by Troyer et al. in which clustering is thought to rely upon temporal lobe processes such as verbal memory and word storage, whereas switching relies upon frontal lobe processes such as strategic search processes, cognitive flexibility, and shifting [11].

Strengths of the present study include the relatively large patient sample and the detailed verbal fluency scoring method that showed a high interrater reliability. A limitation of this study is the fact that the fluency data in this study were part of the diagnostic neuropsychological assessment. Patients with worse performance on semantic fluency are more likely to be classified as having semantic variant PPA than nonfluent/agrammatic PPA. Clustering and switching measures were, however, specifically calculated for this study and were therefore not used for the diagnostic workup. This study included patients with a clinical diagnosis of bvFTD or PPA, autopsy-confirmed cases were unfortunately unavailable. This means that no pathological confirmation of dementia subtype was possible. In addition, some patients with a clinical diagnosis of logopenic variant PPA may have underlying Alzheimer-type pathology. Disease duration is a difficult measure to assess in FTD. We estimated disease duration as the time between the first report of symptoms and the clinical assessment. It is possible that bvFTD is diagnosed in a later stage than PPA as the presenting symptoms (behavioural changes vs. language impairment) are more easily recognized in PPA. Given that the patients with bvFTD tended to outperform PPA patients on most fluency measures this potential bias in the estimation of disease duration is unlikely to significantly influence our results.

Conclusions

The present study showed differences in clustering and switching in verbal fluency between patients with PPA and bvFTD and a significant decline in verbal fluency over time. Clustering was specifically associated with memory and language and switching with executive functioning. These results show that qualitative differences in verbal fluency provide additional information on different cognitive functions in FTD and PPA that can be used in clinical practice to improve diagnostic accuracy.

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4.4

A meta-analytic review of memory impairment in behavioural variant frontotemporal dementia

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Abstract

We performed a meta-analysis into the extent, nature and pattern of memory performance in behavioural variant frontotemporal dementia (bvFTD). Multiple observational studies have challenged the relative sparing of memory in bvFTD as stated in the current diagnostic criteria. The review covered the period 1967 – February 2017 of case-control studies on episodic memory in bvFTD vs. control participants (16 studies, 383 patients, 603 control participants), and patients with bvFTD vs. those with Alzheimer's disease (AD) (20 studies, 452 bvFTD, 874 AD). Differences between both verbal and non-verbal working memory, episodic memory learning and recall, and recognition memory were examined. Data were extracted from the papers and combined into a common metric measure of effect, Hedges' *d*. Patients with bvFTD show large deficits in memory performance compared to controls (Hedges' *d* –1.10 95% confidence interval [-1.23 to -0.95]), but perform significantly better than patients with AD (Hedges' *d* 0.85 95% confidence interval [0.69 to 1.03]). Learning and recall tests differentiate best between patients with bvFTD and AD ($p<0.01$). There is 37%-62% overlap in test scores between the two groups. This study points to memory disorders in patients with bvFTD, with performance at an intermediate level between controls and patients with AD. This indicates that, instead of being an exclusion criterion for bvFTD diagnosis, memory deficits should be regarded as a potential integral part of the clinical spectrum.

Introduction

Frontotemporal dementia (FTD) is an early-onset dementia characterized by a heterogeneous clinical presentation including behavioral changes, frontal-executive deficits and/or language disorders [1], caused by pathophysiological damage in the frontal and temporal lobes [2-3]. Behavioural variant FTD (bvFTD) is the most common clinical syndrome in the spectrum and is associated with deficits in social cognition and executive functioning. Patients with bvFTD frequently exhibit impaired theory of mind, emotional processing, fluency, planning, set shifting, and working memory (e.g. [4-6]). Day-to-day memory is thought to be relatively preserved in the early stage of the disease [7-8], with severe memory impairment as exclusion criterion. However, many patients with bvFTD have self-reported or caregiver reported memory problems [9] and some patients even manifest severe episodic memory disorders, even at initial presentation (e.g. [10-11]).

Systematic investigations of episodic memory functioning in patients with bvFTD are scarce [9] and inconsistent, with some studies revealing no differences between bvFTD and AD memory performance (e.g. [12-14]), and others demonstrating a relative sparing of memory performance in bvFTD compared to AD (e.g. [15-17]). Studies showing memory impairment in patients with bvFTD suggest poor organization and a lack of efficient learning and retrieval strategies as causes (i.e. dysexecutive syndrome), rather than deficits in memory consolidation *per se* [18-20]. In line with the latter, there are indications that patients with bvFTD and AD will not differ on delayed memory testing, but that they will benefit more from cued or recognition memory formats (e.g. [21]). However, specific differential memory processes have, as of yet, not been studied consistently in bvFTD. Involvement of the hippocampal structures, as found in neuroimaging studies of both FTD and AD, suggests that amnesia in bvFTD may be due to real defects in memory storage and consolidation processing (e.g. [22-26]). For example, Papma et al. [25] showed lower perfusion in the right temporal lobe in amnesic patients with FTD compared to non-amnesic patients with FTD. The authors argue that amnesic patients with FTD might represent an anatomical subtype of FTD, with prominent right temporal lobe involvement.

A possible explanation for these contrasting results is the lack of pathological confirmation in most studies. Some have included patients with possible or probable FTD, whereas only a few have looked at memory disorder in pathological confirmed FTD (e.g. post-mortem, genotyping, or excluding AD biomarkers) [7]. Those studies that have looked at memory disorder in pathological confirmed FTD show clear episodic memory deficits (e.g. [22,27-28]. For the differential diagnosis between bvFTD and AD, it is important that the presence of memory impairment is not exclusively related to AD, but that it may also be included in the diagnosis of bvFTD. Clarifying the patterns of specific memory processes in both groups could help differentiate AD and bvFTD.

The primary aim of the present meta-analysis was to quantify the nature and extent of memory impairment in patients with bvFTD compared to AD and control participants. We examined the proposed contrasts in differential memory processes (working memory, episodic memory learning and recall, and recognition memory) to provide further insights into the pattern of memory impairment in

bvFTD. In addition, we tested the occurrence of differences in memory disorders between the studies, including possible, probable or definite diagnoses. By quantifying the nature and extent of bvFTD memory impairment, we provide insights into how memory performance in clinical evaluation can help in differential diagnostics between patients with bvFTD and AD.

Methods

Identification of studies

The meta-analysis included all published studies that provide an estimate of memory performance in patients with bvFTD. See Figure 4.4.1 for the flowchart illustrating the process of inclusion. Studies were selected by means of a Medline literature search covering the period April 1967 to February 18, 2017. Key search terms were ("frontotemporal dementia" or "frontal dementia" or "Pick's disease" or "frontotemporal lobe dementia" or "frontal lobe dementia" or "dementia of the frontal type") in combination with ("memory" or "learning" or "cognition" or "neuropsychology" and its derivatives) in full or truncated versions. Titles and abstracts were scanned and potentially eligible papers were collected in full-text. In addition, lists of references of these studies were examined for additional papers. To be selected for the meta-analysis, a study had to meet the following inclusion criteria: 1) the study was an original English language article; 2) memory performance was assessed in both a bvFTD patient group and healthy control participants or an AD patient group, all with a group size of $n \geq 10$ and matched for demographic variables age and level of education; 3) raw test scores were presented for the patient and the control participant groups (i.e. means and standard deviations). To prevent including the same cohorts of patients across studies, of all the eligible studies (bvFTD vs. healthy controls 26 studies; and bvFTD vs. AD 24 studies) we included the study that had the largest sample and/or included the most detailed memory assessment per cohort for each center. If studies did not specify from which cohort patients were included, only one study per center was selected. Sixteen validated memory measurements were included (see Table 4.4.1 and 4.4.2) with tasks typically involving the presentation of either verbal or visual information in which participants have several trials to memorize the presented items, including immediate and delayed recall trials. Our study was conducted in accordance with the Helsinki Declaration and followed the PRISMA guidelines for systematic reviews and meta-analyses [29]. Since we only reviewed previously published data, no additional medical ethical approval was necessary.

Data synthesis and analysis

Effect sizes were calculated for the difference in test scores between 1) patients with bvFTD and healthy control participants, and 2) patients with bvFTD and AD. We used Hedges' *d* (the standardized difference between the groups) to estimate effect size [30]. We chose Hedges' *d* instead of Cohen's *d* or Hedges' *g* as it corrects for bias due to small sample sizes [30]. The direction of the effect size was negative if the performance of the bvFTD patient group was worse than the control or AD patient group. In the meta-analysis, an overall *d* value was calculated, expressing the magnitude of associations across studies weighted for sample size [30]. According to Cohen's nomenclature [31], $d>0.80$ indicates a large difference. A bias-corrected 95% confidence interval (CI) was calculated based on the standard error. The percentage

of overlap in test scores between groups was also reported according to Zakzanis' calculations [32]; d=0 equates to 100% overlap, d=1.0 equates to 45% overlap and d=3.0 equates to less than 5% overlap in group scores. In addition, the overall effect size was used in a random effects model to determine the total heterogeneity of effect sizes (Q_T) and tested against the χ^2 distribution with n-1 degrees of freedom

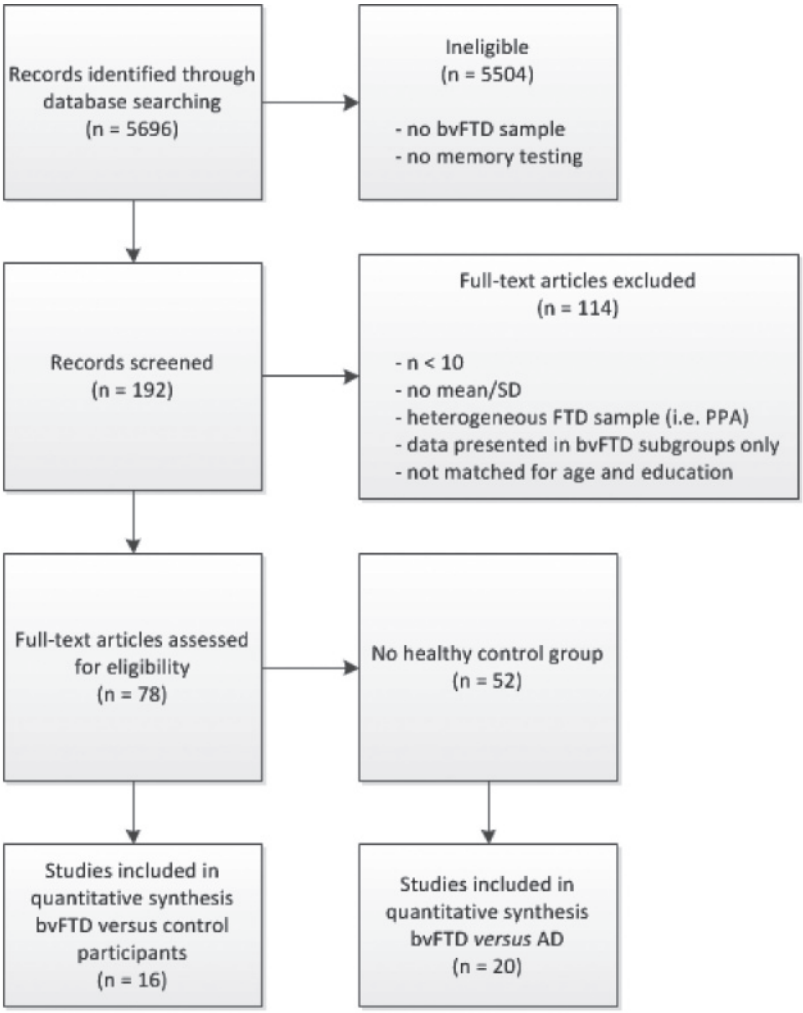

Figure 4.4.1 | Flow chart illustrating the process of inclusion of eligible studies and reasons for exclusion.

Table 4.4.1 | Study characteristics of studies included in the meta-analysis: bvFTD vs. control participants

Study	n		Age		Gender (% female)		Education (years)		MMSE		Dementia diagnosis	Memory measurements
	bvFTD	C	bvFTD	C	bvFTD	C	bvFTD	C	bvFTD	C		
Mandelli et al. [77]	23	34	62.9 (6.5)	62.3 (6.6)	43	65	16.1 (2.6)	16.4 (2.1)	26.6 (3.5)	28.4 (1.2)	Rascovsky et al. [7]	CVLT-SF, RCFT, DS
Balconi et al. [65]	16	20	65.6 (6.9)	68.6 (4.5)	13	50	7 (2.2)	7.8 (2.7)	25.3 (3.3)	28.6 (1.0)	Neary et al. [39]	LM, RCFT
Hardy et al. [78]	24	24	64.6 (7.7)	63.8 (7.8)	17	63	14.8 (3.8)	15.3 (2.9)	24 (5.7)	30 (0.6)	Rascovsky et al. [7]	RMT F/W, DS
Tu et al. [67]	24	23	64.7 (9.3)	68 (3.4)	26	52	11.8 (3.1)	13.3 (3.1)	NS	NS	Rascovsky et al. [7]	RAVLT, RCFT, DS
Smits et al. [66]	20	112	63 (8.0)	61 (8.0)	49	56	5.0 (1.3)*	5.5 (1.1)*	26 (3)	28 (1.0)	Rascovsky et al. [7]	RAVLT, VAT
Lemos et al. [38]	32	32	68.6 (1.2)	68.6 (1.3)	31	31	6.9 (0.8)	7 (0.9)	26.9 (0.4)	29.1 (0.2)	Rascovsky et al. [7]	FCSRT, DS, BVMT-R
Bertoux et al. [27]	44	22	66.9 (8.3)	66.7 (9.3)	43	41	10.8 (3.9)	12.8 (2.4)	23.1 (3.6)	29 (2.6)	Rascovsky et al. [7]	FCSRT
Virani et al. [79]	14	17	65.3 (8.1)	62.4 (10.8)	25	28	11.3 (3.0)	15.1 (3.5)	20.6 (6.9)	27.1 (4.2)	Rascovsky et al. [7]	prose memory
Ricci et al. [36]	15	28	65.7 (8.6)	68.5 (6.7)	40	61	10.3 (3.2)	11.4 (2.8)	26.6 (3.4)	NS	Neary et al. [39]	RAVLT
Ricci et al. [36]	11	15	59.8 (9.0)	60.2 (5.8)	55	60	12.6 (2.4)	13.5 (3.0)	26.5 (2.3)	NS	Neary et al. [39]	RAVLT
Stopford et al. [80]	26	26	64 (6.0)	59 (13.5)	50	69	NS	NS	23 (6)	NS	Neary et al. [39]	LM, DS
Giovagnoli et al. [71]	40	91	61.1 (10.7)	62.3 (10)	38	55	8.9 (4.1)	11.3 (4.4)	NS	NS	Neary et al. [39]	the short story, RCFT, DS, Corsi cube span
Piolino et al. [81]	13	21	67.2 (7.9)	69.9 (8.6)	NS	NS	NS	NS	24.8 (4)	NS	Neary et al. [39]	Grober & Buscke Test, DS
Torralva et al. [82]	20	10	67.2 (8.1)	63.5 (5.8)	45	60	12.8 (5)	13.5 (2.7)	27.9 (1.6)	29.5 (0.8)	Neary et al. [39]	LM, DS
Wicklund et al. [37]	20	48	61.9 (8.4)	72.1 (7.2)	30	79	14.7 (2.9)	15.2 (2.7)	23.8 (4.7)	29.2 (0.9)	Neary et al. [39]	WMS-R, CERAD
Clague et al. [35]	11	41	60.3 (6.9)	64.9 (6.1)	NS	NS	12.4 (1.8)	12.8 (2.2)	27.1 (2.0)	N.S.	Neary et al. [39]	DS, LM, RCFT
Gregory et al. [12]	19	16	58.6 (6.9)	57.1 (5.1)	16	50	11.6 (2.2)	12.1 (1.5)	26.6 (3.2)	28.7 (1.0)	Neary et al. [39]	DS, LM, RCFT

Abbreviations: C, control participants; MMSE, Mini Mental State Examination; CVLT-SF, California Verbal Learning Test – Short version; RCFT, Rey Complex Figure Test; DS, digit span; LM, logical memory; RMT F/W, Recognition Memory Test Words/Faces; RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test; FCSRT, Free and Cued Selective Reminding Test; BVMT-R, Brief Visuospatial Memory Test- Revised; WMS-R, Wechsler Memory Scale – Revised; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; NS, not specified.

Table 4.4.2 | Study characteristics of studies included in the meta-analysis: bvFTD vs. AD

Study	n		Age		Gender (% female)		Education (years)		MMSE		Dementia diagnosis		Memory measurements
	bvFTD	AD	bvFTD	AD	bvFTD	AD	bvFTD	AD	bvFTD	AD	bvFTD	AD	
Balconi et al. [65]	16	14	65.6 (6.9)	72.2 (6.9)	13	71	7 (2.2)	7.2 (3.8)	25.3 (3.3)	21.1 (4.2)	Neary et al. [39]	NINCDS-ADRDA	LM, RCFT
Smits et al. [66]	20	199	63 (8.0)	65 (8.0)	49	44	5.0 (1.3)*	4.9 (1.2)*	26 (3.0)	22 (4.0)	Rascovsky et al. [7]	NINCDS-ADRDA	RAVLT, VAT
Tu et al. [67]	24	23	64.7 (9.3)	68 (3.4)	26	52	11.8 (3.1)	13.3 (3.1)	N.S.	N.S.	Rascovsky et al. [7]	NINCDS-ADRDA	RAVLT, RCFT, DS
Barsuglia et al. [68]	16	18	61.1 (10.6)	59.2 (4.9)	50	67	15.6 (2.3)	16.2 (2.3)	24.6 (4.3)	24.4 (4.6)	Rascovsky et al. [7]	NINCDS-ADRDA	DS, LM, RCFT
Lemos et al. [38]	32	32	68.6 (1.2)	69.7 (1.3)	31	47	6.9 (0.8)	6.9 (0.9)	26.9 (0.4)	21.2 (0.7)	Rascovsky et al. [7]	NINCDS-ADRDA	FCSRT, DS, BVMT-R
Perri et al. [69]	21	22	64.7 (11.5)	66.8 (3.5)	55	48	11.2 (3.4)	10.5 (5.4)	23.4 (2.8)	23.2 (1.9)	Neary et al. [39]	NINCDS-ADRDA	15 word list recall, prose memory
Bertoux et al. [27]	44	56	66.9 (8.3)	66.4 (9.4)	43	57	10.8 (3.9)	12.3 (3.5)	23.1 (3.6)	21.9 (4.4)	Rascovsky et al. [7]	NS	FCSRT
Ricci et al. [36]	15	39	65.7 (8.6)	68.3 (7.7)	40	54	10.3 (3.2)	12.1 (3.2)	26.6 (3.4)	23.5 (3.7)	Neary et al. [39]	NINCDS-ADRDA	RAVLT
Ricci et al. [36]	11	17	59.8 (9.0)	65.3 (7.8)	55	59	12.6 (2.4)	12.3 (3.5)	26.5 (2.3)	24.4 (3.5)	Neary et al. [39]	NINCDS-ADRDA	RAVLT
Mendez et al. [70]	12	12	63.4 (4.4)	64.6 (4.8)	50	50	14.5 (4.1)	14.2 (4.3)	24.3 (2.8)	22.6 (4.1)	Rascovsky et al. [7]	NS	DS, CERAD
Giovagnoli et al. [71]	40	77	61.1 (10.7)	65.5 (9.9)	38	63	8.9 (4.1)	8.9 (4.9)	NS	NS	Neary et al. [39]	NINCDS-ADRDA	the short story, RCFT, DS, Corsi cube span
Heidler-Gary et al. [72]	25	30	64.8 (9.9)	72.6 (8.8)	NS	NS	NS	NS	NS	18.9 (5.4)	Neary et al. [39]	NINCDS-ADRDA	RAVLT
Luzzi et al. [73]	11	14	64 (7.0)	71 (8.0)	27	50	10 (2)	10(4)	24 (6.0)	24 (2.0)	Neary et al. [39]	NINCDS-ADRDA	DS, Hopkins test, RAVLT, RCFT
Castiglioni et al. [74]	33	85	69.8 (8.8)	74.4 (7.4)	33	64	8 (4.8)	7.3 (4.0)	20.8 (3.8)	19.4 (3.0)	Neary et al. [39]	NINCDS-ADRDA	Story memory, RCFT, Corsi span, DS
Wicklund et al. [37]	20	33	61.9 (8.4)	72.6 (9.6)	40	67	14.7 (2.9)	14.2 (2.8)	23.8 (4.7)	23.6 (4.0)	Neary et al. [39]	NINCDS-ADRDA	WMS-R, CERAD
Clague et al. [35]	11	14	60.3 (6.9)	63.8 (6.9)	NS	NS	12.4 (1.8)	11 (1.2)	27.1 (2.0)	24.5 (2)	Neary et al. [39]	NINCDS-ADRDA	DS, LM, RCFT
Glosser et al. [21]	12	30	68.8 (10.1)	73.7 (6.8)	67	47	15.1 (3.1)	14.8 (3.2)	23.8 (2.3)	23.6 (4.6)	Neary et al. [39]	NINCDS-ADRDA	CVLT, BFLT

Table 4.4.2 | Continued

Study	n		Age		Gender (% female)		Education (years)		MMSE		Dementia diagnosis		Memory measurements
	bvFTD	AD	bvFTD	AD	bvFTD	AD	bvFTD	AD	bvFTD	AD	bvFTD	AD	
Gregory et al. [12]	19	12	58.6 (6.9)	66.5 (8.9)	16	50	11.6 (2.2)	14.4 (4)	26.6 (3.2)	27.1 (1.7)	Neary et al. [39]	NINCDS-ADRDA	DS, LM, RCFT
Siri et al. [75]	14	14	74.8 (7.3)	69.6 (7.4)	NS	NS	5.3 (2.8)	7.2 (2.9)	17.8 (4.2)	20.3 (5.8)	Neary et al. [39]	NINCDS-ADRDA	DS, Corsi block span story memory, RCFT
Binetti et al. [76]	44	121	66.9 (9.2)	70.6 (8.5)	41	62	14.1 (3.5)	13.1 (3.5)	NS	NS	DSM-IV, ICD-10	NS	story memory, figure recall, BVRT
Gregory et al. [12]	12	12	63.6	71.1	NS	NS	11.7	9.9	25.3	24.1	Neary et al. [39]	NINCDS-ADRDA	story memory, RCFT, Corsi block span, DS

Abbrevations: bvFTD, bvFTD; AD, Alzheimer's Disease; MMSE, Mini Mental State Examination; CVLT-SF, California Verbal Learning Test – Short version; LM, logical memory; DS, digit span; RCFT, Rey Complex Figure Test; RMT F/W, Recognition Memory Test Words/Faces; RAVLT, Rey Auditory Verbal Learning Test; VAT, Visual Association Test; FCSRT, Free and Cued Selective Reminding Test; BVMT-R, Brief Visuospatial Memory Test- Revised; WMS-R, Wechsler Memory Scale – Revised; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; BVRT, Benton Visual Retention Test; BFLT, Biber Figure Learning Test; NS, not specified.
*According to the Verhage system.

[30]. A significant Q_T means that the variance of the effect sizes is greater than expected from sampling errors and suggests that other explanatory variables should be investigated. The differences between the overall effect sizes of the memory processes (working memory, episodic memory learning recall and recognition memory) were examined with the Q-statistic for heterogeneity. This procedure is analogous to analysis of variance, where a difference among group means is determined. We partitioned the total heterogeneity Q_T in Q_M, which is the variation in effect sizes explained by the model, and Q_E, which is the residual error variance not explained by the model. Q_M is thus a description of the difference among group cumulative effect sizes, and a significant Q_M suggests a difference between the overall effect sizes for the different memory processes [30]. The fail-safe number was computed to explore the robustness of the results to publication bias. The fail-safe number of studies N_R provides an estimation of how many non-significant or missing studies would be needed to render the observed meta-analytical results non-significant (Rosenthal's method: $\alpha<0.05$; [33]). All analyses were performed in MetaWin 2.0 [34]. Data for the different memory processes were separately included in the analysis. In cases where multiple measures of the same cognitive construct were provided (e.g., ≥2 retrieval measures in a study), the effect sizes were averaged to give each construct the same weight in the analysis. To check for differences in effect sizes between verbal and visual memory measurements, effect sizes for both dimensions were calculated; these were found not to differ significantly. This made it possible to include both verbal and visual memory measurements in the same analysis. One study, Clague et al. [35], reported two different experiments. As it was unclear whether the same bvFTD sample was used in both experiments, only data from the first experiment were included in the meta-analysis. Ricci et al. [36] included an Italian and Australian bvFTD patient sample; these were included as two separatestudies. Wicklund et al. [37] and Lemos et al. [38] reported standard errors instead of standard deviations. We calculated the SDs based on the known confidence intervals and degrees of freedom.

The meta-analysis was performed in four consecutive steps. First, the overall effect size for patients with bvFTD *versus* control participants was calculated. Second, overall effect sizes for the four identified types of memory processes were calculated and compared between patients with bvFTD and controls. Third, the overall effect size for patients with bvFTD vs. AD was calculated. Lastly, overall effect sizes for the four memory processes were calculated and compared between patients with bvFTD and AD. Six pairwise comparisons were conducted between the four different types of memory processes. To check for the effect of differences in demographic features and dementia criteria between groups of studies on memory performance, additional analyses were performed with the demographic variables (age, education, gender, MMSE), type of bvFTD dementia criteria (Rascovsky et al., 2011 or Neary et al., 1998), and type of diagnosis (possible, probable, definite, mixed or unknown) as categorical moderators. Rascovsky et al. (2011) [7] revised the publication of consensus criteria by Neary et al. (1998) [39] due to limitations. Among these were the ambiguities of behavioural descriptors, the inflexibility in applying the criteria (i.e. all five core features were required to manifest), and the insensitivity of the criteria in the early stages of the disease. The new criteria provide significant greater sensitivity (86%) than the 1998 criteria (53%). Age, education, percentage females, and MMSE were categorized as being either high or low, based on the median.

Results

In total, 16 studies comparing patients with bvFTD to healthy control participants and 20 studies comparing patients with bvFTD to patients with AD were included in the meta-analysis (Figure 4.4.1). Of these, 10 were included in both analyses as they included both a healthy control group and patients with AD. Tables 4.4.1 and 4.4.2 display the characteristics of these studies.

Memory performance in patients with bvFTD versus healthy control participants

Overall memory performance in bvFTD vs. healthy controls

In total, 383 patients with bvFTD and 603 controls from 16 studies were included in the meta-analysis (Table 4.4.1). The overall weighed effect size for patients *versus* controls was -1.10 [95% CI -1.23 to -0.95]; % overlap=41.1 (Figure 4.4.2) indicating that patients performed significantly worse on overall memory performance than the controls. The test for heterogeneity was not significant (Q_T=47.22; p=0.34), suggesting that the variance among effect sizes was not greater than that expected by sampling error. The fail-safe number of studies was 4209.3, indicating that at least 4209 unpublished null-findings were needed to render the effects on memory statistically non-significant. It is unlikely that this number of unpublished studies with null effects relative to the published studies exists.

Working memory, learning, recall and recognition memory in patients with bvFTD vs. healthy controls

Working memory was assessed in eight studies and had an overall effect size of -0.83 [95% CI -0.99 to -0.63]; % overlap=48.4-52.6. Episodic memory learning was assessed in 14 studies with an overall effect size of -1.22 [95% CI -1.50 to -0.91]; the % overlap=34.7-37.8. Episodic memory recall was assessed in 16 studies and showed an overall effect size of -1.15 [95% CI -1.32 to -0.95]; the % overlap=37.8-41.1. Recognition memory was assessed in seven studies showing an overall effect size of -1.08 [95% CI -1.49 to -0.77]; the % overlap=41.1-44.6. These effect sizes indicate worse performance on all memory processes in patients with bvFTD compared to controls. Despite a trend towards larger effect sizes for episodic memory learning and recall compared to working and recognition memory, the effect sizes were homogeneous, thereby indicating no statistically significant difference between the effect sizes of the four types of memory processes (Q_M=4.32; p=0.23).

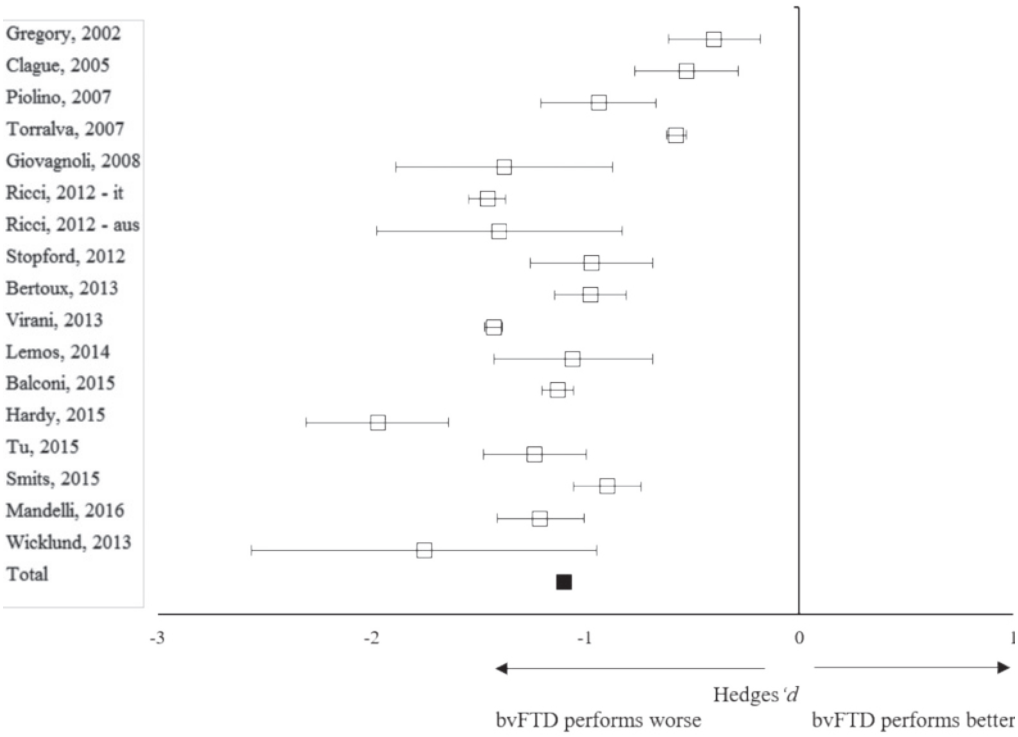

Figure 4.4.2 | Forest plot illustrating effect sizes and bias-corrected 95% confidence intervals for each study comparing bvFTD patients to control participants on overall memory performance. Negative values indicate worse performance for bvFTD patients than control participants.

Memory performance in patients with bvFTD vs. AD

Overall memory performance in bvFTD vs. AD

A total of 452 patients with bvFTD and 874 with AD were included in the meta-analysis (Table 4.4.2). The overall weighed effect size for bvFTD vs. AD was 0.85 [95% CI 0.69 to 1.03]; % overlap=48.4-52.6. Patients with AD performed significantly worse than patients with bvFTD on overall memory performance (Figure 4.4.3). The heterogeneity test was significant (Q_T=96.78; p<0.01), indicating a possible moderating structure to the model (e.g. separate memory processes). The fail-safe number of studies was 3133.2, indicating that at least 3133 unpublished null-findings were needed to render the effects on memory statistically non-significant. It is unlikely that this number of unpublished studies with null effects relative to the published studies exists.

Working memory, learning, recall and recognition memory in patients with bvFTD vs AD

Working memory was assessed in 11 studies with an overall effect size of 0.06 [95% CI -0.12 to -0.24]; % overlap>92.3). Episodic memory learning was assessed in 15 studies with an overall effect size of 1.00

[95% CI 0.78 to 1.26]; the % overlap=44.6. Episodic memory recall was assessed in 20 studies showing an overall effect size of 1.22 [95% CI 1.02 to 1.51]; % overlap=37.8.

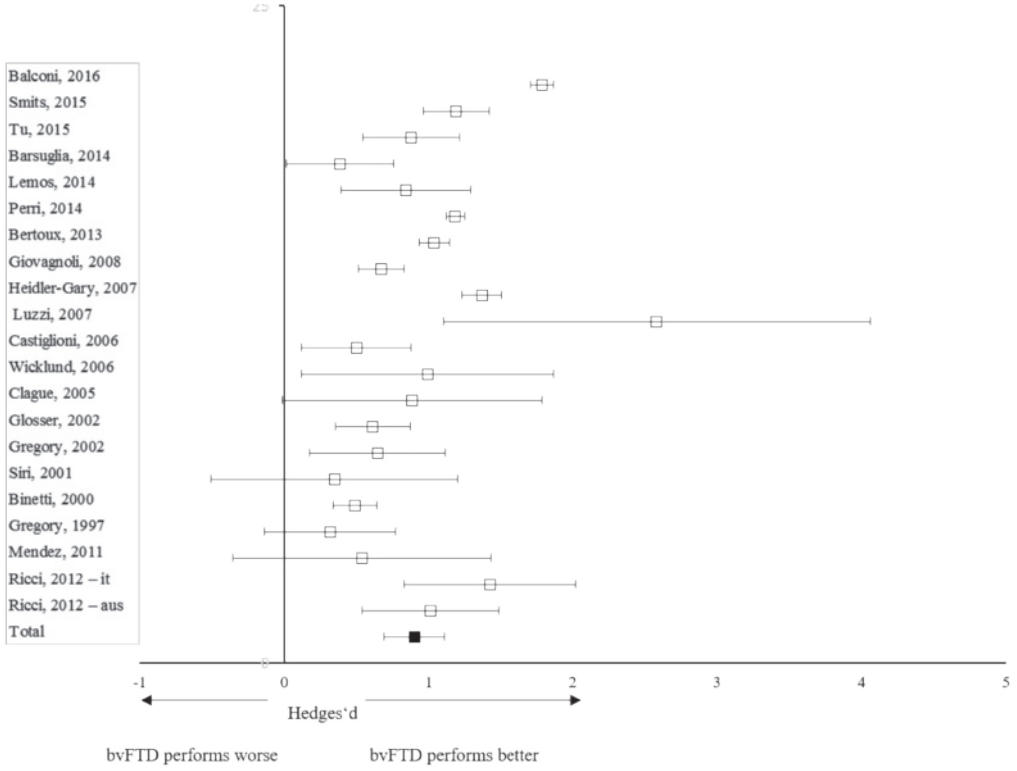

Figure 4.4.3 | Forest plot illustrating effect sizes and bias-corrected 95% confidence intervals for each study comparing bvFTD patients to AD patients on overall memory performance. Positive values indicate better performance for the bvFTD patients than the AD patients.

Recognition memory was assessed in 5 studies with an overall effect size of 0.66 [95% CI 0.43 to 0.87]; % overlap=57-61.8. These effect sizes indicate worse performance on learning and recall tests in patients with AD compared to those with bvFTD. AD patients had a slightly worse performance for recognition memory, but no differences in working memory was seen between patient groups. This is corroborated by the heterogeneous Q-statistic results, indicating statistically significant differences between the effect sizes of the four memory processes (Q_M=43.87; p<0.01). Six pairwise comparisons showed significant differences between episodic memory recall and recognition memory (Q_M=4.87, p=0.027), between episodic memory recall and working memory (Q_M=40.86, p<0.01), between episodic memory learning and working memory (Q_M=27.50, p<0.01) and between working memory and recognition memory (Q_M=7.93, p<0.01).

Moderator variables

Patients with bvFTD vs. control participants

The heterogeneity test for the bvFTD vs. control studies showed no differences in effect sizes between older vs. younger patients (Q_M=1.11, p=0.29), high-educated vs. low-educated (Q_M=0.81, p=0.37), high vs. low percentage of females (Q_M=0.03, p=0.85), and high vs. low overall MMSE scores (Q_M=3.58, p=0.058). In addition, no significant differences were found in effect sizes between studies using different dementia criteria (Rascovsky et al., 2011 [7] or Neary et al., 1998 [39]) (Q_M=1.59, p=0.21), or type of diagnosis (probable, definite, mixed or unknown) (Q_M =2.95, p = 0.39).

Patients with bvFTD vs. AD

The heterogeneity test showed no differences in effect sizes between bvFTD vs. AD studies with older vs. younger (Q_M=0.10, p=0.75), high-educated vs. low-educated (Q_M=1.19, p=0.28), high vs. low percentage of females (Q_M=0.00, p=0.99), high vs. low MMSE score (Q_M=0.07, p=0.79). Furthermore, no differences were found based on type of dementia criteria used (Rascovsky et al., 2011 [7], Neary et al., 1998 [39] or DSM-IV/ICD-10) (Q_M=1.46, p=0.48), or type of diagnosis (possible, probable, definite, mixed or unknown) (Q= *3.83, p = 0.43).*

Discussion

In this study, we conducted a meta-analytic review of memory in patients with bvFTD, to explore the extent, nature and exact pattern of performance in these patients. The results showed large differences in memory performance between patients with bvFTD and controls and between patients with bvFTD and AD. This shows that patients with bvFTD perform at an intermediate level between healthy control participants and patients with AD. Nonetheless, patients with bvFTD show severe memory impairments across studies. Secondary analyses reveal significant differences in the four types of memory processes (i.e. working memory, episodic memory learning and recall, and recognition memory) when comparing bvFTD to AD. Learning and recall tests were found to be most discriminative, with recognition and working memory showing smaller to no discriminative power. This suggests that the patient groups can best be differentiated using learning and recall trials.

Our results are in line with previous studies reporting impaired memory in patients with bvFTD (e.g. [40-41]), and those showing that patients with AD experience even greater memory problems (e.g. [13,16,19,42-49]) with delayed memory testing being the most discriminative (e.g. [19,50]). However, our results contrast with those of other studies reporting similar memory impairment in patients with bvFTD and AD (e.g. [10,51]). Some of these authors argue for similar consolidation problems in patients with bvFTD and AD, as damage to the hippocampal structures was visible in both groups (e.g. [52]). Others theorize selective retrieval disorders in patients with bvFTD, potentially caused by attention and executive problems [21]. They state that because of disrupted attentional and executive control processes, patients with bvFTD may have difficulties generating strategies to encode and retrieve data

from memory in an organized way [21]. The idea is that patients with bvFTD and AD do not differ in free recall measures, but that those with bvFTD would benefit from cued or recognition memory formats [21]. However, our results show a large difference in overall memory performance between patients with bvFTD and AD, with learning and recall tests being the most discriminative. Surprisingly, recognition memory yielded a smaller difference between the patient groups, suggesting that patients with bvFTD do not specifically benefit more from cued memory formats than those with AD. A possible explanation may be the limited number of studies including a recognition memory measure (n=5), but it may also be due to unsatisfactory psychometric characteristics of some of the measures such as RAVLT recognition memory [53]. Importantly, we report an overlap between 37 and 62 percent in the scores of the AD and bvFTD groups on episodic memory. This suggests that, even when the most discriminating memory measurements are used, the differential diagnosis of AD and bvFTD, on the basis of memory performance, remains challenging. These findings have clinical significance, as they suggest that performance on memory tests does not always adequately differentiate bvFTD from AD, thus questioning the inclusion of relative sparing as a diagnostic criterion for bvFTD diagnosis.

A possible explanation for the contrasting results in the literature and what we report here – supporting neither equal memory impairment in bvFTD and AD nor a sparing of episodic memory (as the current clinical criteria for bvFTD diagnosis suggest) – could be the heterogeneity of bvFTD samples within and between studies. In about 30% of patients, FTD is caused by genetic mutations (e.g. progranulin (*GRN*), microtubule-associated protein tau (*MAPT)*, and the chromosome 9 open reading frame 72 (*c9orf72)* repeat expansion). Ber et al. [54] found a high frequency of episodic memory disorders (89%) in *GRN* mutation carriers and suggest an episodic memory disorder to be a distinctive characteristic of the *GRN* mutation, due to the high expression of *GRN* in the hippocampus in which marked atrophy and neuronal loss may be observed [55-57]. However, Mahoney et al. [58] have found similar results for *c9orf72* repeat expansion carriers, and suggest a similar explanation. It is therefore possible that the clinical presentation of memory impairment depends on the mutation involved. For example, Jiskoot et al. [59] found specific recall deficits in presymptomatic *GRN* mutation carriers, whereas *MAPT* mutation carriers showed more prominent recognition deficits. Current and future longitudinal studies including neuropsychological testing should focus on investigating patterns of memory performance in different FTD phenotypes and their underlying pathologies. The development of tests that can disentangle the contributions of underlying pathology to memory impairment in bvFTD is highly recommended. Importantly, other memory processes such as autobiographical memory and future thinking have received increasing attention in recent years and seem to be valuable constructs to further address in future FTD research (e.g. [60-61]).

Strengths of our study include the use of a meta-analytical approach that provides a weighted estimate of the magnitude of effects. Moreover, to our knowledge, this is the first study quantitatively reviewing the contrasting results in the literature on memory impairment (i.e. including working and specific episodic memory processes) specifically in bvFTD. A limitation is the potential heterogeneity of the included studies with regards to the sample size and characteristics of the memory measurements. In addition, some of the secondary analyses included a relatively small number of studies. Importantly,

the majority of the studies in this meta-analysis included patients with bvFTD without pathological confirmation. This introduces a potential selection bias based on the clinical criteria for bvFTD and AD. As relative sparing of episodic memory is considered an inclusion criterion for a bvFTD diagnosis, patients with memory impairment may have been misdiagnosed as AD or other forms of dementia, and were therefore not included in these studies. Several recent clinicopathological studies have highlighted the risk of a misdiagnosis between AD and bvFTD (e.g. [28,62]). Although the Lund and Manchester criteria plus SPECT imaging results are considered to be acceptably accurate in identifying a clinical syndrome predicting the pathologic features of FTD at autopsy [63-64], there is still the possibility that some of the studies missed patients with bvFTD with memory impairment due to the current clinical criteria. This selection bias would have led to an underestimation of our effect sizes. We would like to stress, however, that several studies included pathologically proven patients with bvFTD and still found significant memory deficits (e.g. [22,27-28]). Moreover, by way of moderator analysis, we checked whether studies including pathologically proven patients with bvFTD differed in effect sizes on memory disorder from those that included possible or probable diagnoses or others where this was not specifically stated. Only a few studies included a definite bvFTD diagnoses (n=2), however there was no significant difference in effect sizes.

In summary, our findings suggest that patients with bvFTD show large deficits on both working and episodic memory processes, with patients with AD performing worse on episodic memory. However, the overlap in test scores between the patient groups was too large to be able to make a confident differential diagnosis on the basis of memory performance. Therefore, we advise that clinicians use memory performances carefully, and interpret them in conjunction with other diagnostic information i.e. medical history, behavioral observations and questionnaires, neuroimaging, neuropsychological data of other cognitive domains. In order to improve on existing memory performance measures, we recommend developing tests that can disentangle the contribution of underlying pathology to memory impairment in bvFTD. Importantly, we show that memory impairment in bvFTD is more common than previously thought, thus it should not per definition be considered an exclusion criterion when diagnosing bvFTD.

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Chapter 5

General discussion

Frontotemporal dementia (FTD) is the second most common type of early-onset dementia, in which symptoms commonly become apparent before the age of 65 [1-2]. The clinical spectrum is heterogeneous, ranging from a predominant behavioural manifestation (behavioural variant FTD; bvFTD) to progressive language deterioration (primary progressive aphasia; PPA) and parkinsonism [3-5]. 10-30% of FTD cases have an autosomal dominant pattern of inheritance [6-8]. Mutations in the progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*) genes, and a repeat expansion in chromosome 9 open reading frame 72 (*C9orf72*) are the three most common causes [8]. Familial FTD allows the identification of pathogenic mutation carriers in their presymptomatic phase – a critical time-window for treatment as the pathological damage is at its minimum and potentially still reversible [9]. However, with promising avenues opening for disease-modifying therapies in clinical trials, we currently lack robust biomarkers for (familial) FTD. These biomarkers will be essential for improving diagnostic accuracy, staging and prognosis, onset prediction, and monitoring disease progression and treatment response. In this thesis, we have therefore investigated potential neuroimaging and neuropsychological biomarkers in the familial and sporadic FTD spectrum.

Main findings

What are the most promising candidate MRI biomarkers in presymptomatic familial FTD?

The work performed for this thesis finds clear evidence for the presence of a presymptomatic stage in familial FTD, in which there are mutation-specific changes in both grey matter (GM) volume and white matter (WM) integrity in presymptomatic *MAPT*, *GRN* and *C9orf72* mutation carriers. Not only do these changes happen early in the presymptomatic phase, they can also be used to predict conversion to symptomatic FTD. The following paragraphs will discuss our most interesting findings in more detail.

The uncinate fasciculus is the pathological key hub of FTD

The uncinate fasciculus (UF) is a bidirectional cortico-cortical white matter (WM) tract that connects the (orbito)frontal to the (anterior) temporal lobes [10-11]. The functional role of the UF is still a matter of debate. As described in Chapter 3.1, the UF plays a key role in language processing – being part of the ventral pathway, the UF is implicated in amongst others lexical retrieval, semantic associations, and naming of objects and actions [12-13]. Because of its connections to the limbic system in the temporal lobe, e.g. hippocampus and amygdala, the UF is also known to be involved in episodic memory, emotions and behaviour, and as a result plays a role in a range of mood, psychiatric and neurodegenerative disorders [11]. There has been abundant research into WM changes in the syndromic variants of FTD, that consistently showed that the UF is affected in both bvFTD and PPA, and is one of the first tracts showing integrity breakdown in the symptomatic phase (e.g. [14-23]).

Our work contributes to previous research by demonstrating that mutation carriers already have WM integrity loss of the UF in the *presymptomatic* stage. The UF is one of the two tracts showing the largest decline between the presymptomatic and symptomatic stage – and even more interestingly, its integrity

loss is one of the strongest predictors for conversion to the symptomatic stage (Chapter 2.1). The *MAPT* mutation carriers and converters were most likely driving this signal, as the larger proportion of our converters was carrying a *MAPT* mutation (Chapter 2.1). This is consistent with a previous study, in which symptomatic *MAPT* mutation carriers not only had cross-sectional integrity changes, but also the largest decline over time in the bilateral UF [19]. In the GENFI cohort (Chapter 3.2), we confirm the UF as the pathological hallmark of presymptomatic *MAPT*, as we found consistent diffusion changes in the early presymptomatic stage (-30 to -20 years before estimated symptom onset) in mutation carriers. Regarding its location, the UF is a likely key hub of the first pathological damage in FTD, as the grey matter (GM) structures of the medial temporal lobe preferentially demonstrate early breakdown [19,24]. Speculatively, with the UF being the last to peak maturity during brain development [11], this WM tract could be the most vulnerable to neurodegeneration ("last in, first out" principle). This thesis is the first to describe changes in the UF of presymptomatic *C9orf72* repeat expansion carriers (Chapter 2.3 and 3.2). There have been studies demonstrating UF involvement in symptomatic *C9orf72*-associated FTD [25-26]. The UF changes in *C9orf72* repeat expansion carriers and *MAPT* mutation carriers seem earlier, stronger and more consistent than in *GRN* mutation carriers (Chapter 3.2). This could reflect a genotype-specific pattern, in which the UF is mostly damaged in presymptomatic *MAPT* and *C9orf72*. Alternatively this result could stem from to the large spread in age of onset [27], or masking effects by taking the mean value per WM tract, given the asymmetric neuroimaging phenotype of *GRN* [50], making our estimation of the first UF integrity changes less accurate than for the other two genes. The latter would be consistent with the study of Borroni et al. [28], in which WM diffusion changes were found in presymptomatic *GRN*.

White matter integrity loss is the presymptomatic hallmark of FTD

Research suggests that FTD is a WM rather than a GM disease, as WM damage extends beyond the borders of GM atrophy [18,29], is present in an earlier stage [30], and has a greater rate of decline over time than GM atrophy [19,22]. Our work corroborates this notion, as *C9orf72* repeat expansion carriers had WM integrity loss across our entire cohort, while GM volume loss was confined to a subgroup closer to symptom onset (Chapter 2.3). Mutation carriers demonstrated the first WM integrity changes from 29 years before estimated onset (Chapter 3.2), which was significantly earlier than the first GM volume differences from 10 years before estimated symptom onset in the same cohort [31]. Interestingly, this seems somewhat incongruent with our findings from our four-year follow-up analyses (Chapter 2.2), in which the first changes in both WM integrity and GM atrophy were visible from two years before symptom onset. Sample sizes were however smaller than those of abovementioned studies, thereby lowering power to detect small(er) differences.

In addition to early WM involvement, we found clear gene-specific 'fingerprints' in the presymptomatic stage across the three FTD mutations within the Genetic Frontotemporal dementia Initiative (GENFI) consortium (Chapter 3.2). The presymptomatic *C9orf72* repeat expansion carriers were the first to show changes, as early as 30 years before estimated symptom onset. The two previous studies into presymptomatic *C9orf72* so far have shown inconsistent results, with one study demonstrating WM integrity loss of the right corpus callosum, cingulum bundle, and bilateral internal and external capsule [25], whereas the other did not demonstrate presymptomatic differences between repeat expansion

carriers and controls [32]. In our study (Chapter 3.2), specifically the early involvement of the posterior thalamic radiation and posteriorly located tracts as the splenium of the corpus callosum and posterior corona radiata were interesting findings, as with respect to time and location they are consistent with the GM volume loss of the thalamus and posterior cortical areas from 25 years before estimated onset in the same cohort [31]. Symmetrical atrophy in both cortical (i.c. frontal and temporal lobes) and subcortical (i.c. thalamus, striatum, cerebellum) areas is considered to be the neuroimaging signature of *C9orf72* repeat expansions [24,33-34]. Devenney et al. [35] found that this network forms the underpinning of psychotic symptoms, often described in this mutation [36-37]. One potential hypothesis why the WM is affected early in *C9orf72* repeat expansion carriers is that *C9orf72*-associated FTD has a developmental origin, in which damage is longstanding and non-evolving, or slowly progressing over time from early age onwards [38-40]. The first follow-up study of presymptomatic repeat expansion carriers by Floeter et al. shows a similar profile, with no changes in motor, cognitive or behavioural functioning over an 18-month period [41]. As we did not include mutation carriers more than 30 years away from estimated symptom onset in our study, it could be possible that WM changes were present even earlier, providing additional evidence for the developmental hypothesis. In both *MAPT* and *GRN*, WM changes were consistently found later than in *C9orf72*. The presymptomatic changes in *MAPT* mutation carriers are congruent with tracts affected in bvFTD, the most common clinical phenotype of *MAPT* [8]. Potentially TDP-43 pathology is more closely related to GM than WM loss [54], as our *GRN* mutation carriers had fewer affected tracts, and differences were generally closer to estimated symptom onset than early presymptomatic. Follow-up DTI analyses within our own and larger cohorts such as GENFI will provide more information about WM progression within the presymptomatic phase of familial FTD.

Multimodal neuroimaging does not have complementary value in the presymptomatic stage

Multimodal neuroimaging, refers to the summation of information from different neuroimaging modalities, and can be obtained using either simultaneous imaging measurements (e.g. MRI, positron emission tomography (PET), computed tomography (CT)) or integration of separate measurements (e.g. functional, structural or diffusion MRI) [42]. It is increasingly used in dementia research due to the recognition of its clinical benefits – however, multimodal neuroimaging studies in FTD are thus far scarce [43]. In our four-year follow-up study (Chapter 2.2) we could predict conversion to the symptomatic stage best by WM integrity loss of the right UF and gCC – and not GM volume loss. This is an intriguing finding, as previous studies in FTD showed that the optimal classification could be attained by the combination of GM and WM imaging [44-45], or that WM integrity loss provided complementary information to GM atrophy measures [46]. We should keep in mind that abovementioned studies investigated the symptomatic FTD stage instead of the presymptomatic stage, as well as the classification abilities between different patient groups (i.c. FTD patients vs. AD patients), making a one-to-one comparison of results difficult. Our findings suggest that WM imaging can be regarded as the most sensitive individual modality biomarker in the presymptomatic stage of FTD – and the combination of GM *and* WM is likely optimal in the mild to moderate disease phase. This hypothesis is in line with the notion of FTD as a disconnection syndrome, in which early loss of specific WM tracts connecting cortical GM areas results in larger network failure later in the disease course. With the longitudinal decline of the gCC as strongest

individual predictor for symptom onset in our study, and previous research [47] identifying this tract as the most consistently affected across all FTD syndromes, we suggest this WM tract as potentially the most optimal neuroimaging biomarker to track disease progression in future clinical trials.

What is the value of neuropsychological assessment in (pre)symptomatic FTD?

The work performed for this thesis provides evidence for the presence of subtle mutation-specific cognitive decline in presymptomatic *MAPT*, *GRN* and *C9orf72* mutation carriers, and these cognitive changes can be used to predict conversion to the symptomatic stage. The following paragraphs will discuss some of our most interesting findings in more detail.

Mutation-specific cognitive decline has a rather explosive nature

Our baseline analyses in presymptomatic *MAPT* and *GRN* mutation carriers (Chapter 2.1) and *C9orf72* repeat expansion carriers (Chapter 2.3) demonstrated subtle worse performance in attention, mental processing speed and executive function – comparable to findings from previous case- and small family-based studies (e.g. [48-49]). According to the results from GENFI [31], 5 years before estimated symptom onset, the first neuropsychological decline in mutation carriers becomes visible. These results are largely consistent with the findings from our two-year follow-up study (Chapter 4.1), in which our model picked up the first cognitive decline in mutation carriers from eight years prior to estimated symptom onset. However, it should be noted that both studies used estimated years to onset, based on the average symptom onset of family members, as a proxy – instead of the actual onset age. This likely introduces a source of bias to these estimations, as there is large variation in symptom onset age in specifically *GRN* mutations [50], whereas the variability in other mutations is smaller [31]. However, due to the lack of actual conversion data at the moment these studies were performed, together with the observation that there is a rather comparable pattern of cognitive decline in estimated age at symptom onset to the analyses with current age, as age is the most important risk factor for conversion, we think that its use was justified in an exploratory model. In our second follow-up study (Chapter 4.2), eight mutation carriers had developed FTD symptoms, allowing us to use actual onset data within a 4-year time-window. Here, mutation carriers have stable scores until the last two years before symptom onset – a finding corroborated by previous studies stating that cognitive decline does only commence near or at symptom onset [48,51-53], and suggesting a more explosive mode of clinical onset instead of a gradual cognitive decline over time.

Verbal fluency is a promising candidate biomarker for FTD

In the first follow-up analyses on the neuropsychological data within FTD-RisC (Chapter 4.1), we found that our *MAPT* mutation carriers declined over a two-year time-period regarding categorical fluency, in comparison to both healthy controls from the same families, as well as *GRN* mutation carriers. This result was probably largely driven by the one converter with a *MAPT* mutation, as excluding this participant from the analyses left the comparison non-significant. Furthermore, in the same study we discovered that the performance deterioration of categorical fluency commences six years before estimated symptom onset in *MAPT* mutation carriers, but not *GRN* mutation carriers. Corroborating these findings,

we again found longitudinal decline of categorical fluency in our second (four-year) follow-up (Chapter 4.2) in *MAPT* mutation carriers, driven by the now larger sample of converters (five out of eight converters had a *MAPT* mutation). Interestingly, we found that decline on categorical fluency was predictive of an underlying *MAPT* mutation – whereas decline on letter fluency was predictive of conversion to non-fluent variant PPA. These findings could aid in patient stratification in upcoming clinical trials targeting specific FTD pathologies in an earlier disease stage, as interventions are ideally applied presymptomatically [54]. Furthermore, reliable phenotypic prediction could further optimize diagnosis by shortening the current delay [55], and is helpful for the patient, caregiver and clinician in knowing what disease presentation and course to expect.

Instead of solely examining quantitative differences in verbal fluency, we decided to look into more qualitative aspects of categorical and letter fluency in the symptomatic FTD spectrum as well (Chapter 4.3). Qualitative measures, in this case clustering of words and switching between clusters, can provide additional insights into the decay of semantic knowledge [56], executive control [57] and related cognitive functions, but was not investigated in FTD thus far. Based on the scoring system of Ledoux et al. [58], we demonstrated smaller clusters and a smaller number of clusters in PPA vs. bvFTD, with patients with semantic variant PPA using more switches than non-fluent and logopenic variant PPA. In addition to a better diagnostic differentiation between FTD subtypes, our findings also increase our knowledge regarding the common and distinctive cognitive processes underlying verbal fluency. Clustering in semantic fluency was associated with memory and language, whereas switching in letter fluency was more strongly related to executive functioning. This is in line with the theoretical model as suggested by Troyer et al. [57], stating that clustering is regulated by temporal lobe processes, like verbal memory and word storage, while switching between clusters mostly relies on frontal lobe processes, such as mental flexibility and shifting.

Memory deficits are an integral part of the FTD spectrum

In order to get more insight into the discrepancies, and to determine the nature and extent of memory deficits in FTD, we performed a meta-analytic review on case-control studies in bvFTD, AD and healthy controls (Chapter 4.4). In this review, we demonstrated that bvFTD patients performed worse than healthy controls – but better than AD patients – and can best be discriminated from the latter based on learning and recall, but less so by means of recognition and working memory. FTD patients therefore *can* have significant memory dysfunctions, stressing the need to alter the current diagnostic criteria stating that episodic memory is relatively spared in bvFTD. Considering the large amount of overlap in test performances, the differential diagnosis between AD and bvFTD, based on memory performance, remains challenging. The findings in our meta-analysis thereby contradict previous studies indicating that FTD memory deficits are as severe as those in AD (e.g. [59-61]). Previous research had let to the theory that the memory deficits in FTD have a frontal-executive etiology. Due to poor organization and lack of efficient learning and retrieval strategies [62-65] patients could benefit from cued or recognition memory formats [62]. However, this explanation seems less plausible here, because there were also recognition deficits in FTD, and patient groups did not differ with respect to working memory. Our results are more in line with those of Fernández-Matarrubia et al. [66], pointing out that FTD can present

with "true" amnesia, related to neuropathological damage to mesiotemporal/hippocampal structures and the Papez circuit, affecting both storage and consolidation processes, resulting in disorders in learning, recall *and* recognition. We should consider that most studies in our meta-analysis used clinical diagnostic criteria, potentially leading to a circular reasoning and misdiagnosis (e.g. FTD patients with memory disorders are more likely diagnosed as AD and vice versa), so that the differences between FTD and AD could in fact be even larger. In order to make firmer statements, future studies could greatly benefit from the use of neurodegenerative biomarkers (e.g. amyloid-beta depositions on PET scans or in cerebrospinal fluid) and/or definite pathology (e.g. presence of a known pathogenic mutation) in patient stratification.

With respect to familial FTD, our work in the presymptomatic phase points in the direction of gene-specific memory profiles for *MAPT* and *GRN*, with lower delayed verbal recall scores with age in *MAPT* mutation carriers, and lower recognition scores with age in *GRN* mutation carriers (Chapter 4.1). Our second follow-up study (Chapter 4.2), confirms this notion, with a decline in delayed verbal recall in *MAPT*, but not *GRN* mutation carriers – and is corroborated by the fact that we found significant loss in all memory components (encoding, retrieval, consolidation, visual-associative) in *MAPT* but not *GRN* converters. The decline in retrieval as the first sign of conversion in *MAPT*-associated FTD could be related to the loss of hippocampal volume, critical for episodic memory processing, as early as 15 years before estimated onset, as discovered in *MAPT* mutation carriers in GENFI [31]. Conversely, verbal recall can be affected early on due to prominent semantic impairments seen early in *MAPT*-associated FTD [67]. We can speculate why we do not find longitudinal memory decline in *GRN* converters, as episodic memory disorders have often be described in relation to *GRN* (e.g. [68]), due to high *GRN* gene expression in the hippocampus, resulting in marked atrophy and neuronal loss [1,69]. Most likely, our lack of statistically significant results is due to the relatively large amount of early-phase nfvPPA converters in our *GRN* converter group, mostly characterized by isolated speech disturbances and not memory loss, and/or the small sample size. Alternatively, memory deficits will not develop around conversion, but later in the disease process [8].

Methodological considerations

Neuroimaging

There are several technical considerations when performing a longitudinal cohort study such as FTD-RisC. We were performing our MRI scans using an 8-channel head coil. While this coil was enabling fast and high-resolution imaging of the brain at the start of our study in 2010, the better quality 32-channel head coil could only be taken into permanent use after calculating the difference between the two coils (see 'protocol amendments'). In addition, there was a software update on our MRI scanner in 2015, leading to a higher signal-to-noise ratio in the newer scans, and hence less comparable results in longitudinal analyses. Furthermore, we discovered a frontally located artifact in the DTI scans (forceps minor area), so that some results in that region should be interpreted with somewhat caution. Lastly, our original DTI protocol did not have a large enough field of view (FOV) to include all lower located brain regions,

e.g. cerebellum, in all participants. This protocol was developed with a cortical interest, but with recent insights of also cerebellar and corticospinal tract involvement in FTD [31,70], we were unfortunately not able to explore these brain areas on a group level.

Neuropsychology

The cognitive changes in the presymptomatic to early symptomatic stage of FTD are likely subtle and/or overshadowed by marked decline in personality, behavioural or emotional disturbances. Furthermore, our traditional neuropsychological tests might not be sensitive enough to detect those subtle cognitive changes, and they are not developed for repeated administration in a preclinical population [53]. It is therefore possible that test familiarity, practice and/or ceiling effects are obscuring the cognitive decline within our follow-up study, and we can only identify the first changes from two years prior to conversion while they are present before that. We find evidence for this hypothesis in the fact that we see healthy controls improve over time on tests for memory and social cognition, while we do not see such a trend in mutation carriers – the absence of a learning effect could be interpreted as cognitive decline. Although measuring frontal dysfunctions, and therefore potentially a better screening tool for FTD, the Frontal Assessment Battery (FAB) [71] has proven to be too insensitive for the presymptomatic stage, as even at the moment of conversion we could not find significant differences between converters, non-converters and healthy controls (Chapter 4.2). Other global measures for cognition, such as the Mini-Mental State Examination (MMSE) [72] and Clinical Dementia Rating (CDR) [73], rely too heavily on domains less affected in early stage FTD or do not cover the entire range of potential cognitive problems (e.g. the MMSE does not include executive functions; language and behaviour are not part of the original CDR) [53]. Another problem within our neuropsychological studies was the use of a large battery of cognitive tests. Although this allows us to investigate cognitive decline without any a-priori assumptions and such a protocol is more likely to detect changes over a wider range of cognitive domains and functions, the subtle decline is also more likely filtered out by the statistical corrections for multiple testing. A disadvantage of the study is the fact that the neuropsychological assessment was part of the clinical assessment with which we determined conversion to the symptomatic stage. This has likely led to a circular reasoning, as we demonstrated that converters declined over time, while cognitive decline was considered a prerequisite for conversion. Ideally, the tests assessed in our study should not have been used in the diagnosis of conversion. However, diagnosis setting in our multidisciplinary meeting was done by using all available clinical information – e.g. MR imaging of the brain, anamnestic and heteroanamnestic information, questionnaires, unblinding of genetic status – so that symptom onset did not solely depend on the neuropsychological assessment.

What have we learned from our longitudinal study in familial FTD?

After seven years of following at-risk participants within FTD-RisC, we have learned several things with respect to study design, study participation, and data gathering and analysis, leading to new insights and changes to the study protocol, summarized below:

- *Modeling pathological changes over time* – Originally our study design constituted a two-year follow-up period, as we believed that the changes in mutation carriers in the presymptomatic stage would

be slowly progressive, and we did not want participants to discontinue study participation because yearly visits were considered too much of a burden. However, as our results do suggest more rapid acceleration in the last year(s) before symptom onset, rather than gradual decline over, we think we can model these changes better by means of yearly follow-up assessments. Within GENFI, participants were already followed on a yearly basis. In our study protocol amendment of 2016 we have therefore changed that symptomatic mutation carriers will have a standard one-year follow-up (as disease progression in the symptomatic phase is rather fast), and presymptomatic at-risk participants will have the choice between a one-year or two-year follow-up. More than half of the study participants agreed to a one-year follow-up thus far.

- *The use of estimated vs. actual symptom onset* – With most mutation carriers still being within their presymptomatic stage, we were restricted to using estimated symptom onset as a proxy in a number of the studies described in this thesis (chapter 3.2 and 4.1). We realized the inaccuracy of estimated ages of symptom onset, but believed its use was justified as the first GENFI results showed that the carriers' age at symptom onset significantly correlated with both median and mean age at onset within the family, and that age at symptom onset of symptomatic carriers did not significantly differ from mean family onset age [31]. As an intermediate step, we investigated the correlation between age and cognitive decline (Chapter 4.1) – as age is considered the largest risk factor for conversion – and found rather comparable patterns of cognitive decline using estimated age at onset and current age. A worldwide collaboration between e.g. GENFI, LEFFTDS and ARTFL is currently investigating the familial and parental age at onset of the three large FTD mutations in more detail to develop a more accurate estimate for symptom onset. With longitudinal data becoming available, working with the intrapersonal changes over time (deltas) could provide a more accurate alternative for cross-sectional datasets. Unpublished work within Dominantly Inherited Alzheimer Network (DIAN), presented by Eric McDade (Washington University) at the Alzheimer Association International Conference 2017, shows that although the *order* of pathological changes in presymptomatic AD is similar to the original presymptomatic model [74] when using estimated years to onset, the *timing* of events is significantly different. For example, the first amyloid-beta depositions were found at 25 years before estimated onset in cross-sectional data vs. 10 years to estimated symptom onset using longitudinal data.
- *Study visits in the symptomatic stage* – With a follow-up period of two years at the most, we are able to identify converting mutation carriers in the earliest stages of symptomatic FTD. However, while they showed FTD symptoms, most of the converters formally did not fulfill all diagnostic criteria yet. The small numbers of converters is likely making analyses underpowered and unable us to detect the small increment of pathological change in the early symptomatic stage. With the fast disease progression once mutation carriers convert it has proven difficult to investigate them using the entire study protocol, lasting at least four hours in total (e.g. trouble lying still in the MRI scanner, lack of motivation, language difficulties during testing), resulting in fast study drop-out. Lastly, with the passage of time, our group of aging control subjects might become less comparable to the relatively young group of converting mutation carriers (survival bias).
- *Single-centre vs. larger consortium studies* – FTD-RisC is the largest contributor to GENFI. There are a number of important advantages of consortium above single-center cohort studies [75]. First, FTD is a rare condition, and as such, individual centres are able to recruit only small numbers of participants,

whereas consortia can pool data from a range of different mutations across single-centre cohorts – leading to more statistical power to detect small changes. Secondly, consortia are able to recruit subjects of all ages – from young presymptomatic mutation carriers to subjects close to or converting to the symptomatic stage – allowing a greater understanding of the natural history of FTD. Thirdly, larger cohort studies form ideal platforms for clinical trials, as they allow the recruitment of larger groups for a specific purpose, e.g. only symptomatic *GRN* mutation carriers. From GENFI we have learned how important it is to harmonize study protocols from the start of the project. For instance, variable MRI acquisition parameters and protocols were used in the pilot phase, introducing a large source of bias to the data. From 2015 onwards (GENFI2), scan protocols have been fully harmonized, so that we are building on a more consistent dataset – although vendor differences will remain influential. Another challenge was to find a neuropsychological battery that had tests and norm scores available in every language and population. Specifically finding good language and social cognition tests has proven to be difficult due to language and cultural differences between study sites.

- *Study protocol amendments* – Although we sent out questionnaires about potential behavioural and functional changes in study participants, we felt we were missing important clinical information by not getting in touch with the knowledgeable informants personally. We therefore implemented a structured heteroanamnestic interview either during the study visit or afterwards in a telephone interview. Additionally, we had the impression that the questionnaires in our original study protocol, the Beck's Depression Inventory (BDI) [76], Frontotemporal Rating Scale (FRS) [77] and Neuropsychiatric Inventory (NPI) [78], were not entirely covering the wide range of psychiatric and behavioural changes of FTD. Following the protocol changes in GENFI2, we added the FTD Clinical Dementia Rating Scale (FTD-CDR) [79], Cambridge Behavioural Inventory – Revised (CBI-R) [80], Modified Interpersonal Reactivity Index (MIRI), Revised Self-Monitoring Scale (RSMS) and modified NPI (mNPI) [Rohrer et al.]. Due to our analyses on neuropsychological data (Chapter 4.1-4.2), we had a better understanding of tasks that could be sensitive to presymptomatic change. Based on this, and to make our test protocol more concise and less burdensome, we removed a number of tests, and added new, potentially more sensitive tests (Emotion Recognition Task (ERT) [81], Test Relaties Abstracte ConcEpten (TRACE) [82]) as a pilot. Lastly, with recent insights of cerebellar and corticospinal tract involvement in FTD [31,70], we decided to enlarge the FOV of our DTI scan protocol to explore these tracts presymptomatically. We are currently finishing the transition to a new scan protocol using the 32-channel coil – we have therefore performed the scans using both 8-channel and 32-channel head coil, and are calculating the difference between the two methods to use as a covariate in our longitudinal analyses.
- *Involvement with study participants* – If there is one thing we have learned from FTD-RisC, it is how important personal involvement of the study team with the study participants is. The latter have been highly motivated and dedicated to the project, which is very admirable given that they are experiencing the fear of developing symptoms themselves, and study visits therefore can be quite stressful to them. Participants often report that they find it reassuring that they are under close watch of the study team, in case they might be developing symptoms – and we find it comforting to know that relatives feel free to inform us about worries they have concerning their family members. Without having a medicine that can cure or slow down FTD in close sight, we believe that our study team

should also be involved in what we can do for patients right now. In line with the so-called movement 'Sociale Benadering Dementie' (free translation: "Social Approach Dementia"), developed by Prof. mr. dr. Anne-Mei The, that focusses on the interaction between the disease itself and how people can deal with these changes, we decided to start providing counselling to the at-risk participants via a mindfulness program. Mindfulness or Mindfulness-Based Cognitive therapy (MBCT) is a form of third-generation (cognitive) behavioural therapy that focusses on being 'in the here and now' – providing people with tools to alleviate stress caused by the potentially impending disease development. We are currently developing the course programme.

Future directions

Neuroimaging in presymptomatic FTD

Individual classification

Classification on the single-subject level should be the next step for accurate diagnosis and prognosis, early treatment, and improving patient recruitment into clinical trials. MRI classification algorithms accurately classifying between FTD patients and controls [83-89] have already been developed, however as these models are based on established FTD cases, generalizability to presymptomatic mutation carriers has so far been limited. Our research group is currently performing machine learning on multimodal MRI data (GM and WM density, DTI-based features, and functional connectivity) from presymptomatic FTD mutation carriers.

Automatic quantification

Up to now, the assessment of MRI scans in the (outpatient) memory clinic happens mostly qualitatively, that is through visual inspection. Not only does this method rely heavily on the expertise and experience of the neuroradiologist, it is also rather insensitive to the small changes happening in the early disease stage. Automatic quantification of structural scans can aid in a faster and more accurate diagnosis setting, preventing expensive and invasive additional research (e.g. lumbar puncture). In collaboration with the Biomedical Imaging Group Rotterdam (BIGR), the Alzheimer Centre Erasmus MC had developed specialized software to assess MRI scans quantitatively, which was installed on a workstation of the outpatient memory clinic after extensive validation and optimization within several clinical populations. We expect that automatic quantification will have an important future contribution to the evaluation of longitudinal structural and functional neuroimaging changes in the presymptomatic stage of FTD.

New imaging modalities and data analysis approaches

For clinical trials for FTD to be effective, researchers need to be able to distinguish between tau, TDP-43 and other underlying pathologies. The field had hoped that tau PET would be able to do so, but disappointingly, the current tau tracers do not bind, bind too weakly or bind to regions and targets other than tau in *MAPT* mutation carriers. Most likely, tracers bind best to tau pathology consisting of paired helical filaments made up of 3-repeat (3R) and 4-repeat (4R) isoforms, while most tau pathology in FTD consists

of either pure 4R or 3R tau. Our center is currently involved in the TITAN study (AVID pharmaceuticals), in which we will investigate the binding of the 18F-AV-1451 tau tracer in presymptomatic and symptomatic 3R+4R *MAPT* mutation carriers. The identification of tau fibril strains accessible to each tau tracer would be of critical importance for their use in early and differential diagnosis and as therapeutic application [90]. In addition, the clinical implementation of ASL in the diagnostic work-up of the outpatient memory clinic could lead to more diagnostic certainty in presymptomatic to early phase FTD.

With respect to data analysis approaches, Voxel-Based Morphometry (VBM) [91] is a popular tool for investigating focal GM differences, as it provides a largely automated, whole-brain approach without a priori definition of regions of interest. However, it would be informative to perform additional cortical thickness analyses on our presymptomatic FTD cohort. As VBM cannot distinguish between volume changes due to loss of cortical thickness, cortical surface or both, and GM concentrations can be erroneously high as VBM can mistake adjacent gyri for one single GM area [92] – cortical thickness measurements can overcome these drawbacks and provide more sensitive information on possible pathophysiological changes in presymptomatic FTD. In the same manner, combining Tract-Based Spatial Statistics (TBSS) with fiber tractography methods can give us a better understanding of specifically more complex regions in which both spared and affected tracts cross each other to detect very early WM changes that would otherwise not be detected in the presymptomatic stage [93].

Neuropsychological assessment in FTD

New test development and use of qualitative test measures

A good cognitive biomarker must ideally be sensitive to detect change, specific enough to isolate signal from noise, acceptable to regulatory agencies, suitable for repeated administration and robust to practice effects, provide adequate coverage of the construct of interest, cover the entire range of possible outcomes (no ceiling and floor effects), and be readily available and accessible [53]. Understandably, this imposes challenges for the development of new neuropsychological tasks for presymptomatic FTD and endpoint selection for clinical trials. The Montreal Cognitive Assessment (MoCA) [94] has proven superior psychometric properties over the MMSE, providing a more sensitive and accurate instrument for the detection of FTD [95-96] – although it still has to be validated in a presymptomatic cohort. Studies such as FTD-RisC, but also larger collaborations as GENFI, form ideal platforms to pilot new tests or validate existing tests. With respect to language, we are currently investigating the TRACE [82] within FTD-RisC and the adapted version of the Camel and Cactus Test (CCT; [97]) within GENFI. The TRACE measures dysfunctions in the understanding of abstract words in patients that potentially still have a good understanding of concrete words. The CCT measures semantic association abilities – the adapted CCT only includes the most difficult 32 items from the original 64-item version. Both the TRACE and adapted CCT are therefore considered more difficult language tests, likely better suited for the subtle difficulties in the presymptomatic phase. The field is moving to the systematic investigation of social cognition in the differential diagnosis between FTD and other forms of dementia, as highlighted by recent work by our research group (van den Berg et al., 2018) demonstrating disorders in every level of social cognition in FTD in comparison to controls and AD patients, e.g. social perception, understanding/

interpretation and reasoning/regulating. Within FTD-RisC and GENFI we are currently investigating two new tests; the Emotion Recognition Task (ERT; [81]) and the short version of the Social cognition and Emotional Assessment (mini-SEA; [98]). In the ERT, morphs gradually expressing the six basic emotions on different intensity levels could provide a better understanding of deficits in emotion perception, an important aspect of social cognition that could be missed by only measuring static emotions [81]. Lastly, the mini-SEA, could provide us with a quick clinical tool for evaluating emotion recognition and theory of mind deficits [98].

In addition to new test development, future research should also focus on alternative outcomes of readily available neuropsychological tests as potentially better outcome measures. For instance, in episodic memory tests, one could look into recall-recognition contrast measures or recognition discriminability (i.e. hits vs. false positives) [53]. Previous research has shown that although FTD patients have intact recognition memory in terms of number of correct hits, they scored worse on a sensitivity index (correct hits – false positives), which was correlated to a measure for disinhibition [99]. Thompson et al. [100] also highlight the potential utility of error scores. The authors found that they could improve FTD classification from 71 to 96% by adding qualitative variables in the form of perseverative errors on a naming test, organizational and perseverative errors on a visuoconstruction task, and concrete responses during metaphor interpretation to the prediction model. Within FTD-RisC, we are currently investigating qualitative fluency measures (e.g. cluster size, switches) as an alternative to only using the traditional quantitative output in presymptomatic mutation carriers.

Behavioural and composite measures

As neuropsychiatric and behavioural disturbances are likely an early symptom of presymptomatic to early symptomatic FTD, behavioural measures could form sensitive endpoints for clinical trials. Thus far, greater uniformity has been reached with respect to behavioural than cognitive endpoints in clinical trials, and most have adopted multiple [53]. The most frequently employed, the NPI [53,78], forms part of the FTD-RisC protocol, and has shown to reliably differentiate between FTD subtypes [79] and sensitive to change over time [101] – however, it places more emphasis on 'positive' (e.g. agitation, disinhibition) than 'negative' behavioural symptoms (e.g. apathy), both forming core features of FTD [53]. In collaboration with the Dementia Research Center (DRC) of University College London (UCL), we are therefore currently investigating the modified NPI (mNPI), in which we added eight items (e.g. altered sense of humour, loss of empathy, compulsiveness, increased trusting behaviour, less responsiveness to social cues) to better grasp the characteristic behavioural and psychiatric disturbances in presymptomatic to early phase FTD.

Potentially, clinical trials in FTD could benefit from the use of a composite measure able to quantify several cognitive domains, or cognitive, behavioural *and* functional status in one single metric, in order to increase sensitivity to change, particularly in the presymptomatic to early disease stage [53]. The creation of such composite will be particularly challenging given the heterogeneous nature of the disease, and potentially different composites are required according to the various phenotypes. The FTD-CDR is a step in the right direction, where two domains specific for FTD (language, and behaviour, comportment

and personality) have been added [79]. The FTD-CDR has proven to be sensitive change with disease progression, but warrants validation in a presymptomatic cohort [102].

Conclusions

The work in this thesis has provided us more insight into potential neuroimaging and neuropsychological biomarkers for presymptomatic to early stage FTD. Our findings halt important future clinical and scientific implications for the field, e.g. improving clinical diagnosis, shortening diagnostic delay, better counselling of patients and caregivers, tracking disease progression, and accurate patient stratification and monitoring (dose-respondent) effects in clinical trials.

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Chapter 6

English and Dutch summary

Summary

Frontotemporal dementia (FTD) is a clinically and pathologically heterogeneous early-onset type of dementia, with symptom onset usually before the age of 65. Due to neurodegeneration of the frontal and/or temporal lobes, the disease commonly presents with marked changes in behavioural (behavioural variant FTD; bvFTD) and/or language (primary progressive aphasia; PPA), but also isolated and concomitant parkinsonism and motor neuron disease have been described – making the clinical diagnosis challenging and often delayed. FTD has an autosomal dominant pattern of inheritance in 10-30% of cases. Mutations in progranulin (*GRN*) and microtubule-associated protein tau (*MAPT*) genes, and the more recently discovered repeat expansion in chromosome 9 open reading frame 72 (*C9orf72*) are the three most common causes. Familial forms constitute the ideal disease-model for FTD, as we can identify pathogenic mutation carriers in their presymptomatic stage and follow them longitudinally to develop sensitive biomarkers for e.g. pinpointing disease onset, tracking disease progression, and evaluating the effects of future disease-modifying treatments.

Chapter 1 provides the **general introduction** to the development of clinical biomarkers in familial FTD and outlines the aims of this thesis.

Chapter 2 describes the first investigation of multimodal neuroimaging biomarkers in presymptomatic familial FTD. Multimodal neuroimaging biomarkers are of utmost importance if one wants to unravel the temporal and spatial ordering of pathological events, and have shown to have superior power over the conventional single modality approach in clinical diagnosis setting in other types of dementia. **Chapter 2.1** investigated the changes in WM integrity and grey matter (GM) volume over a 4-year follow-up period in the same cohort. In the time-window of this study, eight mutation carriers converted to the clinical stage of FTD, developing either bvFTD (n=5) or non-fluent variant PPA (nfvPPA; n=3). By comparing the changes within converters with non-converting mutation carriers, the researchers found increasing loss of frontotemporal WM integrity and GM volume from two years prior to symptom onset, and that symptom onset can be predicted by accurately by decline in selected WM tracts and GM regions. The results confirm the presence of a presymptomatic neuroimaging stage of FTD, and specifically highlight the potential of multimodal structural neuroimaging to become sensitive prognostic and diagnostic biomarkers for presymptomatic to early symptomatic familial FTD. Also in the same cohort, but involving a different mutation – the *C9orf72* repeat expansion – **Chapter 2.2** describes the first results of the study into presymptomatic changes in cognitive correlates of, and WM integrity and GM volume loss in this more recently described FTD genotype. Presymptomatic *C9orf72* repeat expansion carriers had subtle cognitive deficits in attention and executive function, as well as WM integrity loss of tracts connecting the frontal lobe, thalamus and motor areas. In a subgroup of carriers closer to symptom onset, also GM volume loss of the thalamus, cerebellum, parietal and temporal lobes was found. These findings illustrate that cognitive measures, T1-weighted and diffusion tensor MRI could be used as biomarkers to identify presymptomatic familial FTD and/or ALS.

Chapter 3 continues in the field of neuroimaging, outlining the application of DTI in speech and language research and the investigation of WM parameters as potential biomarkers in presymptomatic familial FTD. **Chapter 3.1** summarizes the normal anatomy of the major language WM tracts, and provides a detailed description of the seed/ target placement for fibre tracking, most often used for presurgical evaluation of brain tumours. Lastly, it lists important clinical research applications of DTI, namely in cerebrovascular disease, and PPA. **Chapter 3.2** reports on WM integrity changes in a large internal cohort (GENFI) of presymptomatic familial FTD. In comparison to non-carriers, FTD mutation carriers had early presymptomatic changes in WM integrity – up to 30 years prior to estimated symptom onset, with WM integrity consistently decreasing from minus 3 years to 10 years post-onset. Moreover, different patterns of WM integrity loss were found for the 3 different gene mutations, potentially underlying the different phenotypic expressions of *GRN*, *MAPT* and *C9orf72*. The results suggest that WM integrity loss is a consistent hallmark of FTD and, with changes developing earlier in the disease process than GM volume loss, DTI is a potential sensitive FTD biomarker.

Neuropsychological assessment is considered an essential tool in the diagnostic process of dementia, e.g. determining the existence of cognitive dysfunctions, differential diagnosis between subtypes of dementia and FTD. From a clinical research perspective, cognitive measures could also be valuable as diagnostic and staging biomarkers. **Chapter 4** lists four neuropsychological studies performed in presymptomatic and symptomatic FTD. **Chapter 4.1** reports on the 2-year follow-up study of presymptomatic *MAPT* and *GRN* mutation carriers within FTD-RisC. *MAPT* mutation carriers showed a steeper decline than *GRN* mutation carriers in social cognition, and memory significantly declined from 8 to 6 years before estimated onset in *MAPT* and *GRN* mutation carriers, and language and social cognition declined only in *MAPT* mutation carriers from respectively 7 to 5 years before estimated onset. The results confirm the prognostic value of neuropsychological assessment as potential clinical biomarker in the presymptomatic phase of familial FTD. **Chapter 4.2** continues on this work, by investigating cognitive trajectories over a 4-year follow-up in the same cohort. *MAPT* converters declined in language, attention, executive function, social cognition and memory, and *GRN* declining in attention and executive function. Cognitive decline in social cognition, language, attention and executive function was predictive for conversion. Interestingly, also lower scores on phonology and letter fluency were predictive for conversion to nfvPPA, and decline on categorical fluency was predictive for an underlying *MAPT* mutation. These results suggest mutation-specific patterns of cognitive decline from the presymptomatic to early symptomatic stage, and confirm the prognostic value of neuropsychological trajectories in conversion to FTD. **Chapter 4.3** reports on the use of qualitative aspects of commonly used verbal fluency tasks in bvFTD and PPA. Not only did PPA patients generate smaller clusters than bvFTD patients, also svPPA patients used more switches between clusters than the other two types of PPA. The results point out that qualitative aspects of verbal fluency provide additional information that can be used for clinical diagnostic purposes. **Chapter 4.4** provides a meta-analytic review on the extent and nature of memory impairments in bvFTD. The results of the meta-analysis point out that bvFTD patients have large deficits in working and episodic memory in comparison to controls, and encoding and retrieval processes discriminate well between bvFTD and AD patients. This suggests that instead of being an exclusion criterion for FTD, memory deficits should be regarded as a potential integral part of the clinical spectrum, and comprehensive memory tasks should be incorporated into the standard FTD diagnostic work-up of memory clinics.

Chapter 5 discusses the most important findings of this thesis, places them in light of previous literature, and suggests considerations and directions for future research with respect to the investigation of neuroimaging and neuropsychological biomarkers for familial FTD.

Samenvatting

Frontotemporale dementie (FTD) is een klinisch en pathologisch heterogene vorm van dementie op jonge leeftijd, waarbij de eerste symptomen zich meestal openbaren voor de leeftijd van 65 jaar. Als gevolg van degeneratie van de frontale en/of temporale hersenkwabben wordt de ziekte gekenmerkt door uitgesproken veranderingen in het gedrag (gedragsvariant FTD; bvFTD) en/of de taal (primair progressieve afasie; PPA), maar ook geïsoleerde of bijkomende verschijnselen van parkinsonisme en motorneuronziekte zijn beschreven. De diagnose is moeilijk te stellen, en er bestaat vaak veel tijd tussen de eerste klachten en de uiteindelijke diagnose. FTD heeft in 10-30% een autosomaal dominant overervingspatroon. Mutaties in de progranuline (*GRN*) en microtubule-associated protein tau (*MAPT*) genen, en de meer recent ontdekte repeat expansie in chromosoom 9 open reading frame 72 (*C9orf72*) zijn de drie meest voorkomende oorzaken. Deze familiaire vormen van FTD bieden een uniek ziektemodel, omdat we mutatiedragers kunnen identificeren in hun presymptomatische fase, en hen over tijd kunnen volgen om zodoende gevoelige biomarkers te ontwikkelen voor o.a. het vaststellen van ziekte, het volgen van ziekteprogressie, en het evalueren van toekomstige ziektemodificerende medicatie.

Hoofdstuk 1 geeft de **algemene introductie** over de ontwikkeling van klinische biomarkers in familiaire FTD en beschrijft de doelstellingen van dit proefschrift.

Hoofdstuk 2 beschrijft het eerste onderzoek naar multimodale beeldvormingsbiomarkers in presymptomatische familiaire FTD. Multimodale beeldvormingsbiomarkers zijn van groot belang bij het ontrafelen van het ziektemechanisme, en hebben bij andere vormen van dementie al bewezen grote diagnostische meerwaarde boven het conventionele gebruik van slechts één modaliteit. **Hoofdstuk 2.1** onderzoekt veranderingen in de integriteit van de witte en het volume van de grijze stof na vier jaar follow-up van het FTD-RisC cohort. In deze periode converteerden acht mutatiedragers naar FTD, en ontwikkelden zij bvFTD (n=5) of niet-vloeiende variant PPA (nfvPPA; n=3). Door geconverteerde met niet-geconverteerde mutatiedragers met elkaar te vergelijken, vonden de onderzoekers een toenemend verlies van witte stof integriteit en grijze stof volume vanaf twee jaar voorafgaand aan de eerste symptomen, maar ook dat conversie voorspeld kan worden door achteruitgang binnen geselecteerde witte stof banen en grijze stof gebieden. Dit bevestigt de aanwezigheid van subtiele hersenveranderingen (gemeten met MRI) in presymptomatische FTD, en onderstreept dat multimodale MRI-maten in potentie gevoelige prognostische en diagnostische biomarkers voor presymptomatische tot vroeg-symptomatische familiaire FTD kunnen zijn. Ook in dit cohort, zij het bij de *C9orf72* repeat expansie – beschrijft **Hoofdstuk 2.2** de eerste resultaten van de studie naar presymptomatische veranderingen in witte stof integriteit en grijze stof volume, en hun relatie met cognitieve achteruitgang. Bij presymptomatische *C9orf72* mutatiedragers was er reeds sprake van een subtiele achteruitgang in de aandachts- en executieve functies, alsmede witte stof integriteitsverlies van banen die de frontale kwabben, thalamus en motorische gebieden met elkaar verbinden. In een oudere subgroep van mutatiedragers (dus dichterbij debuut van de ziekte), was er daarnaast sprake van verlies van het volume van de grijze stof in de thalamus, het cerebellum, en de pariëtale en temporale kwabben. Deze resultaten

illustreren dat cognitieve maten, T1-gewogen MRI en DTI gebruikt kunnen worden als biomarkers om presymptomatische familiaire FTD en/of ALS aan te tonen.

Hoofdstuk 3 gaat verder op het gebied van beeldvorming, en beschrijft het gebruik van DTI in spraak- en taalonderzoek en het onderzoek naar witte stof parameters als potentiële biomarkers in presymptomatische familiaire FTD. **Hoofdstuk 3.1** geeft een samenvatting van de normale anatomie van de belangrijkste witte stofbanen die betrokken zijn bij taal, en geeft een gedetailleerde beschrijving van de optimale plaatsing van seeds/targets voor DTI-tractografie, welke meestal wordt gebruikt voor pre-operatieve evaluaties van hersentumoren. Als laatste geeft het hoofdstuk een overzicht van de meest gebruikte klinische onderzoeksapplicaties van DTI, te weten in cerebrovasculaire aandoeningen en PPA. **Hoofdstuk 3.2** beschrijft veranderingen in de integriteit van de witte stof in een groot internationaal cohort (GENFI) van presymptomatische FTD mutatiedragers en gezonde niet-dragers uit dezelfde families. In vergelijking met niet-dragers was er bij FTD mutatiedragers sprake van zeer vroege veranderingen in de witte stof integriteit – vanaf wel 30 jaar voorafgaand aan de eerste symptomen, en WS integriteit daalde bij hen consistent vanaf 3 jaar voor tot 10 jaar na het geschatte ontstaan van de eerste symptomen. Daarnaast werden en verschillende patronen van WS integriteitsverlies gevonden in de 3 mutaties, hetgeen waarschijnlijk onderliggend is aan de verschillende fenotypische uitingsvormen van *GRN*, *MAPT* en *C9orf72*. De resultaten suggereren dat verlies van de integriteit van de witte stof een consistent kenmerk is van FTD, en omdat de veranderingen hierin eerder in het ziekteproces optreden dan grijze stof volumeverlies, is DTI mogelijk een gevoeligere FTD biomarker.

Neuropsychologisch onderzoek wordt gezien als een belangrijk hulpmiddel in het diagnostisch proces bij dementie. Zo kan het niet alleen het bestaan van cognitieve stoornissen vaststellen, maar ook differentiëren tussen verschillende vormen van dementie en FTD. Vanuit een klinisch onderzoeksperspectief zouden cognitieve maten ook waardevol kunnen blijken als biomarker voor diagnostiek en ziektefasering. **Hoofdstuk 4** geeft vier neuropsychologische studies in presymptomatische en symptomatische FTD weer. **Hoofdstuk 4.1** beschrijft de 2-jarige follow-up van presymptomatische *MAPT* en *GRN* mutatiedragers in FTD-RisC. Bij *MAPT* mutatiedragers was er sprake van een sterkere achteruitgang in sociale cognitie dan bij *GRN* mutatiedragers. Geheugenprestaties gingen significant achteruitgang vanaf 8 (in *MAPT*) en 6 (in *GRN*) jaar voor het geschatte ontstaan van de eerste symptomen. Taal en sociale cognitie gingen alleen in *MAPT* mutatiedragers achteruit vanaf respectievelijk 7 en 5 jaar voor het geschatte onstaan van symptomen. De resultaten bevestigen de prognostische waarde van neuropsychologisch onderzoek als potentiële klinische biomarker in de presymptomatische fase van familiaire FTD. **Hoofdstuk 4.2** gaat verder op dit werk, en onderzoekt cognitieve achteruitgang in een 4-jarige follow-up periode binnen hetzelfde cohort. Geconverteerde mutatiedragers met een *MAPT* mutatie vertoonden achteruitgang binnen de domeinen taal, aandacht, executief functioneren, sociale cognitie en geheugen, en geconverteerde *GRN* mutatiedragers gingen alleen achteruitgang in de aandachts- en executieve functies. Cognitieve achteruitgang in sociale cognitie, taal, aandacht en executieve functies was voorspellend voor conversie. Daarnaast was achteruitgang op fonologie en lettervloeiendheid predictief voor conversie naar nfvPPA, en achteruitgang op categorische woordvloeiendheid predictief voor een onderliggende *MAPT* mutatie. Deze resultaten suggereren een mutatiespecifiek patroon van cognitieve achteruitgang van

de presymptomatische naar vroeg-symptomatische ziektefase, en bevestigen de prognostische waarde van neuropsychologische trajecten in conversie naar symptomatische FTD. **Hoofdstuk 4.3** beschrijft het gebruik van kwalitatieve aspecten van veelgebruikte verbale vloeiendheidstaken in bvFTD en PPA. Niet alleen maakten PPA patiënten kleinere clusters dan bvFTD patiënten, ook wisselden patiënten met een semantische variant van PPA (svPPA) meer tussen clusters dan de andere typen PPA. De resultaten wijzen erop dat kwalitatieve aspecten van verbale vloeiendheid extra informatie kunnen bieden, die gebruikt kunnen worden voor diagnostische doeleinden. **Hoofdstuk 4.4** beschrijft een meta-analyse over de mate en aard van geheugenstoornissen in bvFTD. De resultaten wijzen uit dat bvFTD patiënten evidente stoornissen hebben in het werk- en episodisch geheugen in vergelijking tot controles, en dat testen die een beroep doen op het encoderen en ophalen van informatie goed onderscheiden tussen Alzheimer dementie en FTD patiënten. Dit suggereert dat in plaats van een exclusiecriterium bij FTD, geheugenstoornissen juist gezien zouden moeten worden als integraal onderdeel van het klinische spectrum, en uitgebreide geheugentaken daarom standaard onderdeel uit moeten maken van de neuropsychologische testbatterij bij FTD.

In Hoofdstuk 5 worden de belangrijkste bevindingen van dit proefschrift geïntegreerd weergeven, geplaatst in het kader van eerdere literatuur, en overwegingen en mogelijke richtingen voor toekomstig onderzoek geschetst m.b.t. onderzoek naar MRI en neuropsychologische biomarkers voor FTD.

Dankwoord

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Curriculum vitae

Lize Corrine Jiskoot was born on June 8, 1987 in Dordrecht, the Netherlands. After finishing secondary school at the Johan de Witt Gymnasium in Dordrecht in 2005, she started studying Psychology at Leiden University. Her interest in neurology was spiked during courses in cognitive and biological psychology, and she therefore chose to finish her degree with a Master in Clinical Neuropsychology (cum laude) in February 2010. She decided to prolong her studies with a research master in Neurosciences, which she started in September 2010. She got involved in dementia research during her first-year master thesis at the VUmc Alzheimer Centre in Amsterdam, after which she finished her research master (summa cum laude) with an internship at the Department of Neurology of the Erasmus Medical Centre (Erasmus MC) and Department of Radiology of the Leiden University Medical Center (LUMC) – which formed the basis of the research presented in this thesis. In 2016, she spent four months in London (United Kingdom) to perform a research fellowship at the Dementia Research Center (DRC) of University College London (UCL), under supervision of Dr. Jonathan Rohrer. Alongside her PhD, Lize has been working as a neuropsychologist for the Alzheimer Centre Erasmus MC at the Department of Neurology from October 2012 onwards. In September 2017 she continued her clinical training to become GZ-psychologist at the Departments of Neurology and Psychiatry of the Erasmus MC. Additionally, she is working as a postdoctoral researcher at the Alzheimer Centre Erasmus MC, continuing her work on the presymptomatic FTD Risk cohort, and collaborating with the Dementia Research Center of University College London (UCL). Lize is living together with her boyfriend Philipp, enjoying life dividing their time between Rotterdam and London.

List of publications

2018

- **Jiskoot LC**, Panman JL, van Asseldonk L, Dopper EGP, Franzen S, Meeter LH, Donker Kaat L, van der Ende EL, Timman R, van Minkelen R, van Swieten JC, van den Berg E, Papma JM. Longitudinal cognitive biomarkers in presymptomatic familial frontotemporal dementia. J Neurol 2018; 265(6): 1381-1392.
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PhD portfolio

PhD training	Year	ECTS
General courses		
■ BROK, Erasmus Medical Center, Rotterdam	2014	1.5
■ Specific courses		
■ FSL course, Leiden University Medical Center	2012	1.5
■ SNP course, MolMed, Erasmus Postgraduate School	2012	1.5
■ Masterclass 'Writing a competitive project for a personal grant of a Dutch charity organization	2017	0.5
■ Acceptance Commitment Therapy (ACT) basiscursus	2017	1
■ Basisopleiding tot Mindfulnesstrainer	2018	2
■ Female Talent Class, Erasmus MC	2018	2
Conferences/seminars		
■ 10th International Conference on Frontotemporal Dementias (ICFTD), Manchester, UK – attendance	2012	1
■ 9th International Conference on Frontotemporal Dementias (ICFTD), Vancouver, Canada – oral presentation	2014	2
■ 8th International Conference on Frontotemporal Dementias (ICFTD), Munich, Germany – oral presentation	2016	2
■ Alzheimer's Association International Conference (AAIC), Boston, USA – poster presentation	2013	1
■ Alzheimer's Association International Conference (AAIC), Washington, USA – oral presentation	2015	2
■ Alzheimer's Association International Conference (AAIC), Toronto, Canada – oral presentation	2016	2
■ Alzheimer's Association International Conference (AAIC), London, UK – poster presentations	2017	1
■ 6th Scientific Meeting of the Federation of the European Societies of Neuropsychology (FESN), Maastricht, the Netherlands – oral presentation	2017	2
■ European Society for Magnetic Resonance in Medicine and Biology (ESMRMB), Edinburgh, Scotland – poster presentation	2015	1
■ NWO Brain & Cognition Health Pillar Meeting, Utrecht, the Netherlands – oral presentation	2014	1
■ Nederlandse Vereniging voor Neuropsychologen (NVN) conferences	2012-'18	1
■ GENFI Investigators meetings	2014-'18	1
■ Alzheimer Nederland Mix&Match meetings	2012-'18	1

PhD training	Year	ECTS

Other

■ Genetic Frontotemporal dementia Initiative (GENFI) site study coordinator and member of neuropsychology core	2014-'18	25
■ Parelsnoer Initiative (PSI) Neurodegenerative Diseases site study coordinator	2012-'18	20
■ Clinical trials psychologist (FORUM, TauRx, Marguerite RoAD), Alzheimer center southwest Netherlands	2013-'16	5
■ Alzheimer center southwest Netherlands weekly research meetings	2013-'17	4
■ Alzheimer center southwest Netherlands monthly journal club meetings	2017	1
■ Member of the Dutch FTD Expert group	2016-'18	0.5
■ Regular speaker and attendant FTD Lotgenoten	2012-'18	2.5
■ Regular speaker Alzheimer cafes	2012-'18	1
■ Weekly project group meeting FTD-RisC	2017	1
■ Organizing information meetings for FTD-RisC study participants	2013-'17	10
■ Monthly multidisciplinary meeting with the Department of Psychiatry, Erasmus Medical Center	2016-'18	1
■ Organizing PhD day, Erasmus Medical Center	2013	0.5

Teaching activities	Year	ECTS

Lecturing

■ Vaardigheidsonderwijs (VO), Erasmus Medical Center	2012-'18	5
■ Career prospects talk, Utrecht University	2015	0.5
■ Alzheimercafé 2016, Laurens Antonius Binnenweg	2016	0.5
■ Neurology resident education, Erasmus Medical Center	2015	0.5
■ Supervising Master Theses 16 students	2013-'18	24
■ Supervising Clinical Internships 35 students	2012-'18	70
Total		**200**

List of abbreviations

ACC	anterior cingulate cortex
ACR	anterior corona radiata
AD	Alzheimer's disease
ADC	apparent diffusion coefficient
AF	arcuate fasciculus
ALIC	anterior limb of the internal capsule
ALS	amyotrophic lateral sclerosis
aMCC	anterior midcingulate cortex
ARTFL	Advancing Research and Treatment for FTLD
ASL	arterial spin labeling
ATL	anterior temporal lobe
ATR	anterior thalamic radiation
AUC	area under the curve
AxD	axial diffusivity
BADS	Behavioural Assessment of the Dysexecutive Syndrome
bCC	body of the corpus callosum
BDI	Beck's depression inventory
BFLT	Biber Figure Learning Test
BNT	Boston Naming Test
bvFTD	behavioural variant FTD
BVMT-R	Brief Visuospatial Memory Test – Revised
BVRT	Benton Visual Retention Test
C9orf72	*chromosome 9 open reading frame 72*
C9orf72RE	*chromosome 9 open reading frame 72* repeat expansion
CBD	corticobasal degeneration
CBF	cerebral blood flow
CBI	Cambridge Behavioural Inventory
CBS	corticobasal syndrome
CC	corpus callosum
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHMP2B	*Charged multivesicular body protein 2b*
CI	confidence interval
CSF	cerebrospinal fluid
CSVD	cerebral small vessel disease
CVD	cerebrovascular disease
CVLT	California Verbal Learning Test
CT	computed tomography

DEC	directionally encoded colour coded
DINAD	Dominantly Inherited Non-Alzheimer Dementias
DMN	default mode network
DNA	deoxyribonucleic acid
DS	Digit Span
DTI	diffusion tensor imaging
DWI	diffusion weighted imaging
EC	external capsule
EYO	estimated years from symptom onset
FA	fractional anisotropy
FAB	Frontal Assessment Battery
FCSRT	Free and Cued Selective Reminding Test
FDG	fluorodeoxyglucose
FI	frontoinsula
FLAIR	fluid-attenuated inversion recovery
FM	forceps minor
FOV	Field of View
FPI	FTD Prevention Initiative
fMRI	functional magnetic resonance imaging
FSL	FMRIB's Software Library
FTD	frontotemporal dementia
FTD-RisC	Frontotemporal Dementia Risk Cohort
FTLD	frontotemporal lobar degeneration
FUS	*fused in sarcoma*
FWE	family-wise error
FWHM	full width at half maximum
gCC	genu of the corpus callosum
GENFI	Genetic Frontotemporal dementia Initiative
GM	grey matter
GRN	*progranulin*
HC	healthy control
IFOF	inferior fronto-occipital fasciculus
ILF	inferior longitudinal fasciculus
JHU	John Hopkins University
LDST	Letter Digit Substitution Test
LEFFTDS	Longitudinal Evaluation of Familial FTD Subjects
LM	Logical Memory
lvPPA	logopenic variant primary progressive aphasia
MAPT	*microtubule-associated protein tau*
MATLAB	Matrix Laboratory
MCI	mild cognitive impairment

MD	mean diffusivity
MMSE	Mini-Mental State Examination
MND	motor neuron disease
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
NfL	neurofilament light chain
nfvPPA	non-fluent variant primary progressive aphasia
NifTI	Neuroimaging Informatics Technology Initiative
NPI(-Q)	Neuropsychiatric Inventory (Questionnaire)
OFC	orbitofrontal cortex
PCC	posterior cingulate cortex
PCR	polymerase chain reaction / posterior corona radiata
PET	positron emission tomography
PFC	prefrontal cortex
PiB	Pittsburgh compound B
PLIC	posterior limb of the internal capsule
PMC	premotor cortex
PPA	primary progressive aphasia
PSP	progressive supranuclear palsy
PTR	posterior thalamic radiation
RAVLT	Rey Auditory Verbal Learning Test
RBMT	Rivermead Behavioural Memory Test
RCFT	Rey Complex Figure Test
RD	radial diffusivity
RMT W/F	Recognition Memory Test Words/Faces
ROC	receiver operating characteristics
ROI	region-of-interest
RPIC	retrolenticular part of the internal capsule
rs-fMRI	resting-state functional magnetic resonance imaging
SAT	Semantic Association Test
sCC	splenium of the corpus callosum
SCR	superior corona radiata
SD	standard deviation
SLF	superior longitudinal fasciculus
SN	salience network
SPECT	single-photon emission computed tomography
SPSS	Statistical Package for the Social Sciences
STAI	State-Trait Anxiety Inventory
svPPA	sematic variant primary progressive aphasia
TARDP	*TAR-DNA binding protein*
TBK	*TANK-binding kinase*

TBSS	Tract-Based Spatial Statistics
TDP	transactive response DNA-binding protein
TE	echo time
TFCE	threshold-free cluster enhancement
TMT	Trailmaking Test
ToM	Theory of Mind
TR	repetition time
UF	uncinate fasciculus
VAT	Visual Association Test
VBM	Voxel-Based Morphometry
VCP	*valosin-containing protein*
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WM	white matter
WMS	Wechsler Memory Scale