CLINICAL INSIGHTS INTO FRONTOTEMPORAL DEMENTIA

A neuropsychological perspective on disease onset and progression

Jackie Martine Poos

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Een neuropsychologisch perspectief op ziekte begin en progressie

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CHAPTER 1

General introduction

General introduction

Frontotemporal dementia (FTD) encompasses a clinically, genetically and pathologically heterogeneous group of neurodegenerative disorders that manifest at a young age[1]. Symptoms typically develop before the age of 65, and have devastating effects on daily living[1]. It is the second most common form of early-onset dementia after Alzheimer's disease (AD) with a prevalence of approximately 10/100.000 and incidence of 1.5-2/100.000 persons per year[2]. FTD is pathologically characterized by frontotemporal lobar degeneration (FTLD) which results in behavioral disturbances and/or language impairments, and may be accompanied by motor and psychiatric symptoms as well[1, 3].

Clinical syndromes

Behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA) are the two main clinical manifestations within the FTD spectrum[4, 5]. Moreover, some patients with FTLD also develop movement disorders such as motor neuron disease (MND), amyotrophic lateral sclerosis (ALS), corticobasal syndrome (CBS), and progressive supranuclear palsy (PSP)[1, 3].

bvFTD is the most common clinical phenotype and accounts for more than 50% of all cases[6]. It is characterized by an insidious onset with gradually progressive behavioral disturbances such as disinhibition, apathy, loss of empathy and sympathy, perseverative/stereotypic or compulsive behavior, and hyperorality[4]. Caregivers or family members frequently report loss of social and personal conduct, impulsive decision-making, diminished personal warmth, and decreased interest in daily-life activities. Patients often fail to recognize these symptoms themselves due to anosognosia[7]. Characteristic neuroimaging features are grey matter atrophy in the prefrontal cortex and anterior temporal areas as well as the anterior cingulate, anterior insula and thalamus[8].

Approximately 40% of patients with FTLD present with primary language impairment at symptom onset, which is insidiously progressive in nature, with minimal changes in other cognitive modalities in the first one to two years[9]. This clinical presentation, denoted as PPA, can de distinguished into three subtypes: semantic variant PPA (svPPA), nonfluent variant PPA (nfvPPA) and logopenic variant PPA (lvPPA), with the latter commonly also manifesting as a result of AD pathology[5]. svPPA is characterized by gradual degradation of semantic memory, leading to profound confrontation naming difficulty and impaired comprehension of single words as a result of left anterior temporal lobe atrophy, including the anterior hippocampus and amygdala[5, 9]. In contrast, the characteristic feature of nfvPPA is effortful, nonfluent speech that consists of highly simplified sentence structures, and agrammatism. This is caused by grey matter atrophy of the left inferior frontal lobe[5, 9]. Core clinical features of patients with

lvPPA include impaired lexical retrieval in conversational speech, and impaired repetition of sentences and phrases, and MRI observations have associated this phenotype with grey matter atrophy in posterior perisylvian regions, including the inferior parietal lobule and posterolateral temporal regions[5, 9].

Importantly, overlap in symptoms exists between subtypes of PPA and bvFTD[3]. For example, patients with bvFTD may show semantic deficits, whilst patients with svPPA may develop behavioral disturbances[3, 10]. Similarly, some patients exhibit symptoms of both nfvPPA and lvPPA, resulting in a mixed PPA diagnosis[11]. Patients with bvFTD or PPA can also develop atypical parkinsonism as a part of CBS or PSP, or MND-associated symptoms[3].

Neuropsychology of FTD

Neuropsychological assessment is an important part of the diagnostic process of FTD as it can be used to determine the presence, nature and/or severity of cognitive impairment. A neuropsychological assessment is crucial to differentiate between FTD subtypes and other neurodegenerative disorders, thereby contributing to a timely and accurate diagnosis[12, 13]. A comprehensive neuropsychological assessment to elucidate the cognitive profile is especially important in patients with bvFTD, as cognitive impairments may be overlooked by the behavioral symptoms that typically dominate the clinical presentation[7]. The cognitive profile of patients with bvFTD is, according to current clinical criteria, characterized by executive/generation deficits with relative sparing of memory and visuospatial functions[4]. The majority of studies confirm that patients with bvFTD show deficits in executive functions such as abstract reasoning, cognitive flexibility, response inhibition, planning, and multitasking[14-22]. However, most executive function tests seem to be of low specificity and do not consistently discriminate patients with bvFTD from other types of dementia[15, 18, 20, 23]. Furthermore, several studies report episodic memory impairment in patients with bvFTD at initial presentation, equally in severity to AD dementia[24]. One promising avenue to improve the differential diagnosis between bvFTD and other types of dementia is the domain of social cognition. Social cognition refers to a set of cognitive processes that are involved in normal social interactions[7]. Particularly in patients with bvFTD, severe deficits have been demonstrated in multiple aspects of social cognition, such as theory of mind, emotion recognition and the processing of social norms and rules[7]. However, ecologically valid instruments for measuring social cognitive processes are typically not part of the standard diagnostic work-up.

The clinical distinction between svPPA, nfvPPA or lvPPA also remains challenging, despite the availability of the international guidelines on the classification of PPA subtypes[25]. The neuropsychologist plays a crucial role in the diagnostic process by evaluating the language and speech abilities of a patient in spontaneous speech and by administering language tests

for fluency, comprehension, repetition and naming. Nevertheless, a clinical diagnosis of PPA remains complex as not all cases fit within one of the three classifications, especially in the early stages, due to overlap in symptoms and additional impairments in other domains such as memory, executive functions and social cognition[25, 26].

Another challenge in the field is the lack of sensitive tests that can detect cognitive impairments in the earliest stages of the disease. Most paper-and-pencil tasks included in the standard diagnostic work-up have been developed for populations with evident cognitive impairments. However, FTD is characterized by an insidious onset where cognitive changes are often very subtle in the early stage. This hampers early clinical recognition and can lead to a substantial diagnostic delay. Yet, a timely diagnosis is crucial for proper patient management and early treatment planning, including patient stratification in upcoming clinical trials. Thus, sensitive cognitive instruments that can 1) detect deficits and track progression in the earliest stages, and 2) aid the differential diagnosis between FTD subtypes and other neurodegenerative disorders need to be identified and examined.

Genetic FTD

FTD is a highly heritable disease, with 20-30% of cases having an autosomal dominant pattern of inheritance with high penetrance[27]. The three most common causes of genetic FTD are a repeat expansion in the chromosome 9 open reading frame 72 gene (*C9orf72*), and mutations in microtubule-associated protein tau (*MAPT*) or progranulin (*GRN*) genes[27]. Rarer forms of genetic FTD include for example mutations in the *TARDBP*, *VCP*, *TBK1* and *CHMP2B* gene[27].

C9orf72

The *C9orf72* repeat expansion accounts for approximately 42% of genetic cases, making it the most common cause of genetic FTD and/or ALS[28-30]. It is associated with a diffuse atrophy pattern of widespread grey matter volume decrease in both frontal and temporal cortices, but also more posterior cortical and subcortical areas, including the cerebellum. This typically results in a clinical diagnosis of bvFTD, ALS or a combination of both (i.e. FTD-ALS), and sporadically PPA[30]. A variable age at symptom onset is observed both between and within families, ranging from the 20s to the 90s, although most cases develop symptoms between 50 and 70 years old[28]. Disease duration differs depending on clinical phenotype, with ALS and FTD-ALS cases deteriorating more progressively than bvFTD cases[28]. Notably, patients can also present with severe psychiatric symptoms, including obsessive compulsive behavior and psychotic features such as hallucinations and delusions[30].

GRN

Mutations in the *GRN* gene are less common and account for ~35% of genetic FTD cases[28]. *GRN* mutations often lead to an asymmetrical pattern of atrophy in the frontal, temporal and parietal lobes, which most frequently results in a clinical diagnosis of bvFTD or nfvPPA, and is often accompanied by parkinsonism[30]. Age at symptom onset ranges from the late 30s to 90 years of age, with most cases presenting between age 55 and 70[28]. Disease duration ranges from less than a year to over 20 years, but varies between and within mutation types[28].

MAPT

MAPT mutations are the least common amongst the three major genetic causes, with large geographical variability, accounting for approximately 23% of genetic FTD cases[28]. Patients show localized anterior temporal lobe involvement, which is associated with behavioral and semantic deficits. bvFTD is the main phenotype, but is occasionally accompanied by Parkinson-related phenotypes such as CBS or PSP[30]. Mean age at symptom onset is lowest for this group compared to other gene groups, usually ranging from the early 40s to 60s, although patients have been reported as young as 17 years old[28]. Disease duration is highly variable, ranging from less than a year to over 40 years. Similar to the *C9orf72* repeat expansion, disease duration is shorter in patients with (concomitant) motor disorder phenotypes[28].

The presymptomatic stage

The offspring of patients with a genetic form of FTD have a 50 percent chance of carrying the mutation and thus developing the disease in the future. Mutation carriers can be identified before symptom onset through DNA genotyping, a stage that is referred to as the presymptomatic stage – and presymptomatic mutation carriers. Studying genetic forms of FTD provides an unique opportunity to study pathological and clinical changes from the presymptomatic to symptomatic stage of the disease, thereby identifying the most sensitive (bio)markers for measuring this transition. Studies on the presymptomatic stage of FTD have confirmed that disease pathology emerges years before symptom onset, similar to what has been shown in autosomal dominant AD and Huntington's disease (HD)[31-37]. This suggests that potential disease-modifying treatments may have the most profound effect before overt clinical onset when neuronal loss is still minimal[31-37]. Next steps within the field include studying presymptomatic mutation carriers longitudinally to provide insight into the timeframe when pathological and clinical changes occur and how they progress, to identify the best time window to start potential treatment. Prospective longitudinal cohort studies for genetic presymptomatic FTD have been set-up in Europe, USA and Australia to develop such novel biomarkers. The first longitudinal cohort study was the Dutch Frontotemporal Dementia Risk Cohort (FTD-RisC), which tracks presymptomatic mutation carriers and non-carrying family members since 2009 on a (two)yearly interval with a standardized clinical assessment

consisting of a comprehensive neuropsychological assessment, physical examination, MRI of the brain, venipuncture and lumbar puncture at the Erasmus MC University Medical Center[34]. Thus far, more than 200 participants have been included in this study. In 2012, the Genetic FTD Initiative (GENFI) started, an international multicenter study, in which currently 34 academic centers across Europe and Canada, including the Erasmus MC University Medical Center, have recruited more than 1000 participants[33]. The Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) and the Australian Dominantly Inherited Non-Alzheimer Dementias (DINAD), collaborate with GENFI within the FTD Prevention initiative (FPI) to align studies more closely and facilitate global clinical trials[28, 38].

These cohort biomarker studies in 50% at-risk individuals, have taught us that some individuals may experience significant psychological distress as a result of being at-risk. Individuals may choose to undergo predictive testing to determine if they are carriers of a mutation for FTD, with a positive test result implicating unavoidable approaching onset of a debilitating, fatal illness[39]. As most of these individuals have first-hand experience with the consequences of the disease in close family members, this influences their views and plans for the future[39, 40]. It is not surprising that carrying a mutation causative of FTD or the ambiguity of being at risk of such a mutation, without availability of a cure, can cause symptoms of anxiety and depression[41, 42], similar to what has previously been demonstrated in familial AD dementia and HD[43-45]. In the absence of disease-modifying treatment, psychological interventions are necessary to reduce symptoms of anxiety and depression in presymptomatic mutation carriers and 50% at-risk individuals. Thus far no study has been published on psychological approaches in first-degree family members of patients with genetic FTD, but a mindfulness-based intervention has proven beneficial in premanifest HD individuals. The three core principles of mindfulness are 1) conscious awareness, 2) the present moment, and 3) a non-judgmental attitude. Mindfulness programs focus on cultivating these three aspects by performing meditation-based exercises, and special emphasis is given to accepting things as they are without trying to change them. The latter particularly makes this a promising avenue for populations with chronic diseases, including presymptomatic FTD mutation carriers and 50% at-risk individuals for FTD.

Outline of this thesis

Currently, no cure exists for FTD but clinical trials testing new treatments are now underway and sensitive clinical endpoints to monitor treatment response are urgently needed. Furthermore, diagnostic accuracy in the early stages of the disease is still hampered by the wide range of overlapping clinical features between phenotypes, and with other neurodegenerative and psychiatric disorders, often causing a significant diagnostic delay. Therefore, the development and validation of novel sensitive cognitive markers for FTD to

track clinical onset and progression are crucial within the field of clinical neuropsychology. This will aid an early diagnosis and could inform clinical trials in selecting sensitive endpoints for measuring treatment effects as well as characterizing the best time window for starting treatment. In the absence of disease-modifying treatment for presymptomatic individuals, tailored psychotherapeutic interventions reducing psychological distress are necessary for individuals that are at-risk.

The aims of this thesis were to **1**) **identify sensitive clinical and cognitive markers** for early detection of clinical onset and tracking disease progression in presymptomatic, prodromal and symptomatic stages of FTD, and **2) to evaluate a psychosocial intervention** for reducing feelings of anxiety and depression in the presymptomatic stage.

Chapter 2 characterizes disease trajectories of different types of genetic FTD. In Chapter 2.1 we describe gene-specific cognitive profiles in symptomatic *C9orf72*, *GRN* and *MAPT* mutation carriers to identify sensitive cognitive tests for signaling disease onset in these subtypes. Chapter 2.2 reports on longitudinal cognitive assessment across disease stages, including mutation carriers in the asymptomatic, prodromal and symptomatic stage, to identify sensitive cognitive tests for tracking disease progression. In Chapter 2.3 longitudinal brain volume loss is investigated in presymptomatic mutation carriers using normative brain volumetry software.

In Chapter 3, we describe the differential ability of new cognitive instruments in the FTD spectrum. In Chapter 3.1, performance on a newly developed language test for abstract semantic associations is evaluated in patients with bvFTD, svPPA, nfvPPA and lvPPA. Chapter 3.2 describes the development of gene-specific cognitive composite scores in the three major genetic causes of FTD. Chapter 3.3 describes the performance of patients with bvFTD, AD, and presymptomatic mutation carriers on an emotion recognition test for morphed facial expressions.

Chapter 4 focuses on memory performance in the FTD spectrum. In Chapter 4.1, we report a meta-analysis on episodic memory performance in patients with bvFTD compared to healthy controls and patients with AD. Chapter 4.2 reports on a study assessing free and cued memory recall in presymptomatic and symptomatic *C9orf72*, *GRN* and *MAPT* mutation carriers. In Chapter 4.3, a study assessing the differences in recognition memory between patients with bvFTD and AD is described.

In Chapter 5 we describe a pilot study on the efficacy and feasibility of a mindfulness-based stress reduction program on reducing feelings of anxiety and depression in presymptomatic mutation carriers and individuals that are 50% at-risk of having a genetic mutation causative of FTD.

Chapter 6 summarizes and interprets the findings of this thesis, discusses how they relate to other findings in the field, and provides suggestions for future research.

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CHAPTER 2

Characterizing disease trajectories in genetic frontotemporal dementia

CHAPTER 2.1
Cognitive profiles discriminate between genetic variants of frontotemporal dementia

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Abstract

Introduction: Trials to test disease-modifying treatments for frontotemporal dementia are eagerly awaited and sensitive instruments to assess potential treatment effects are increasingly urgent, yet lacking thus far. We aimed to identify gene-specific instruments assessing clinical onset and disease progression by comparing cognitive functioning between bvFTD patients across genetic mutations.

Methods: We examined differences in 7 cognitive domains between bvFTD patients with GRN (n=20), MAPT (n=29) or C9orf72 (n=31) mutations, and non-carriers (n=24), and described longitudinal (M=22.6 months, SD=16.6) data in a subsample (n=27).

Results: Patients showed overall cognitive impairment, except memory recall, working memory and visuoconstruction. GRN patients performed lower on executive function (mean difference -2.1; 95%CI -4.1 to -0.5) compared to MAPT and lower on attention compared to MAPT (mean difference -2.5; 95%CI -4.7 to -0.3) and C9orf72 (mean difference -2.4; 95%CI -4.5 to -0.3). Only MAPT patients were impaired on delayed recall (mean difference -1.4; 95%CI -2.1 to -0.7). GRN patients declined rapidly on attention and memory, MAPT declined in confrontation naming, whereas C9orf72 patients were globally impaired but remained relatively stable over time on all cognitive domains.

Discussion: This study shows gene-specific cognitive profiles in bvFTD, which underlines the value of neuropsychological tests as outcome measures in upcoming trials for genetic bvFTD.

Background

Frontotemporal dementia (FTD) includes a large spectrum of neurodegenerative disorders with a variable clinical presentation of either progressive behavioral and executive deficits (behavioral variant FTD [bvFTD]) or language dysfunction (primary progressive aphasia [PPA]), associated with prominent frontal and/or anterior temporal lobe degeneration[1]. bvFTD is the most common phenotype in the clinical spectrum and the neuropsychological profile is generally characterized by impaired executive function (e.g. planning, set shifting and working memory), social cognition (e.g. theory of mind, emotional processing), whereas memory and visuoconstruction are relatively spared in comparison to executive dysfunction[2]. However, it is becoming increasingly clear that these cognitive impairments vary in severity and progression. Executive dysfunction may be absent or overshadowed by behavioral dysfunctions and/or significant episodic memory impairment can be present even at the earliest stages of the disease[1, 3]. Factors influencing the variety in cognitive impairments between patients with bvFTD are not yet understood.

In 20-30% of cases, FTD has an autosomal dominant pattern of inheritance (i.e. mutations in microtubule-associated protein tau [MAPT], progranulin [GRN] genes, or a repeat expansion in chromosome 9 open reading frame 72 [C9orf72] gene)[4]. GRN mutations often lead to a prominent asymmetrical pattern of atrophy in the frontal, temporal and parietal lobes, and are associated with behavioral deficits, apraxia and language disorders, most frequently resulting in a clinical diagnosis of bvFTD or non-fluent variant PPA (nfvPPA) and is often accompanied by parkinsonism[1, 5]. MAPT mutations show localized temporal lobe involvement associated with behavioral and semantic deficits, resulting in bvFTD as the main phenotype, and is occasionally accompanied by a parkinson-dominant phenotype with corticobasal syndrome (CBS) or progressive supranuclear palsy (PSP) syndrome[1, 6]. The atrophy associated with C9orf72 repeat expansion is rather diffuse, and as a result leads to a more widespread pattern of clinical and cognitive features such as behavioral and executive impairment but also notable psychiatric features including psychosis and anxiety[7, 8]. This is usually accompanied by a clinical diagnosis of bvFTD and/or motor neuron disease (MND)[1]. Cognitive differences between genetic variants of FTD can, in part, be explained by the associated phenotypes (i.e. bvFTD or PPA). Yet, there is also a high variability in the profile of cognitive decline between patients with bvFTD. This might be due to the different atrophy patterns associated with each genetic mutation.

Implementation of clinical trials to test disease-modifying treatments for bvFTD is eagerly awaited and instruments that can signal clinical onset and measure potential longitudinal treatment effects are increasingly urgent. Although a small number of studies have presented comprehensive clinical descriptions of FTD patients with mutations in MAPT, GRN or C9orf72[5, 8-11], there are even less studies that concisely and elaborately describe the specific cognitive

profiles associated with each mutation or make direct comparisons between genetic variants. Investigating the distinct cognitive profiles between genetic variants of bvFTD will enable us to identify gene-specific sensitive cognitive outcome measures for signaling disease onset, tracking disease progression and measuring potential treatment effects in upcoming therapeutic trials.

We compared cognitive profiles cross-sectional in patients with bvFTD due to mutations in GRN, MAPT or C9orf72 and report patterns of cognitive decline in a subset of patients with follow-up data.

Methods

Participants

Patients were included in an ongoing genetic-epidemiological study, after referral to the outpatient clinic of the Erasmus Medical Center between 1994 and 2018. We reviewed data of patients with a known pathogenic mutation in MAPT or GRN, or repeat expansion in C9orf72, who had a clinical diagnosis of bvFTD and underwent one or multiple neuropsychological assessments (n=81)[2]. Standardized work up consisted of a neurological and neuropsychological assessment, laboratory testing and brain imaging. Diagnosis was determined in a multidisciplinary consensus meeting of the FTD Expertise Center of the Erasmus MC University Medical Center, involving experienced neurologists, neuropsychologists, neuroradiologists, geriatricians, and a care consultant according to established diagnostic criteria for bvFTD[2]. Patients were categorized into three subtypes based on their clinical presentation; disinhibited (e.g. loss of social manners, inappropriate and impulsive behavior), apathetic (e.g. lack of interests in life activities and/or interactions with others, little motivation to undertake action) and stereotypic (e.g. pacing, picking, ritualistic behavior)[12]. For a separate analysis, patients with a GRN mutation were divided based on predominant left-sided (n=10), right-sided (n=4) or generalized atrophy (n=4) as described in the report of the radiologist. For two patients there was no report available. Twenty four non-carrier participants that were part of an ongoing epidemiological study of Dutch pathologically confirmed genetic FTD families (FTD Risk cohort (FTD-RisC[13])), were used as a reference (matched for age, education and sex).

Neuropsychological assessment

As the standardized neuropsychological test battery underwent some changes over the time period of 24 years, the protocol differed between patients. We only included tests with ten or more subjects in each group. Global cognitive functioning was screened with the Mini-Mental State Examination (MMSE)[14] and the Frontal Assessment Battery (FAB)[15]. For executive functioning we used the Trail making Test (TMT) part B[16], Stroop Color Word Test (SCWT) interference card III[17], Modified Wisconsin Card Sorting Test (mWCST)[18], and Similarities of the

Wechsler Adult Intelligence Scale III-NL (WAIS-III)[19]. For attention and concentration we used TMT part A[16], and the SCWT word reading (I) and color naming card (II)[17]. For language we used the Boston Naming Test (BNT)[20], and semantic and letter fluency. For episodic memory – immediate recall, we used the Rey Auditory Verbal Learning Test (RAVLT) Dutch version[21] – immediate recall trial, the Rivermead Behavioral Memory Test (RBMT)[22] Dutch version – immediate recall, and the short version of the Visual Association Test (VAT)[23]. For episodic memory – delayed recall, we used the RAVLT Dutch version – delayed recall trial and the RBMT Dutch version – delayed recall trial. For working memory we used the total score of the WAIS-III Digit Span (forward upper limit 9; backward upper limit 8)[19]. For visuoconstruction we used the Clock Drawing test[24]. For the BNT, the VAT and Clock Drawing Test different test versions were used (respectively 15-item/30-item/60-item, 12-item/24-item, 3-item/14-item). For these respective tests, the scores were extrapolated to match performance on the version with the maximum score. The TMT and SCWT scores were truncated to 300 seconds for patients that exceeded the time limit or were unable to complete the test. The mean was calculated for SCWT card I and II, as both tests are measures of attention/processing speed. When patients underwent multiple neuropsychological assessments in a short period of time (≤ 4 months) we considered this as one baseline assessment (n=3); for tests that were performed at both assessments, the score of the first assessment was included in the cross-sectional baseline analyses.

Statistical analyses

Statistical analyses were performed using SPSS Statistics 21.0 (IBM Corp., Armonk, NY). To aid interpretation, we standardized all raw neuropsychological test scores by converting them into z-scores (i.e., individual test score minus the mean of non-carriers, divided by the standard deviation (SD) of non-carriers). Composite domain scores constituted the mean of the z-scores for the tests within one domain (as described in Section Neuropsychological assessment). When a neuropsychological test was missing, the domain was calculated based on the remaining test scores in that specific domain. On TMT A and B, SCWT card I+II and card III, WCST, and VAT, a log10 transformation was applied to normalize the data. We set the significance level at $p<0.05$ (2-tailed) across all comparisons. We compared demographic data with one-way analyses of variance. We analyzed sex and subtype differences between groups using Pearson χ^2 tests. Neuropsychological data between groups were analyzed by means of one-way analysis of covariance. For the comparison of each mutation carrier group to non-carriers we used age as a covariate, and performed planned contrasts between each mutation carrier group and non-carriers. We compared mutation carrier groups in pairwise comparisons with disease duration as an additional covariate. Additional analyses were performed to compare cognitive domains in GRN patients with a predominant left-sided, right-sided or generalized atrophy pattern. All post-hoc analyses were Bonferroni corrected for multiple comparisons. Effect sizes (Cohen's d) were calculated for the (significant) differences in test scores. According to Cohen's Nomenclature[25] $d>0.80$ indicates a large difference. A

bias-corrected 95% confidence interval (CI) was calculated based on the standard error. The percentage overlap (%OL) in (significant) test scores between groups was also reported according to Zakzanis' calculations[26] ;d=0 equates to 100% overlap, d=1 equates to 45% overlap and d=3 equates to less than 5% overlap in group scores. In addition, we report a description of a subset of patients with longitudinal data both on composite cognitive domains and neuropsychological tests (as described in Section Neuropsychological assessment). Due to the small sample size, we did not perform longitudinal statistical analysis.

Results

Demographics

Demographic data are shown in Table 1. MAPT mutation carriers were significantly younger than the other mutation carrier groups. C9orf72 repeat expansion carriers were older and had a significantly longer disease duration than the other mutation carrier groups. GRN mutation carriers performed significantly lower on MMSE and FAB.

Table 1. Demographic features.

	MAPT (n=29)	*GRN* (n=20)	*C9orf72* (n = 31)	Non-carriers (n=24)	*p* value	Group differences
Age at baseline, y	52.6 ± 5.5	60.4 ± 7.4	62.1 ± 9.1	56.1 ± 5.7	<0.01	*MAPT* < *GRN* = *C9orf72* NC < *C9orf72*
Sex (% female)	10 (34.5%)	12 (57.1%)	13 (41.9%)	11 (45.8%)	0.6	n.s
Educational level [a] (median (IQR))	5 (2)	5 (2)	5 (2)	5 (0)	0.8	n.s
Disease duration, y	1.4 ± 2.0	1.0 ± 1.1	3.1 ± 2.7	NA	<0.01	*MAPT* = *GRN* < *C9orf72*
Subtype dis – apa – ster	9 15 5	6 14 0	6 21 3	NA	0.3	n.s
MMSE	25.9 ± 2.9	22.5 ± 6.3	26.5 ± 2.7	29.3 ± 0.8	<0.01	*GRN* < *MAPT* < NC *GRN* < *C9orf72*
FAB	14.7 ± 3.2	10.0 ± 4.7	13.9 ± 3.4	16.1 ± 1.7	<0.01	*GRN* < *MAPT* = NC

Abbreviations: MAPT = microtubule-associated protein tau; GRN = progranulin; C9orf72 = chromosome 9 open reading frame 72; NC = non-carriers; dis = disinhibited; apa = apathetic; ster = stereotypic; MMSE = Mini-Mental State Examination; FAB = Frontal Assessment Battery; n.s = not significant. Values indicate mean ± SD or n (%) unless otherwise specified. [a] Verhage Dutch educational system categorized into levels from 1 = less than 6 years of primary education to 7 = academic schooling.

Cross-sectional analysis – comparison to non-carriers

Table 2 shows the baseline z-scores of neuropsychological tests for the three mutation carrier groups. Compared to non-carriers, all mutation carrier groups were significantly impaired on language, attention/mental processing speed and executive functioning, but not on working memory and visuoconstruction. Executive functioning was most sensitive to differentiate GRN mutation carriers from non-carriers (mean difference -5.1; 95%CI -6.5 to 3.7, p<0.01, d=2.9, %OL=8.8-7.2), whereas language was most sensitive to differentiate C9orf72 (mean

difference -2.1; 95%CI -2.8 to -1.3, p<0.01, d=2.0, %OL=18.9) and MAPT mutation carriers (mean difference -2.3; 95%CI -3.0 to -1.6, p<0.01, d=1.8, %OL=22.6) from non-carriers. On neuropsychological test level this translated into logWCST being most sensitive to differentiate GRN mutation carriers from non-carriers (mean difference -1.0; 95%CI -1.4 to -0.7, p<0.01, d=3.0, %OL=7.2), RBMT direct (mean difference -2.0; 95%CI -2.9 to -1.2, p<0.01, d=2.4, %OL=13) and delayed (mean difference -2.2; 95%CI -3.1 to -1.3, p<0.01, d=2.4, %OL=13) recall were most sensitive to differentiate MAPT mutation carriers from non-carriers, and logSCWT I and II was most sensitive to differentiate C9orf72 mutation carriers from non-carriers (mean difference 0.34; 95%CI 0.2 to 0.5, p<0.01, d=2.4, %OL=13). Concerning memory, GRN (mean difference -4.5; 95%CI -7.6 to -1.3, p=0.02, d=1.1, %OL=41.1) and MAPT (mean difference -3.8; 95%CI -6.8 to -0.8, p=0.04, d=0.7, %OL=57) mutation carriers were equally impaired in immediate recall, also with significant impairment in delayed recall in the latter group (mean difference -1.4; 95%CI -2.1 to -0.7, p<0.01, d=1.2, %OL=37.8). Analyses showed that C9orf72 repeat expansion (mean difference -1.2; 95%CI -2.0 to -0.4, p=0.01, d=1.4, %OL=31.9) and MAPT mutation (mean difference -1.2; 95%CI -2.0 to -0.5, p<0.01, d=1.0, %OL=44.6) carriers were equally impaired on RAVLT– immediate recall, but in addition with significant impairment on RAVLT– delayed recall in the latter group (mean difference -1.1; 95%CI -1.8 to -0.3, p=0.02, d=0.8, %OL=52.6). GRN mutation carriers were only significantly impaired on the VAT (mean difference -0.5; 95% CI -0.8 to -0.1, p=0.02, d=0.7, %OL=57).

Cross-sectional analysis – comparison between mutation carrier groups

On domain level, GRN mutation carriers could be differentiated from MAPT mutation carriers by significantly lower attention and mental processing speed (mean difference -2.5; 95%CI -4.7 to -0.3, p=0.02, d=1.0, %OL=44.6), and executive functioning (mean difference -2.1; 95%CI -4.1 to -0.5, p=0.03, d=1.1, %OL=41.1) (Table 2). On test level, GRN mutation carriers performed significantly worse on letter fluency (mean difference -1.3; 95%CI -2.2 to -0.4, p<0.01, d=1.6, %OL=26.9), TMT A (mean difference -0.48; 95%CI -0.1 to -0.09, p=0.02, d=1.2, %OL=37.8), TMT B (mean difference -0.5; 95%CI -0.1 to -0.9, p=0.02, d=1.1, %OL=41.1), and SCWT card III (mean difference -0.4; 95%CI -0.1 to -0.8, p=0.01, d=0.7, %OL=57). GRN mutation carriers could be differentiated from C9orf72 repeat expansion carriers by significant lower attention and mental processing speed (mean difference -2.4; 95%CI -4.5 to -0.3, p=0.02, d=0.7, %OL=57). On test level, GRN mutation carriers performed significantly worse on letter fluency (mean difference -1.1; 95%CI -2.0 to -0.3, p=0.01, d=1.3, %OL=34.7) and WCST (mean difference -0.6; 95%CI -1.1 to -0.1, p=0.02, d=1.2, %OL=37.8) compared to C9orf72 mutation carriers. The other tests did not differentiate between mutation carrier groups. On domain level, GRN patients with predominant left-sided atrophy performed significantly worse on language compared to GRN patients with predominant right-sided atrophy (mean difference -2.3; 95%CI -4.3 to -0.3, p=0.02, d=2.3, %OL=13). There were no other significant differences between GRN mutation carriers with different atrophy patterns (see Supplementary Table 1).

Table 2. Differences between genetic mutation carrier groups on neuropsychological tests within seven cognitive domains.

Domain	*MAPT* mutation carriers	*n*	*GRN* mutation carriers	*n*	*C9orf72* mutation carriers	*n*	*p* value	Group differences
Language	-2.2 ± 1.5	26	-2.5 ± 1.4	20	-2.3 ± 1.4	28	< 0.01	*GRN* = *MAPT* = *C9orf72* < NC
BNT60	-2.4 ± 2.6	23	-2.3 ± 2.5	17	-2.1 ± 1.9	22	< 0.01	*GRN* = *MAPT* = *C9orf72* < NC
Semantic fluency	-2.5 ± 1.2	26	-2.7 ± 1.3	20	-2.6 ± 1.3	27	< 0.01	*GRN* = *MAPT* = *C9orf72* < NC
Letter fluency	-0.6 ± 1.3	17	-2.2 ± 0.6	13	-1.2 ± 0.8	18	< 0.01	*GRN* < *MAPT* = *C9orf72* < NC
Attention and mental processing speed	-1.2 ± 1.9	25	-4.3 ± 4.1	18	-2.1 ± 2.3	24	< 0.01	*GRN* < *MAPT* = *C9orf72* < NC
TMT A*	-0.8 ± 1.2	25	-3.9 ± 4.1	18	-2.3 ± 3.6	24	< 0.01	*GRN* < *MAPT* < NC *C9orf72* < NC
SCWT card I and II*	-2.7 ± 3.2	21	-4.9 ± 5.8	17	-3.0 ± 1.6	19	< 0.01	*GRN* = *MAPT* = *C9orf72* < NC
Executive functioning	-2.7 ± 2.5	25	-5.3 ± 2.5	18	-4.0 ± 2.6	24	< 0.01	*GRN* < *MAPT* < NC *C9orf72* < NC
TMT B*	-2.3 ± 2.8	24	-5.5 ± 2.7	18	-3.8 ± 2.6	23	< 0.01	*GRN* < *MAPT* < NC *C9orf72* < NC
SCWT card III*	-3.2 ± 4.0	20	-7.7 ± 4.6	17	-5.3 ± 3.4	19	< 0.01	*GRN* < *MAPT* < NC *C9orf72* < NC
WCST concepts*	-1.6 ± 1.6	16	-2.8 ± 0.6	14	-1.1 ± 1.6	14	< 0.01	*GRN* < *C9orf72* < NC *MAPT* < NC
WAIS-III Similarities	-1.6 ± 2.2	11	-2.8 ± 1.4	10	-1.8 ± 1.3	10	< 0.01	*GRN* = *C9orf72* = *MAPT* < NC
Memory–learning	-3.3 ± 6.6	25	-4.7 ± 6.1	18	-3.0 ± 5.3	24	0.02	*MAPT* = *GRN* < NC
RAVLT-learning	-1.1 ± 1.2	21	-1.1 ± 1.8	14	-1.4 ± 1.1	19	<0.01	*MAPT* = *C9orf72* = *GRN* < NC
RBMT-learning	-2.1 ± 0.7	10	-2.0 ± 1.0	10	-1.7 ± 1.0	11	< 0.01	*GRN* = *MAPT* = *C9orf72* < NC
VAT*	-6.3 ± 10.7	12	-10.6 ± 11.8	12	-5.0 ± 9.4	16	0.02	*GRN* < NC
Memory–recall	-1.3 ± 1.3	24	-1.0 ± 1.6	16	-0.9 ± 1.2	22	< 0.01	*MAPT* < NC
RAVLT-recall	-0.9 ± 1.3	21	-0.7 ± 1.7	14	-0.5 ± 1.1	19	0.05	*MAPT* < NC
RBMT-recall	-2.2 ± 0.8	9	-1.7 ± 1.0	10	-1.6 ± 1.1	11	< 0.01	*GRN* = *MAPT* = *C9orf72* < NC
Working memory	-0.4 ± 1.7	11	-1.1 ± 2.2	8	-1.2 ± 1.2	10	0.09	n.s
WAIS-III Digit Span	-0.4 ± 1.7	11	-1.1 ± 2.2	8	-1.2 ± 1.2	10	0.09	n.s
Visuoconstruction	-0.7 ± 2.4	20	-1.0 ± 1.6	18	-1.2 ± 2.7	22	0.30	n.s
Clock drawing	-0.7 ± 2.4	20	-1.0 ± 1.6	18	-1.2 ± 2.7	22	0.30	n.s

Abbreviations: *MAPT* = microtubule-associated protein tau; *GRN* = progranulin; *C9orf72* = chromosome 9 open reading frame 72; BNT = Boston Naming Test; TMT = Trail Making Test; WCST = Wisconsin Card Sorting Test; RAVLT = Rey Auditory Verbal Learning Test; RBMT = Rivermead Behavioral Memory Test; VAT = Visual Association Test; n.s = not significant. Values indicate mean ± SD. The *p* values constitute interaction terms of univariate analyses of covariance (corrected for age) (on z-scores and *log10 transformed data). Non-carriers were excluded as they had means of zero and SDs of one by definition.

Within-individual longitudinal trajectories of cognitive decline

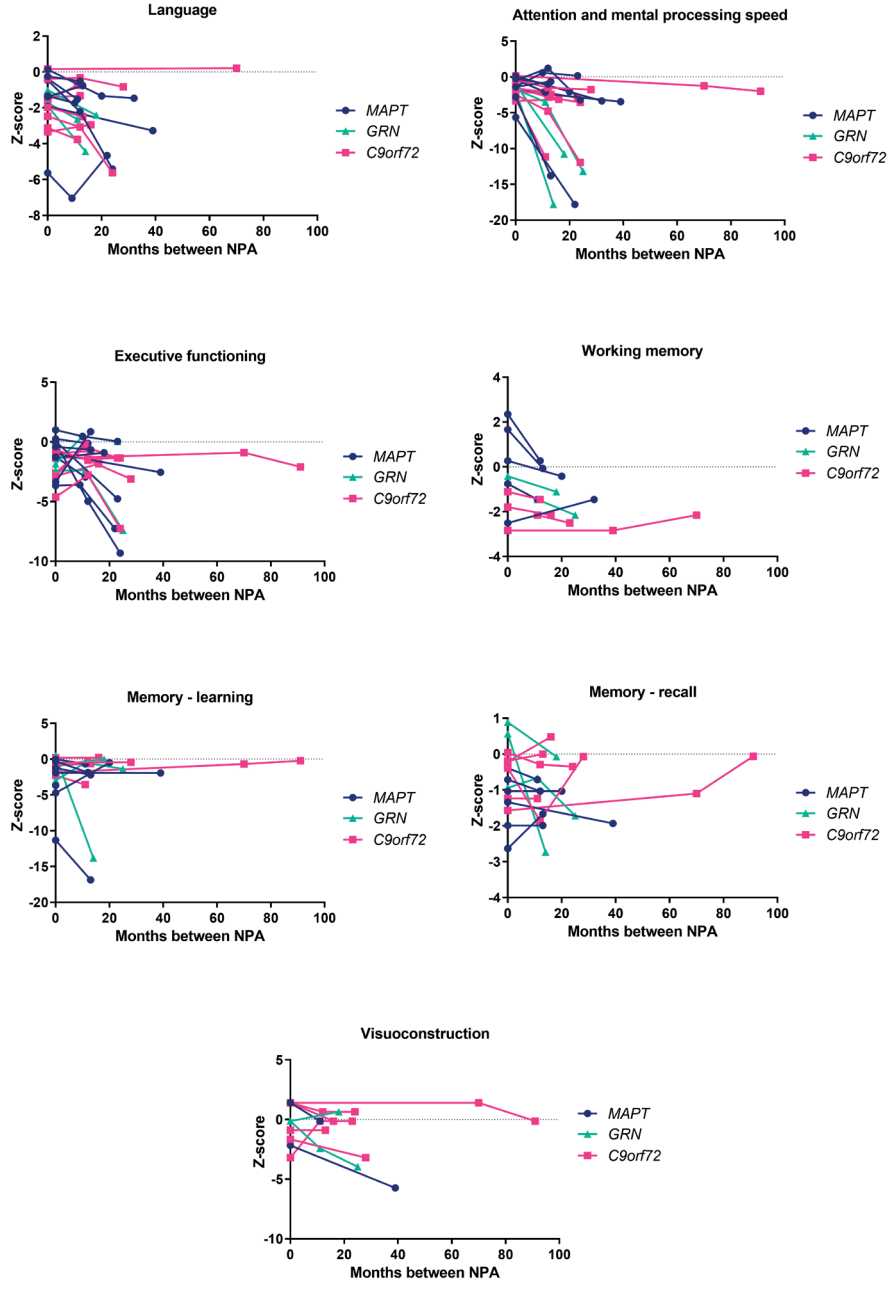
We explored individual trajectories of cognitive decline in a subset of patients (n=27) that underwent multiple neuropsychological assessments (Figure 1; Supplementary Figures 1-2). Overall, GRN mutation carriers (n=3) showed the largest decline of all mutation carrier groups in the first year after diagnosis. Specifically, these patients declined most on attention, mental processing speed and memory. MAPT mutation carriers (n=13) performed at an intermediate level between GRN and C9orf72 mutation carriers (n=11) on all tests, but did not seem to decline more profoundly on a specific cognitive domain compared to other domains. C9orf72 repeat expansion carriers showed the most stable trajectories with minimal decline on most domains. MAPT mutation carriers performed lower and declined most on the BNT, whereas GRN mutation carriers declined most on the TMT A and B (Supplementary Figure 1). Although the RAVLT showed lower performance in MAPT mutation carriers, a steeper decline over time was seen in GRN mutation carriers (Supplementary Figure 2).

Discussion

This study demonstrated gene-specific neuropsychological profiles within the clinical phenotype of bvFTD. The three mutation carrier groups were impaired on all cognitive domains compared to non-carriers, except for working memory and visuoconstruction. Interestingly, patients with bvFTD could be differentiated according to genetic mutation both on cognitive domain level and on neuropsychological test level. Attention and mental processing speed, as well as executive functioning differentiated GRN from MAPT and C9orf72, and memory recall deficits seemed a distinctive feature of MAPT. Executive functioning was most sensitive to differentiate GRN mutation carriers from non-carriers, whereas language was most sensitive to differentiate MAPT and C9orf72 mutation carriers from non-carriers. Within-individual trajectories indicated a more rapid decline on attention and memory in GRN mutation carriers and confrontation naming in MAPT in the first year after diagnosis, whereas C9orf72 repeat expansion carriers remained relatively stable on all domains.

Studies in both presymptomatic[27] and symptomatic GRN mutation carriers[5] have shown impairment and/or decline in attention and mental processing speed. An explanation for this decline (in fronto-subcortical functions) is the extensive subcortical white matter lesions that are regularly seen in GRN mutation carriers[28]. The subcortical structures of the brain are thought to be especially important for information processing speed, and lesions in these structures have therefore been primarily associated with difficulties in attention and mental processing speed as well as executive functioning[29]. Interestingly, multiple neuroimaging studies have shown that GRN mutations are associated with marked asymmetrical cortical atrophy, with either left or right sided predominance[5]. It has been argued that these differences in patterns of neurodegeneration can be reflected in different cognitive profiles[5].

Figure 1. Within-individual trajectories of cognitive decline on seven cognitive domains.



Abbreviations: NPA = neuropsychological assessment; *MAPT* = microtubule-associated protein au, *GRN* = progranulin, *C9orf72* = chromosome 9 open reading frame 72. Raw data for each neuropsychological test were first converted to z-scores by standardization to the baseline data of non-carriers. Composite cognitive domain scores were calculated. Each subplot present the trajectory on a specific cognitive domain. Data availability: language (*MAPT*: n=9; *GRN*: n=3; *C9orf72*: n=8), executive functioning (*MAPT*: n=9; *GRN*: n=2; *C9orf72*: n=8), working memory (*MAPT*: n=5; *GRN*: n=2; *C9orf72*: n=6), memory learning (*MAPT*: n-7; *GRN*: n=3; *C9orf72*: n=8); memory recall (*MAPT*: n=7; *GRN*: n=3; *C9orf72*: n=7); visuoconstruction *(MAPT*: n=6; *GRN*: n=2; *C9orf72*: n=7

Additional analyses showed that GRN patients with more pronounced left-sided atrophy performed worse on language than patients with more pronounced right-sided atrophy. This is unsurprising given that language processing is strongly left lateralized[30]. There were no other cognitive differences between patients with either primarily left-sided, right-sided or bilateral atrophy. Due to small sample sizes groups were not stratified according to the pattern of neurodegeneration in the main part of the analyses, but grouping them together may have influenced results (particularly language performance) for this group.

Within-individual trajectories in GRN mutation carriers showed a rapid decline on all cognitive domains in the first year after diagnosis. This rapid cognitive decline in GRN mutation carriers is also partially reflected by the finding that the majority of 17 cases that did not undergo repeated neuropsychological assessment were too severely cognitively impaired for testing at follow-up (i.e. residing in nursing home or unable to complete multiple neuropsychological tests at baseline). This finding is confirmed by other studies reporting a shorter disease duration[31] and more rapid changes following symptom onset in GRN mutation carriers[32]. The most profound decline was seen on attention/mental processing speed and memory. Memory problems have previously been described in GRN as a symptom characterizing progressed disease stages[33], although it could also be associated with the profound impairment in attention/mental processing speed[34].

MAPT mutation carriers were the only group impaired on both immediate and delayed recall at baseline, whereas GRN and C9orf72 mutation carriers were only impaired on immediate recall. This is in line with a previous study by Jiskoot et al.[32] that demonstrated significant decline on the RAVLT recall test in the presymptomatic stage of MAPT mutation carriers, with a further decline in participants that converted to symptomatic FTD during follow-up. This is further corroborated by the finding that the RBMT direct and delayed recall trials were most sensitive to differentiate MAPT mutation carriers from non-carriers. Memory impairment has previously been described as a prominent symptom in patients with a MAPT mutation, possibly due to anteromedial temporal lobe atrophy that is often seen in MAPT[35]. This is an area that has been associated with defects in memory storage and consolidation, as is the case in for instance Alzheimer's disease[36]. Another hypothesis that has been suggested is that memory deficits in bvFTD are a consequence of executive dysfunctioning (i.e. poor organization and lack of efficient learning strategies) due to prefrontal atrophy[27]. This suggests that memory impairment differs between bvFTD patients depending on the underlying mutation and thus atrophy pattern, with MAPT mutation carriers demonstrating a "pure" memory impairment resulting in lower performance on both immediate and delayed recall, whereas the immediate recall impairment in C9orf72 and GRN mutation carriers are potentially a consequence of prefrontal and thus dysexecutive impairment, with relatively spared delayed recall performance.

In contrast to the findings of previous studies, MAPT mutation carriers in the current cohort did not show worse semantic functioning compared to GRN and C9orf72 mutation carriers[9]. This discrepancy might be explained by the use of estimated 60-item versions of the BNT, a "semantic" confrontation naming test, from 15-item BNT administrations. A validation study has shown that the 15-item BNT has lower sensitivity and diagnostic accuracy compared to the 60-item version of the BNT[37]. Another explanation might be that the nature of naming errors differed in each genetic variant. MAPT mutation carriers were relatively more impaired on BNT and semantic fluency compared to letter fluency, whereas GRN performed equally impaired on all language tests, suggesting different underlying mechanisms (e.g. semantic problems versus dysexecutive control) (e.g.[38]). We included all fluency tasks in the language domain, but it has been previously demonstrated that fluency also involves other cognitive functions such as executive functioning and semantic memory[38, 39]. Furthermore, within-individual trajectories showed that MAPT mutation carriers declined most on the BNT. It might also be possible that the occurrence of semantic impairments become more prominent in MAPT in a later stage of the disease[35], as anterior medial temporal lobe atrophy progresses, an area that has been linked to semantic naming errors in for instance Alzheimer's disease[40] and is known to also deteriorate bilaterally in patients with a MAPT mutation[34].

Patients with a C9orf72 repeat expansion showed a widespread and non-progressive pattern of cognitive impairment in language, attention/mental processing speed, executive functioning and immediate recall and no distinctive cognitive impairment compared to GRN and MAPT mutation carriers. This cognitive profile is corroborated by studies indicating that the neurodegenerative process associated with the C9orf72 repeat expansion is also widespread, with degeneration in the frontal and temporal cortices but also subcortical and cerebellar regions[8]. It has been demonstrated that the first brain changes start to emerge already in early adulthood but do not evolve, suggesting that they reflect an abnormal neurodevelopmental trajectory rather than early neurodegeneration[41]. This possibly also explains the slowly progressive bvFTD cases that have, in particular, been associated with the C9orf72 repeat expansion[42], and were also seen in our within-individual trajectories. One theory suggests that neuropsychiatric symptoms represent the clinical prodrome of bvFTD in C9orf72 repeat expansion carriers, with cognitive deterioration occurring only in progressed disease stages[41].

Overall, results show that it is possible to distinguish between genetic variants of bvFTD using specific neuropsychological domains and tests. This enables the identification of sensitive tests for signaling disease onset and predicting disease progression in clinical practice and could inform future therapeutic trials in selecting clinical endpoints to monitor treatment response. The former could be helpful in providing psycho-education and counseling to the patient and caregiver on the expected clinical presentation and disease course. Moreover, selection of the most sensitive tests per genetic defect enables shortening of the

neuropsychological test battery thereby relieving patient burden[33]. Executive tasks, such as letter fluency, and tasks for attention and mental processing speed, such as TMT and SCWT, were most sensitive to detect GRN-associated FTD, whereas memory recall deficits seem a promising marker in MAPT-associated FTD. There does not appear to be a specific cognitive domain/test that can differentiate C9orf72 from other genetic variants, possibly due to the widespread neurodegenerative process affecting multiple cognitive domains equally and the slow progression. Importantly, though this study shows statistical differences between mutation carriers groups, there is still a considerable percentage of overlap on all cognitive domains and tests, with letter fluency having the lowest %OL between groups (26.9 – 34.7%OL). In addition, GRN mutation carriers performed relatively worse on all cognitive tests, possibly due to an altogether greater disease severity. Although we corrected for disease duration in our analyses, a reliable instrument for disease severity (e.g. FTD-CDR) was lacking. Similarly, exploratory longitudinal descriptions provided valuable information on rate of cognitive decline with indeed rapid cognitive decline in GRN, but slow progression in C9orf72 and MAPT showing intermediate decline. Taking this together, results should be interpreted carefully. We report several clear differences between genetic mutations, but given the relatively wide range of cognitive impairments (i.e. multiple domains affected) found in our patient sample, and the high percentage of overlap between patient groups, it remains challenging to identify a gene-specific cognitive profile in individual patients. Our results should be viewed as guidance for selecting clinical endpoints in future therapeutic trials rather than recommendations for the 'best' neuropsychological test to be used.

The current longitudinal descriptions should be carefully interpreted as sample sizes are small. Further limitations are the changes in neuropsychological test protocol with different tests and test versions used over time during the extended time of the study. In addition, we did not include tasks measuring social cognition, a key feature in diagnosing bvFTD[2], as social cognitive tasks were only added to the standard neuropsychological assessment in our memory clinic since 2012, resulting in too small sample sizes for the current analysis (n <10 in each group). A more clear dissociation between attention/mental processing speed and executive functioning tasks could have been made by analyzing the inter-relationship between TMT A and B, and SCWT II and III. However, for several patients who were unable to complete the test, we truncated the score to 300 seconds. These patients typically already had a much higher completion time on TMT A or SCWT II, and calculating the ratio would therefore have resulted in optimizing the ratio-score specifically for those patients that were too cognitively impaired to complete the test.

This study presents a large cohort of genetic bvFTD patients, including three major genetic causes of FTD, with unique neuropsychological data covering a wide variety of tests in seven cognitive domains. We provide evidence of gene-specific cognitive profiles within patients with bvFTD and provide recommendations for the use of specific tests to assess gene-specific

clinical onset and disease progression. This is important information for future clinical trials targeting specific pathologies as clinical endpoints to monitor treatment response are increasingly urgent.

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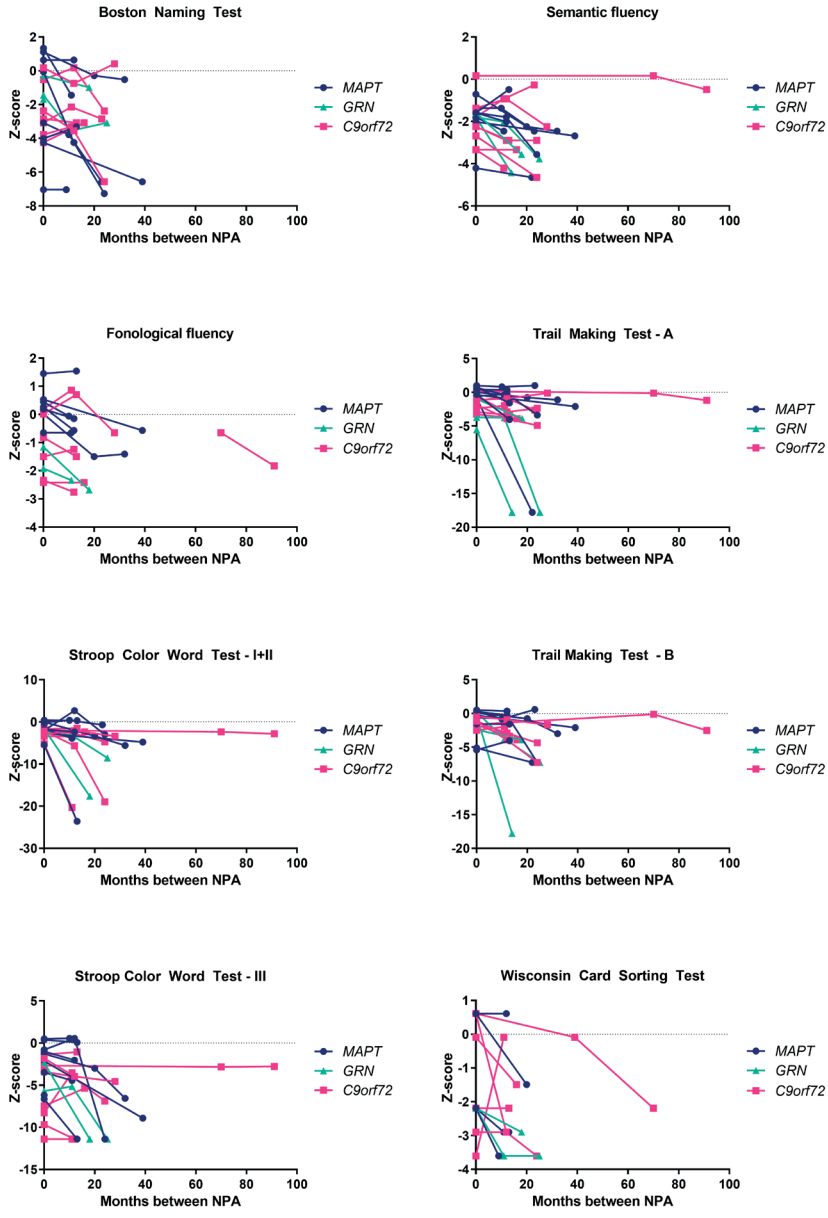
Supplementary tables and figures

Supplementary Table 1. Differences between GRN patients with predominant right-sided, left-sided or generalized atrophy on seven cognitive domains.

Domain	Left	*n*	Right	*n*	Generalized	*n*	*p* value
Language	-3.3 ± 1.2	10	-1.0 ± 0.7	4	-2.1 ± 0.9	4	0.02
Attention and mental processing speed	-6.6 ± 4.2	9	-0.7 ± 0.7	4	-3.6 ± 3.8	3	0.2
Executive functioning	-6.2 ± 2.0	9	-2.2 ± 1.5	4	-5.1 ± 2.2	4	0.09
Memory–learning	-5.6 ± 6.5	9	-3.5 ± 5.2	4	-7.0 ± 9.3	3	0.8
Memory–recall	-1.1 ± 1.6	7	-0.3 ± 2.2	4	-1.0 ± 1.7	3	0.8
Working memory	-2.1 ± 1.0	4	-0.1 ± 2.7	4	-	0	0.5
Visuoconstruction	-1.2 ± 1.7	9	-0.3 ± 0.8	4	-0.9 ± 2.0	3	0.4

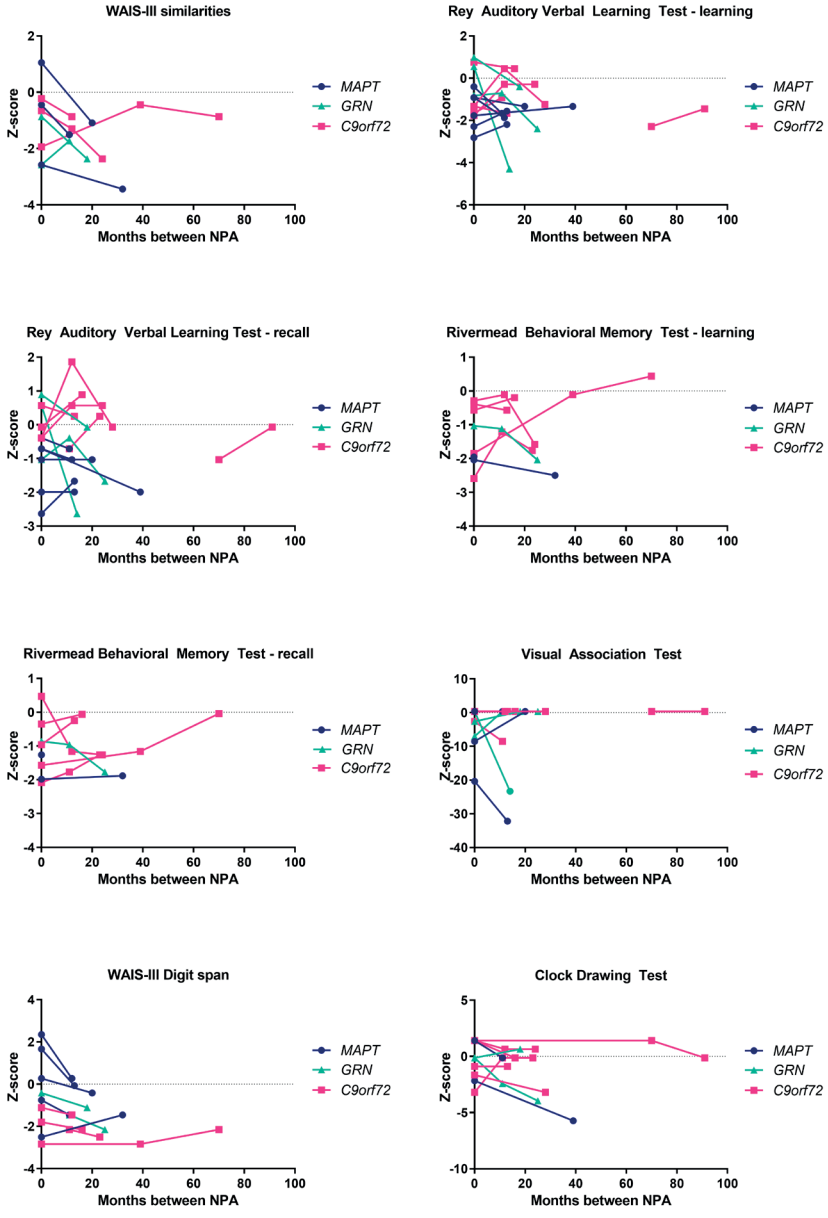
Values indicate mean ± SD. The p values constitute interaction terms of univariate analyses of covariance (corrected for age and education).

Supplementary Figure 1. Within-individual trajectories on neuropsychological tests.



Abbreviations: NPA = neuropsychological assessment; *MAPT* = microtubule-associated protein tau; *GRN* = progranulin; *C9orf72* = chromosome 9 open reading frame 72. Raw data for each neuropsychological test were first converted to z-scores by standardization to the baseline data of healthy controls. Data availability: Boston Naming Test (*MAPT* n=8; *GRN* n=2; *C9orf72* n=7); semantic fluency (*MAPT*: n=8; *GRN*:n=3; *C9orf72:* n= 8); letter fluency (*MAPT:* n=7; *GRN:* n=2; *C9orf72/:* n=6); Trail Making Test–A (*MAPT:* n=9; *GRN:* n=3; *C9orf72:* n= 8); Stroop Color Word Test I+II (*MAPT:* n=8; *GRN:* n=2; *C9orf72:* n=8); Trail Making Test–B (*MAPT:* n=8; *GRN:* n=3; *C9orf72:* n=9); Stroop Color Word Test III (*MAPT:* n= 8; *GRN:* n=2; *C9orf72:* n=8); Wisconsin Card Sorting Test (*MAPT:* n=4; *GRN:* n=2; *C9orf72:* n=6).

Supplementary Figure 2. Within-individual trajectories on neuropsychological tests.



Abbreviations: NPA = neuropsychological assessment; *MAPT* = microtubule-associated protein tau; *GRN* = progranulin; *C9orf72* = chromosome 9 open reading frame 72. Raw data for each neuropsychological test were first converted to z-scores by standardization to the baseline data of healthy controls. Data availability: WAIS-III Similarities (*MAPT:* n= 3; *GRN:* n=2; *C9orf72:* n= 3); Rey Auditory Verbal Learning Test – learning (*MAPT:* n= 6; *GRN:* n=3; *C9orf72:* n=6); Rey Auditory Verbal Learning – recall (*MAPT:* n=6; *GRN:* n=3; *C9orf72:* n=6); Rivermead Behavioral Memory Test–learning (*MAPT:* n=1; *GRN:* n=1; *C9orf72:* n=6); Rivermead Behavioral Memory Test–recall (*MAPT:* n=5; *GRN*: n=1; *C9orf72*: n= 6); Visual Association Test (*MAPT*: n= 3; *GRN*: n=3; *C9orf72*: n=3); WAIS-III Digit Span (*MAPT*: n= 5; *GRN*: n=2; *C9orf72*: n=4); Clock Drawing Test (*MAPT*: n=2; *GRN*: n=2; *C9orf72:* n=6).

CHAPTER 2.2

Longitudinal cognitive changes in genetic frontotemporal dementia within the GENFI cohort

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Abstract

Background and Objectives: Disease-modifying therapeutic trials for genetic frontotemporal dementia (FTD) are underway, but sensitive cognitive outcome measures are lacking. The aim of this study was to identify such cognitive tests in early stage FTD by investigating firstly, cognitive decline in a large cohort of genetic FTD pathogenic variant carriers, and secondly, whether gene-specific differences are moderated by disease stage (asymptomatic, prodromal and symptomatic).

Methods: C9orf72, *GRN* and *MAPT* pathogenic variant carriers as well as controls underwent a yearly neuropsychological assessment covering eight cognitive domains, as part of the Genetic FTD Initiative (GENFI), a prospective multicenter cohort study. Pathogenic variant carriers were stratified according to disease stage using the global CDR® plus NACC FTLD score (0, 0.5 and ≥1). Linear mixed-effects models were used to investigate differences between genetic groups and disease stages, as well as the three-way interaction between time, genetic group and disease stage.

Results: 207 *C9orf72*, 206 *GRN*, 86 *MAPT* pathogenic variant carriers and 255 controls were included. *C9orf72* pathogenic variant carriers performed lower on attention, executive function and verbal fluency from CDR plus NACC FTLD 0 onwards, with relatively minimal decline over time regardless of the CDR plus NACC FTLD score (i.e., disease progression). The cognitive profile in *MAPT* pathogenic variant carriers was characterized by lower memory performance at CDR plus NACC FTLD 0, with decline over time in language from the CDR plus NACC FTLD 0.5 stage onwards, and executive dysfunction rapidly developing at CDR plus NACC FTLD ≥1. *GRN* pathogenic variant carriers declined on verbal fluency and visuoconstruction in the CDR plus NACC FTLD 0.5 stage, with progressive decline in other cognitive domains starting at CDR plus NACC FTLD ≥1.

Discussion: We confirmed cognitive decline in the asymptomatic and prodromal stage of genetic FTD. Specifically, tests for attention, executive function, language and memory showed clear differences between genetic groups and controls at baseline, but the speed of change over time differed depending on genetic group and disease stage. This confirms the value of neuropsychological assessment in tracking clinical onset and progression and could inform clinical trials in selecting sensitive endpoints for measuring treatment effects as well as characterizing the best time window for starting treatment.

Introduction

Frontotemporal dementia (FTD) is a common cause of dementia, often presenting at a young age with devastating effects on daily living[1]. The typical cause of FTD is neurodegeneration of the frontal and temporal lobes resulting in behavioural disturbances (behavioural variant FTD (bvFTD)), and/or language impairment (primary progressive aphasia (PPA))[2, 3]. FTD is highly heritable and is autosomal dominantly inherited in up to ~30% of cases. The most common causes are pathogenic variants in the microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), or chromosome 9 open reading frame 72 (*C9orf72*) genes[4]. Deficits in executive function, language and social cognition are often predominant, but may vary in severity and progression due to the heterogeneous nature of the disease [1-3, 5].

Research into genetic FTD has shown that disease pathology emerges years before symptom onset[6-13]. Initiating disease-modifying interventions at this early stage of the disease may have the most profound effect because neuronal loss is minimal and cognitive functions are still preserved[14]. It is therefore important to identify sensitive clinical instruments that can signal disease onset and track disease progression. Furthermore, identifying such instruments for this early stage of the disease is also important because they can be used as clinical endpoints in upcoming therapeutic trials.

Gene-specific cognitive decline during the presymptomatic period has been demonstrated by both cross-sectional and longitudinal studies[6, 10, 15-26]. For example, previous reports have shown decline in memory[17, 19, 20, 26], language[17, 20, 23] and social cognition[17, 19, 20] in *MAPT* pathogenic variant carriers, decline in attention[15, 16, 19, 20] and executive function[15, 16, 18, 20] in *GRN* pathogenic variant carriers and a decline in social cognition in *C9orf72* pathogenic variant carriers[22, 24, 25]. However, other studies on genetic FTD failed to find these results[13, 21, 26, 27].

To date, most studies investigating cognitive decline in presymptomatic genetic FTD have had a small sample size, a limited number of yearly follow-ups, and/or did not include all three major causes of genetic FTD. Furthermore, most studies split their sample of pathogenic variant carriers either according to the artificial boundary of presymptomatic *versus* symptomatic, or according to estimated years to symptomatic onset. As a result, none of the studies fully highlight the complexity of the disease trajectory[28].

Larger international cohort studies with longer follow-up time are crucial to identify cognitive markers that signify disease onset at the earliest stage and can measure changes during disease progression. In addition, clinical instruments for disease severity, such as the Clinical Dementia Rating (CDR)® scale plus National Alzheimer's Coordinating Center (NACC) frontotemporal lobar degeneration (FTLD) module[29], could stratify pathogenic variant carriers

and provide valuable insight into cognitive decline during the different stages of the disease per genetic group.

This study aims to investigate longitudinal cognitive decline in genetic FTD pathogenic variant carriers. We performed a 5-year follow-up study in which we investigated baseline and longitudinal differences on neuropsychological test performance between *C9orf72, GRN, MAPT* pathogenic variant carriers and control participants, and stratified pathogenic variant carriers according to the CDR® NACC FTLD global score.

Methods

Participants

Data was included from the fifth GENFI data freeze in which participants from confirmed genetic FTD families were recruited in 24 centres across Europe and Canada between 30th January 2012 and 31th May 2019. Pathogenic variant carriers were included in this study if they performed at least one or more neuropsychological assessment(s). A total of 207 *C9orf72*, 206 *GRN* and 86 *MAPT* pathogenic variant carriers and 255 pathogenic variant negative family members (who served as control group) were included. 109 *C9orf72,* 112 *GRN* and 60 *MAPT* pathogenic variant carriers, and 154 controls had completed at least one follow-up visit (Table 1). Pathogenic variant carriers were divided into three categories based on the CDR® plus NACC FTLD global score at baseline: 0, 0.5 and ≥1. Of those with a CDR plus NACC FTLD global score of ≥1, 51 *C9orf72*, 27 *GRN* and 21 *MAPT* pathogenic variant carriers met diagnostic criteria for bvFTD[2], 16 *GRN* and three *C9orf72* pathogenic variant carriers met criteria for PPA[3] and 8 *C9orf72* pathogenic variant carriers met criteria for FTD with amyotrophic lateral sclerosis (FTD-ALS)[30]. 10% of *C9orf72*, 8% of *GRN* and 8% of *MAPT* pathogenic variant carriers progressed from CDR category 0 to 0.5, and 4% of *C9orf72*, 2% of *GRN* and 4% of *MAPT* pathogenic variant carriers progressed to ≥1. 6% of *C9orf72*, 16% of *GRN* and 20% of *MAPT* pathogenic variant carriers progressed from CDR category 0.5 to ≥1. (Supplementary Table 1).

Standard Protocol Approvals, Registrations, and Patient Consents

All GENFI sites had local ethical approval for the study and all participants gave written informed consent.

Table 1. Cumulative frequency of the number of participants at each yearly follow-up.

	Year				
	1	**2**	**3**	**4**	**5**
C9orf72	207	109	105	34	0
GRN	206	112	72	31	3
MAPT	86	60	40	11	1
Controls	255	154	105	34	1

Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau.

Procedures

Participants underwent a yearly standardized clinical assessment including the CDR® plus NACC FTLD and a comprehensive neuropsychological test battery covering attention and processing speed (WMS-R Digit span forward[31]; Trail Making Test (TMT) part A[32]; WAIS-R Digit Symbol test[31]; D-KEFS Color-Word Interference Test colour and word naming[33]), executive function (WMS-R Digit span backward[31]; TMT part B[32]; D-KEFS Color-Word Interference Test ink naming[33]), language (modified Camel and Cactus Test[34]; Boston Naming Test (short 30 item version)[31]), verbal fluency (category fluency [31]; phonemic fluency[35]), memory encoding (Free and Cued Selective Reminding Test (FCSRT) immediate free and total recall[26]), memory recall (FCSRT delayed free and total recall; Benson Complex Figure recall), social cognition (Facial Emotion Recognition Test[24]), and visuoconstruction (Benson Complex Figure copy). Previous studies have shown that verbal fluency can involve both language and executive function processes and, therefore we included it as a separate domain[36, 37]. The Mini-Mental State Examination (MMSE[38]) measured global cognitive functioning.

Statistical analysis

Statistical analyses were performed using Stata version 14.2 and R version 4.0.4. We compared continuous demographic data between groups with two-way ANOVAs and a chi-square test for sex. The significance level was set at $p<0.05$ (2-tailed) across all comparisons.

All neuropsychological data were standardized to Z-scores (i.e., raw score – mean score controls at baseline/ standard deviation controls at baseline). Z-scores for tests with reaction times (i.e. TMT and D-KEFS Color-Word Interference Test) were inversed so that lower Z scores indicate worse performance. Cognitive domains were calculated by averaging the mean Z-scores of the neuropsychological tests in that domain. Only the FCSRT total recall was included in the memory domains, as the free recall scores are a part of the total recall scores. The memory encoding, social cognition and visuoconstruction domains are represented by only one test.

As this is a prospective cohort study, not all pathogenic variant carriers had completed all study visits which resulted in missing data. We used linear mixed-effects models for each

cognitive domain to examine whether differences existed between *C9orf72, GRN, MAPT* pathogenic variant carriers and controls in cognitive decline since baseline. This type of model allows for the analysis of longitudinal data with unbalanced time points and missing data[39]. Age and years of education were included in all models as covariates. In each model a different cognitive outcome was used as the dependent variable and we specified the following fixed effects: time since baseline in years, gene group, CDR category at baseline, age at baseline, years of education, the two-way interactions between time and group, time and CDR category, and gene group and CDR category and the three-way interaction between time, group and CDR category. We included random intercepts for participants who were nested within families, but not random slopes as this did not improve model fit. A natural cubic splines model did not improve model fit. We performed post-hoc pairwise comparisons in intercepts and slopes between genetic groups within CDR categories. Results are shown as a difference between pathogenic variant group and the control group, or a different pathogenic variant group if stated. The letter β indicates an estimated difference in z-score at baseline, β_1 indicates a difference in change over time (slope). An example of the model and its outputs is shown in Supplementary file 2.

Results

Demographics

There were more females in CDR categories 0 and 0.5, and more males in CDR category≥1 for *C9orf72* ($\chi^2(2)=9.8$, $p=0.007$) and *MAPT* ($\chi^2(2)=6.6$, $p=0.036$) pathogenic variant carriers. We found differences in age at baseline between gene groups ($F(3, 744)=5.6$, $p<0.001$) and between CDR categories ($F(2, 744)=91.4$, $p<0.001$). Post-hoc pairwise comparisons revealed that *C9orf72* and *GRN* pathogenic variant carriers were older than *MAPT* pathogenic variant carriers (all $p\leq0.02$) and controls (all $p<0.001$), and each CDR category represented older pathogenic variant carriers than the categories with a lower CDR category (all $p\leq0.008$). We found differences between CDR categories in years of education at baseline ($F(2, 744)=8.8$, $p<0.001$), with CDR category ≥1 having had less years of education than the other categories (all $p<0.03$). There was an interaction effect between gene group and CDR category on MMSE at baseline ($F(4, 742)=4.3$, $p=0.002$). Post-hoc simple main effects illustrated a difference in MMSE at baseline between CDR categories in all three gene groups, and a difference in MMSE at baseline between gene groups in CDR category ≥1. Descriptive and neuropsychological data at baseline are reported in Table 2 and Supplementary Table 2.

Table 2. Demographics and neuropsychological data per genetic group and FTLD CDR global score category at baseline.

	C9orf72			*GRN*			*MAPT*			Controls
Demographic data										
CDR® NACC FTLD category	0	0.5	≥1	0	0.5	≥1	0	0.5	≥1	0
n	109	32	66	129	31	46	48	14	24	255
Sex ratio f:m	64:45	20:12	24:42	84:45	16:15	23:23	29:19	10:4	8:16	145:110
Age, y	44.0 (11.6)	47.7 (10.7)	62.2 (8.9)	45.9 (12.2)	51.8 (13.2)	63.6 (7.9)	39.3 (10.5)	45.7 (12.6)	57.3 (10.2)	45.3 (12.8)
Education, y	14.3 (3.0)	14.3 (2.6)	13.2 (3.7)	14.7 (3.4)	14.0 (4.0)	11.9 (3.3)	14.4 (3.4)	13.5 (2.4)	13.7 (3.9)	14.4 (3.3)
MMSE	28.9 (3.1)	28.8 (2.0)	23.7 (6.1)	29.0 (3.9)	27.8 (5.8)	20.2 (7.6)	29.5 (0.8)	28.2 (2.3)	23.7 (6.7)	29.2 (2.2)
CDR® plus NACC FTLD sum of boxes	0.0 (0.0)	1.1 (0.8)	10.9 (5.5)	0.0 (0.0)	1.0 (0.8)	9.2 (5.8)	0.0 (0.0)	1.1 (0.8)	9.3 (5.5)	0.0 (0.1)
Neuropsychological data										
Language	-0.2 (1.0)	-0.3 (1.3)	-3.1 (2.7)	0.1 (0.6)	-0.5 (1.4)	-3.1 (2.4)	-0.1 (0.8)	-0.7 (1.2)	-4.1 (3.3)	-
Attention	-0.3 (0.8)	-0.3 (1.0)	-2.7 (1.7)	-0.0 (0.6)	-0.4 (1.2)	-2.9 (2.0)	0.2 (0.7)	-0.1 (0.9)	-1.5 (1.4)	-
Verbal fluency	-0.2 (0.8)	-0.3 (0.9)	-2.0 (0.9)	0.1 (0.8)	-0.1 (0.9)	-1.8 (1.0)	0.1 (0.8)	0.1 (1.0)	-1.4 (1.2)	-
Executive function	-0.4 (1.1)	-0.4 (1.2)	-3.3 (1.9)	-0.0 (0.7)	-0.6 (1.9)	-3.5 (2.1)	0.1 (0.8)	-0.2 (0.9)	-1.9 (1.8)	-
Memory – immediate recall	-0.5 (1.8)	-0.8 (2.3)	-3.3 (4.0)	0.1 (0.7)	-0.7 (2.3)	-5.7 (5.5)	0.0 (1.1)	-0.9 (2.6)	-5.2 (4.0)	-
Memory – delayed recall	-0.3 (0.9)	-0.1 (1.2)	-2.6 (2.6)	-0.0 (0.7)	-0.5 (1.6)	-3.3 (3.4)	-0.1 (1.1)	-0.8 (2.3)	-4.3 (3.0)	-
Social cognition	-0.1 (1.0)	-0.7 (1.3)	-3.1 (2.2)	0.1 (1.1)	-0.7 (1.4)	-2.8 (1.9)	0.1 (0.8)	-0.5 (1.2)	-2.2 (2.1)	-
Visuoconstruction	-0.1 (1.2)	-0.2 (1.6)	-2.3 (2.9)	0.2 (0.8)	0.2 (1.0)	-1.9 (3.2)	-0.2 (0.9)	-0.2 (0.9)	-1.3 (2.7)	-

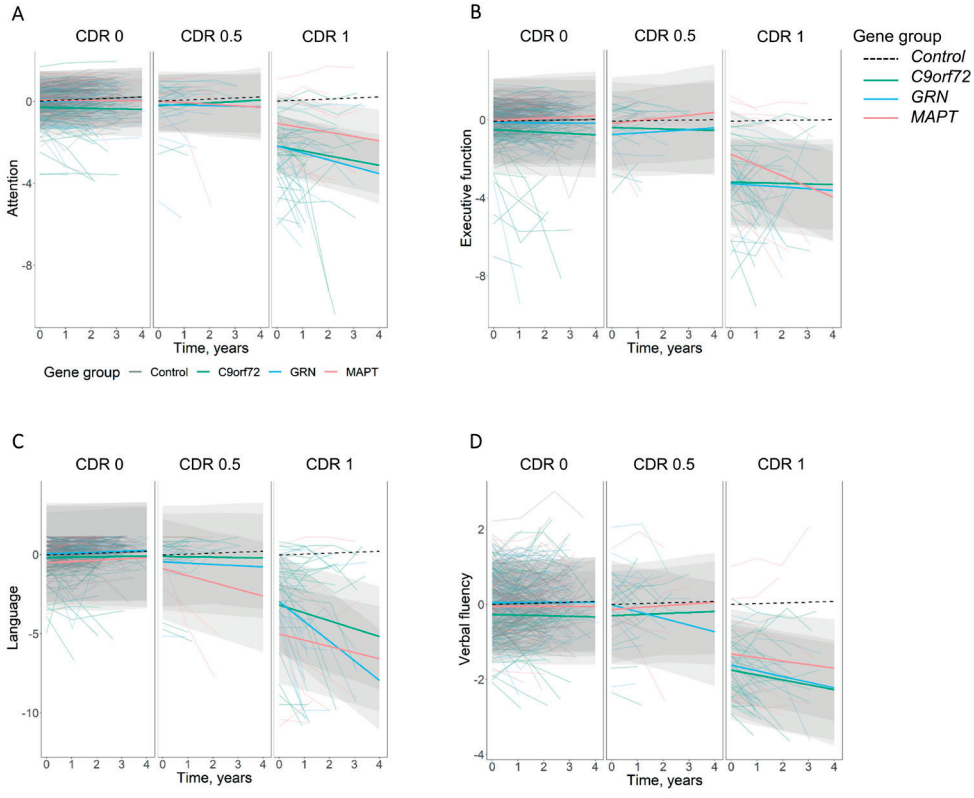
Values are represented as mean Z-score compared to controls (standard deviation) unless otherwise specified. Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration; y = years; MMSE = Mini-Mental State Examination.

Baseline and longitudinal results for each cognitive domain were as follows (Table 3, Figures 1 and 2, and summarized in Figure 3):

Attention

We found strong evidence for differences in the attention domain between CDR categories (χ^2(2)=23.2, p<0.001) and between gene groups (χ^2(3)=26.0, p<0.001) at baseline. *C9orf72* (β=-2.2, SE=0.14, p<0.001), *GRN* (β=-2.2, SE=0.16, p<0.001) and *MAPT* (β=-1.1, SE=0.21, p<0.001) pathogenic variant carriers with CDR category ≥1 all performed worse than controls, with both *C9orf72* (β=-1.1, SE=0.23, p<0.001) and *GRN* (β=-1.2, SE=0.25, p<0.001) pathogenic variant carriers performing worse than *MAPT* pathogenic variant carriers. *C9orf72* pathogenic variant carriers with CDR category 0 also performed worse at baseline than *GRN* (β=-0.3, SE=0.13, *p*=0.010) and *MAPT* (β=-0.4, SE= 0.16, *p*=0.030) pathogenic variant carriers, and controls

Figure 1. Linear mixed effects models displaying longitudinal trajectories in composite domain z-score stratified by the CDR plus NACC FTLD for *C9orf72*, *GRN* and *MAPT* pathogenic variant carriers and healthy controls. Models are displayed per cognitive domain: (A) attention, (B) executive function,(C) language, and (D) verbal fluency.



Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration.

Table 3. Slopes and confidence interval stratified by genetic group and CDR plus NACC FTLD global score for each cognitive domain.

					C9orf72				
CDR plus NACC FTLD	0			0.5			≥1		
	β	95%CI		*β*	95%CI		*β*	95%CI	
Language	0.02	-0.09	0.14	-0.03	-0.37	0.32	-0.50	-0.70	-0.30
Attention	-0.03	-0.10	0.05	0.07	-0.15	0.29	-0.24	-0.36	-0.11
Verbal fluency	-0,01	-0.07	0.04	0.03	-0.14	0.19	-0.13	-0.22	-0.04
Executive function	-0.07	-0.16	0.02	-0.04	-0.31	0.23	-0.03	-0.20	0.14
Memory–immediate recall	0.26	0.11	0.40	0.45	0.06	0.84	-0.01	-0.25	0.24
Memory–delayed recall	0.14	0.05	0.23	0.14	-0.09	0.37	0.00	-0.16	0.16
Social cognition	0.06	-0.06	0.17	0.14	-0.15	0.43	0.20	0.00	0.40
Visuoconstruction	-0.07	-0.25	0.11	-0.13	-0.58	0.32	0.02	-0.25	0.28
					GRN				
CDR plus NACC FTLD	0			0.5			≥1		
	β	95%CI		*β*	95%CI		*β*	95%CI	
Language	0.05	-0.04	0.14	-0.08	-0.39	0.23	-1.24	-1.51	-0.97
Attention	0.02	-0.04	0.07	-0.03	-0.22	0.17	-0.34	-0.52	-0.16
Verbal fluency	0.00	0.04	0.05	-0.18	-0.33	-0.03	-0.15	-0.28	-0.02
Executive function	-0.01	-0.08	0.06	0.09	-0.16	0.33	-0.09	-0.32	0.15
Memory–immediate recall	0.06	-0.05	0.17	0.17	-0.17	0.52	-0.24	-0.64	0.17
Memory–delayed recall	0.05	-0.02	0.12	-0.03	-0.24	0.18	-0.06	-0.32	0.20
Social cognition	0.09	0.00	0.18	0.11	-0.16	0.39	-0.47	-0.70	-0.23
Visuoconstruction	-0.09	-0.23	0.05	-0.45	-0.88	-0.02	-0.13	-0.48	0.23
					MAPT				
CDR plus NACC FTLD	0			0.5			≥1		
	β	95%CI		*β*	95%CI		*β*	95%CI	
Language	0.08	-0.06	0.22	-0.43	-0.76	-0.10	-0.39	-0.67	-0.10
Attention	-0.01	-0.09	0.08	-0.08	-0.28	0.13	-0.21	-0.39	-0.04
Verbal fluency	0.00	-0.07	0.07	0.05	-0.10	0.21	-0.09	-0.23	0.04
Executive function	0.07	-0.04	0.17	0.14	-0.12	0.41	-0.55	-0.77	-0.33
Memory–immediate recall	0.02	-0.15	0.18	0.19	-0.20	0.57	-0.06	-0.46	0.34
Memory–delayed recall	0.03	-0.07	0.13	0.07	-0.16	0.31	-0.16	-0.41	0.09
Social cognition	0.08	-0.05	0.21	0.20	-0.12	0.52	-0.13	-0.37	0.12
Visuoconstruction	0.04	-0.17	0.25	0.11	-0.36	0.58	0.20	-0.17	0.58
					Controls				
	β			95%CI					
Language	0.06			-0.02		0.13			
Attention	0.05			0.00		0.10			
Verbal fluency	0.02			-0.02		0.05			
Executive function	0.02			-0.03		0.08			
Memory–immediate recall	0.00			-0.11		0.22			
Memory–delayed recall	0.05			-0.01		0.10			
Social cognition	0.04			-0.03		0.12			
Visuoconstruction	0.13			0.04		0.12			

Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration.

(β=-0.4, SE= 0.11, p<0.001; Figure 1A). In addition, we found an interaction effect between time and gene group (χ^2(3)=37.1, p<0.001). All gene groups with CDR category ≥1 declined over time compared to controls (*C9orf72*: β_1=-0.3, SE=0.07, p<0.001; *GRN*: β_1=-0.4, SE=0.10, p<0.001; *MAPT*: β_1=-0.3, SE=0.09, p=0.004). There was some weak evidence that *C9orf72* pathogenic variant carriers with CDR category 0 declined over time compared to controls (β_1=-0.4, SE=0.11, p=0.086; Figure 1A).

Executive function

We found strong evidence for differences on the executive function domain between CDR categories (χ^2(2)=27.2, p<0.001), and between gene groups (χ^2(3)=23.3, p<0.001) at baseline. A similar profile was seen in all gene groups with CDR category ≥1 performing worse at baseline than controls (*C9orf72*: β=-3.1, SE=0.25, p<0.001; *GRN*: β=-3.2, SE=0.23, p<0.001; *MAPT*: β=-1.7, SE=0.29, p<0.001), and *C9orf72* (β=-1.0, SE=0.32, p=0.003), and *GRN* (β=-1.1, SE=0.35, p=0.002) pathogenic variant carriers performing worse than *MAPT* pathogenic variant carriers (Figure 1B). *C9orf72* pathogenic variant carriers with CDR category 0 also performed worse than *GRN* (β=-0.4, SE=0.17, p=0.016) and *MAPT* (β=-0.6, SE=0.23, p=0.012) pathogenic variant carriers, and controls (β=-0.5, SE=0.15, p<0.001), and *GRN* pathogenic variant carriers with CDR category 0.5 performed worse than controls (β=-0.7, SE=0.25, p=0.006). We found interaction effects between time and gene group (χ^2(3)=24.7, p<0.001), time and CDR category (χ^2(2)=25.8, p<0.001) and time, gene group and CDR category (χ^2(4)=18.6, p=0.001). *MAPT* pathogenic variant carriers with CDR category ≥1 demonstrated steeper decline over time than *C9orf72* (β_1=-*C9orf72* (β_1=-0.5, SE=0.14, p=0.002) and *GRN* pathogenic variant carriers (β_1=-0.5, SE=0.17, p=0.005) and controls (β_1=-0.6, S=0.12, p<0.001) (Figure 1B).

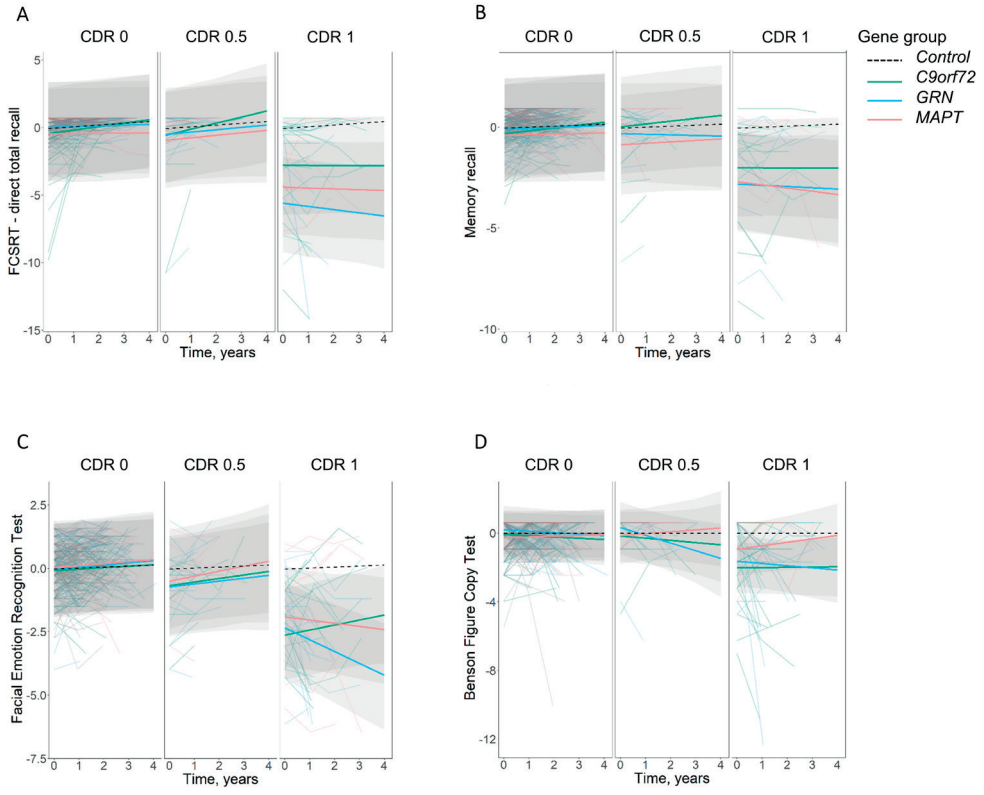
Language

Language differed between CDR categories (χ^2(2)=96.7, p<0.001) and between gene groups (χ^2(3)=21.5, p<0.001) at baseline. Again, all gene groups with CDR category ≥1 performed worse than controls (*C9orf72:* β=-3.2, SE=0.28, p<0.001; *GRN:* β=-2.9, SE=0.31, p<0.001; *MAPT*: β=-5.0, SE=0.41, p<0.001) at baseline, but in this case *MAPT* pathogenic variant carriers performed worse than *C9orf72* (β=-1.7, SE=0.34, p=0.002) and *GRN* (β=-1.3, SE=0.33, p=0.009) pathogenic variant carriers (Figure 1C). We also found interaction effects between time and gene group (χ^2(3)=104.8, p<0.001), time and CDR category (X^2(2)=14.0, p=0.001) and time, gene group and CDR category (X^2(4)=25.5, p<0.001). *MAPT* pathogenic variant carriers with CDR category 0.5 (β_1=-0.5, SE=0.17, p=004) and ≥1 (β_1=-0.5, SE=0.15, p=0.003) as well as *C9orf72* (β_1=-0.6, SE= 0.11, p<0.001) and *GRN* (β_1=-1.3, SE=0.14, p<0.001) pathogenic variant carriers with CDR category ≥1 declined over time compared to controls. In CDR category ≥1, *GRN* pathogenic variant carriers demonstrated steeper decline over time than *C9orf72* (β_1=-0.7, SE=0.17, p<0.001) and *MAPT* (β_1=-0.0.9, SE=0.20, p<0.001) pathogenic variant carriers (Figure 1C).

Verbal fluency

For verbal fluency we found strong evidence for differences between CDR categories ($\chi^2(2)=40.0$, $p<0.001$) at baseline. All gene groups with CDR category ≥1 performed worse than controls (*C9orf72*: β=-1.8, SE=0.12, $p<0.001$; *GRN*: β=-1.6, SE=0.14, $p<0.001$; *MAPT:* β=-1.3, SE=0.18, $p<0.001$), with *C9orf72* performing worse than *MAPT* pathogenic variant carriers (β=-0.5, SE=0.19, p=0.018; Figure 1D). In CDR category 0, *C9orf72* pathogenic variant carriers performed worse than controls (β=-0.3, SE=0.09, p=0.003) and *GRN* pathogenic variant carriers (β=-0.3, SE=0.11, p=0.002). We found an interaction effect between time and gene group ($\chi^2(3)=14.5$, $p<0.002$). *C9orf72* pathogenic variant carriers with CDR category ≥1 (β_1=-0.2, SE=0.05, p=0.004) and *GRN* pathogenic variant carriers with CDR categories 0.5 (β_1=-0.2, SE=0.08, p=0.013) and ≥1 (β_1=-0.2, SE=0.07, p=0.015) declined over time compared to controls (Figure 1D).

Figure 2. Linear mixed effects models displaying longitudinal trajectories in composite domain z-score stratified by the CDR plus NACC FTLD for *C9orf72*, *GRN* and *MAPT* pathogenic variant carriers and healthy controls. Models are displayed per cognitive domain: (A) memory – immediate recall, (B) memory – delayed recall, (C) social cognition, and (D) visuoconstruction



Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration.

Memory – immediate recall

For immediate recall, we found strong evidence for differences between CDR categories (χ^2(2)=51.4, p<0.001), and between gene groups (χ^2(3)=40.2, p<0.001) at baseline. All gene groups with CDR category ≥1 performed worse than controls (*C9orf72*: β=-2.7, SE=0.32, p<0.001; *GRN*: β=-5.5, SE=0.40, p<0.001; *MAPT*: β=-4.3, SE=0.51, p<0.001), with *MAPT* performing worse than *C9orf72* pathogenic variant carriers (β=-1.7, SE=0.56, p=0.003) and *GRN* pathogenic variant carriers performing worse than *C9orf72* (β=—3.0, SE=0.47, p<0.001) and *MAPT* pathogenic variant carriers (β=-1.2, SE=0.62, p=0.032; Figure 2A).

Memory – delayed recall

For delayed recall, we also found evidence for differences between CDR categories (χ^2(2)=36.9, p<0.001), and between gene groups (χ^2(3)=10.4, p=0.015), at baseline. Again, all gene groups with CDR category ≥1 performed worse than controls (*C9orf72*: β=-2.0, SE=0.21, p<0.001; *GRN*: β=-2.8, SE=0.27, p<0.001; *MAPT:* β=-2.7, SE=0.35, p<0.001), with *GRN* (β=-0.9, SE=0.32, p=0.007) and *MAPT* (β=-0.8, SE=0.38, p=0.033) performing worse than *C9orf72* pathogenic variant carriers. *MAPT* pathogenic variant carriers with CDR category 0.5 (β=-0.8, SE=0.36, p=0.021) performed worse than controls and *C9orf72* pathogenic variant carriers (β=-0.9, SE=0.42, p=0.023). In addition, there was some weak evidence indicating that *MAPT* pathogenic variant carriers with CDR category 0 performed worse than controls (β=-0.4, SE=0.21, p=0.081; Figure 2B). None of the groups declined significantly over time.

Social cognition

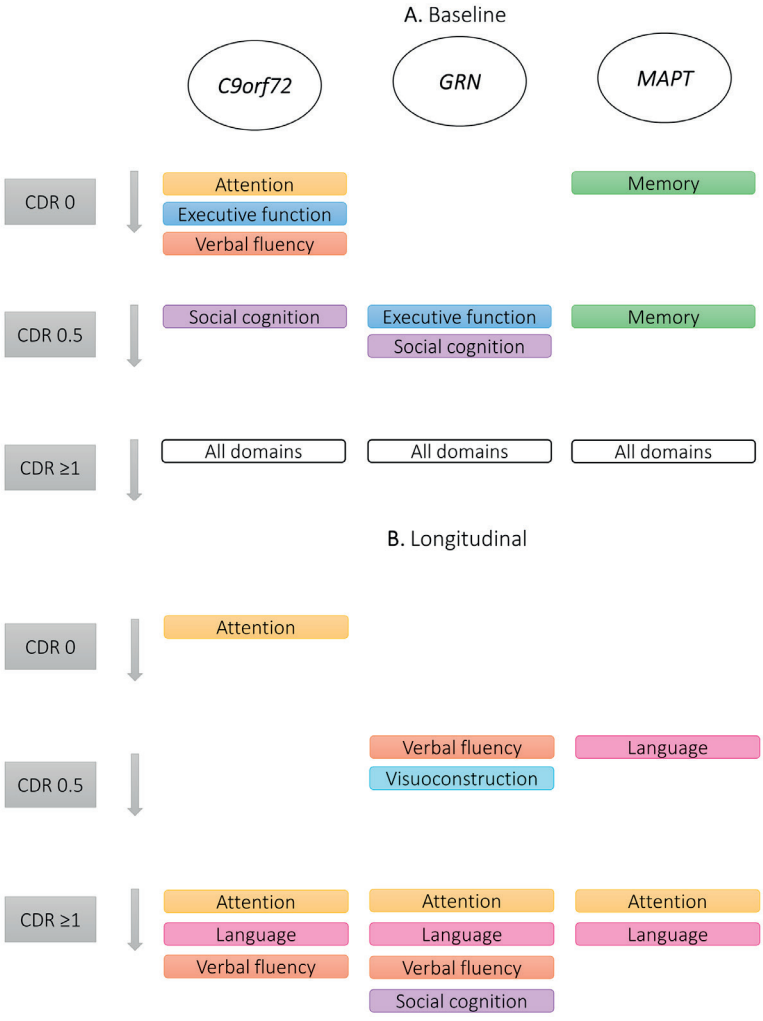
We found strong evidence for differences between CDR categories (χ^2(2)=35.7, p<0.001) at baseline on social cognition. All gene groups with CDR category ≥1 performed worse than controls (*C9orf72:* β=-2.6, SE=0.19, p<0.001; *GRN:* β=-2.3, SE=0.23, p<0.001; *MAPT:* β=-1.9, SE=0.28, p<0.001), with *GRN* performing worse than *MAPT* pathogenic variant carriers (β=-0.7, SE=0.33, p=0.033; Figure 2C). *C9orf72* (β=-0.7, SE=0.24, p=0.001) and *GRN* (β=-0.7, SE=0.25, p=0.001) pathogenic variant carriers with CDR category 0.5 also performed worse at baseline than controls. We found interaction effects between time and gene group (χ^2(3)=21.3, p<0.001) and time, CDR category and gene group (X^2(4)=16.3, p<0.003). *GRN* pathogenic variant carriers with CDR category ≥1 showed steeper decline over time compared to controls (β_1=-0.5, SE=0.13, p=<0.001), *C9orf72* (β_1=-0.7, SE=0.16, p<0.001) and *MAPT* (β_1=-0.3, SE=0.17, p=0.049) pathogenic variant carriers and *MAPT* pathogenic variant carriers with CDR category ≥1 showed steeper decline over time compared to *C9orf72* pathogenic variant carriers (β_1=-0.3, SE=0.16, p=0.047; Figure 2C).

Visuoconstruction

We found differences between gene groups on visuoconstruction (χ^2(3)=11.0, p=0.012) at baseline. All gene groups with CDR category ≥1 performed worse than controls (*C9orf72*: β=-2.0, SE=0.22, p<0.001; *GRN*: β=-1.6, SE=0.26, p<0.001; *MAPT*: β=-0.9, SE=0.32, p=0.004), with

C9orf72 (β=-1.2, SE=0.33, p=0.002) and *GRN* (β=-1.0, SE=0.36, p=0.008) performing worse than *MAPT* pathogenic variant carriers. *GRN* pathogenic variant carriers with CDR category 0.5 (β_1=-0.5, SE=0.23, p=0.050) showed steeper decline over time than controls (Figure 2D).

Figure 3. Summary of (A) cross-sectional and (B) longitudinal differences between each genetic group and controls.



Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration.

Discussion

This study demonstrated gene-specific baseline differences and decline over a 5-year time period in a large cohort of genetic FTD pathogenic variant carriers that was moderated by the CDR plus NACC FTLD global score. *C9orf72* pathogenic variant carriers performed lower on attention, executive function, and verbal fluency from CDR plus NACC FTLD 0 onwards, with relatively minimal decline over time compared to other genetic groups regardless of the CDR plus NACC FTLD score (i.e., disease progression). The cognitive profile in *MAPT* pathogenic variant carriers was characterized by early impaired memory (already at CDR plus NACC FTLD 0.5), with language decline starting at CDR plus NACC FTLD 0.5, and executive dysfunction developing rapidly at CDR plus NACC FTLD ≥1. *GRN* pathogenic variant carriers showed no differences or decline compared to controls at CDR plus NACC FTLD 0, but verbal fluency and visuoconstruction started to decline at CDR plus NACC FTLD 0.5. *GRN* pathogenic variant carriers showed the most rapid decline compared to the other groups in language and social cognition from CDR plus NACC FTLD ≥1 onwards. The results from this study confirm cognitive decline in the asymptomatic and prodromal stages of genetic FTD and hold potential for upcoming therapeutic trials by 1) identifying the most sensitive cognitive measures to track disease progression and treatment effects, and (2) identifying the speed of change over time, thereby providing insight into the best time-window to start disease-modifying treatment.

Asymptomatic *C9orf72* pathogenic variant carriers performed worse at baseline than controls on attention/mental processing speed, executive function and verbal fluency. In the prodromal stage, social cognition was also lower at baseline, whereas at the fully symptomatic stage all cognitive domains were lower at baseline. There was no decline over time in the asymptomatic stage or prodromal stage, but attention/mental processing speed, language and verbal fluency declined over time in the symptomatic stage, although less rapidly than in other gene groups. The other cognitive domains remained relatively stable, and of note, there were signs of possible practice effects for memory and social cognition. This is largely in line with previous studies demonstrating widespread cognitive impairment in *C9orf72* pathogenic variant carriers with relatively minimal decline over time[5, 40, 41]. It is further corroborated by the fact that the neurodegenerative process associated with the *C9orf72* pathogenic variant is widespread, with neurodegeneration in the frontal and temporal cortices but also in more posterior cortical, subcortical and cerebellar regions[40, 42]. Interestingly, this group performed lowest compared to the other groups on a wide range of neuropsychological tests, specifically tests for attention/mental processing speed and executive function, at the asymptomatic stage. Although these performances were not at an 'impaired' level (i.e. Z-score ≤ -2), these deficits might represent the earliest signs of neurodegeneration with very slow decline over time. Alternatively, the lack of decline over time in all three disease stages raises the intriguing possibility that these deficits are not merely preclinical signs of FTD as a result of early neurodegeneration, but might be indicative of a neurodevelopmental disorder in *C9orf72*

which at a certain age is superimposed by additional neurodegeneration. This hypothesis has been suggested by several previous studies that found gray and white matter deficits and connectivity disruption as well as psychiatric conditions and cognitive deficits many years before the estimated age of symptom onset without evidence of disease progression over time[43, 44]. Future studies should focus on ascertaining early-life radiological and clinical assessments to test this hypothesis.

In *MAPT* pathogenic variant carriers, there was a trend towards lower memory performance than controls at baseline in the asymptomatic stage, which became significant at the prodromal stage. All cognitive domains were lower than controls at baseline in the symptomatic stage. There was no decline over time in the asymptomatic stage, but language declined from the prodromal stage onwards. In addition, attention/mental processing speed, executive function and social cognition declined progressively during the symptomatic stage. These results confirm that the first changes for this group occur in cognitive functions that are strongly associated with the temporal lobe, an area that already shows early degeneration in presymptomatic *MAPT* pathogenic variant carriers[6]. Several previous studies have demonstrated that episodic memory impairment is a distinct feature in *MAPT*-related FTD, even in presymptomatic pathogenic variant carriers[19, 20, 26]. Strikingly, we demonstrated lower memory performance in asymptomatic and prodromal pathogenic variant carriers but with practice effects over time that disappeared at the fully symptomatic stage only. A likely explanation for these practice effects is that the same items for memory tests were used at all time points, stressing the need for the use of tests that have multiple versions with different stimuli in longitudinal cohort studies. The lower performance and decline seen in the language domain was largely driven by the BNT, a test that strongly depends on the semantic memory system[45]. This is unsurprising given that semantic memory is strongly associated with the anteromedial temporal lobe, an area known to deteriorate early and progressively in *MAPT*-associated FTD[26]. Deficits in semantic memory have been described as a key symptom in *MAPT* pathogenic variant carriers in a more progressed disease stage[5], but our results illustrate that the first changes occur at a much earlier stage, suggesting that semantic tests might be a good candidate to serve as a sensitive endpoint in upcoming therapeutic trials of *MAPT*-associated FTD. Only at a later progressed stage, when atrophy spreads from the temporal to frontal areas of the brain, impairment in cognitive functions that are typically associated with bvFTD develops, such as executive function and social cognition[22, 46].

There were no cross-sectional differences between asymptomatic *GRN* pathogenic variant carriers and controls at baseline, and there was no decline over time in this stage. In the prodromal stage, pathogenic variant carriers performed worse than controls on executive function and social cognition, and they declined over time on verbal fluency and visuoconstruction. All cognitive domains were lower than controls at baseline in the symptomatic stage, and they showed progressive decline over time on attention/

mental processing speed, verbal fluency, language and social cognition. This is in line with previous studies showing minimal changes in grey and white matter but also cognition in presymptomatic *GRN* pathogenic variant carriers, often with fast progressive decline after symptom onset[5, 20]. Although in our study no change over time was detected in the asymptomatic stage, *GRN* pathogenic variant carriers performed worse on executive function and social cognitive tasks at the prodromal stage suggesting some decline between these stages. Possible explanations could be that the asymptomatic pathogenic variant carriers were too far from symptom onset, and/or that the time-window between these stages where these changes occur is relatively short. Interestingly, verbal fluency declined progressively in the prodromal period indicating an early deficit in specifically verbal fluency. This could be interpreted as an early sign of pathogenic variant carriers developing nfvPPA, a clinical phenotype that is often seen in *GRN* pathogenic variant carriers[42]. However, verbal fluency measures are also known to strongly depend on executive function[37], a cognitive domain known to deteriorate in bvFTD[46]. Surprisingly, visuoconstruction also declined in the prodromal stage, whereas this is considered to be relatively spared in FTD[2]. However, most visuoconstructive tasks also strongly depend on executive functions such as planning, organizing and keeping overview[47]. It seems, therefore, more likely that these tasks were influenced by impaired executive function rather than a pure impairment in language and visuoconstruction per se.

This is to our knowledge the first study to longitudinally investigate a large cohort of all three major causes of genetic FTD over a 5-year period. A major strength of this study is the use of the CDR plus NACC FTLD to stratify pathogenic variant carriers from asymptomatic to prodromal and fully symptomatic (i.e., 0, 0.5, ≥1). Most previous studies have stratified pathogenic variant carriers as either presymptomatic or symptomatic according to whether they fulfilled diagnostic criteria for FTD syndromes, but this does not fully grasp the clinical trajectory of FTD. Importantly, the cognitive profile between the presymptomatic and symptomatic phase has not been well-characterized. Some other studies have used estimated years to symptom onset based on mean family age at onset, but a recent paper demonstrated that the correlations between age at symptom onset and mean family age at symptom onset were weak for *C9orf72* and *GRN* pathogenic variant carriers, indicating that this might not be a reliable proxy[28]. By stratifying according to CDR plus NACC FTLD, we have provided insight into cognitive decline during different disease stages. There are, however, a few limitations to this study. Firstly, the sample size at the CDR plus NACC FTLD 0.5 stage was smaller than the other stages, which probably influenced the statistical power in this specific group. Secondly, due to ongoing recruitment within GENFI, participants varied in the number of completed visits resulting in missing data at later time points. Therefore, we analyzed the data with linear mixed-effects model as these models allow for unbalanced time points and missing data[39]. We could not use a non-linear mixed effects model (e.g. natural cubic splines) due to the limited number of follow-up visits. However, similar to what has been performed in

studies of familial AD[48], non-linear models might be more suitable for the analysis of clinical progression in FTD. Future studies with longer follow-up should therefore investigate the use of non-linear models in analyzing clinical disease progression in FTD. Thirdly, we did not take progression over time on the CDR plus NACC FTLD into account, but stratified groups according to their global score at baseline. Future research should investigate the cognitive trajectories of progressors compared to non-progressors on the CDR plus NACC FTLD more in depth. Importantly, individual trajectories demonstrated high variability between individuals in each group. A possible explanation for this inter-individual variability could be that some individuals with a CDR plus NACC FTLD global score of 0 might be closer to symptom onset than others. Similarly, individuals with a CDR plus NACC FTLD score of 0.5 or ≥1 at baseline might vary in time since progression to that CDR category (i.e. individuals that had a global score of 0.5 for several years at inclusion will likely progress faster than individuals that progressed to a score of 0.5 more recently). Validation in other cohorts such as ALLFTD or DINAD is warranted. Fourthly, practice effects were strikingly visible for the FCSRT and Facial Emotion Recognition Test stressing the need for different test versions in the former, but more sensitive tasks for emotion recognition (e.g. the use of morphed facial expressions[22]) and social cognition in general. Lastly, in the interpretation of the memory – immediate recall, social cognition and visuoconstruction results it should be taken into account that they were represented by only a single cognitive test, and those individual tests might not be a representation of the entire cognitive domain.

To conclude, we provide evidence for gene-specific cognitive decline in the prodromal stage of genetic FTD. Specifically tests for attention/mental processing speed, executive function, language and memory showed clear differences between gene groups and controls at baseline, but the speed and nature of change over time differed depending on 1) the gene group and 2) the CDR plus NACC FTLD global score. These results confim the value of neuropsychological assessment in tracking disease progression and could inform upcoming clinical trials in selecting sensitive endpoints for measuring treatment effects as well as in characterizing the best time window for starting treatment.

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Supplementary file 1: Tables

Supplementary Table 1. Number of pathogenic variant carriers that changed in CDR® plus NACC FTLD global score during study follow-up.

Genetic group	Difference in CDR® plus NACC FTLD global score between the first and last visit		
	0 to 0.5	0 to ≥1	0.5 to ≥1
C9orf72	11	4	2
GRN	10	3	5
MAPT	4	2	3

Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration.

Supplementary Table 2. Neuropsychological data per genetic group and CDR® plus NACC FTLD global score category at baseline.

	C9orf72			*GRN*			*MAPT*		
CDR® plus NACC FTLD category	0	0.5	≥1	0	0.5	≥1	0	0.5	≥1
Camel and Cactus Test	-0.2 (1.3)	-0.5 (1.7)	-3.6 (3.9)	0.1 (0.8)	-0.5 (1.3)	-3.5 (3.9)	-0.2 (1.2)	-0.4 (1.5)	-4.5 (4.3)
Boston Naming Test	-0.2 (1.7)	-0.1 (1.9)	-3.8 (4.0)	0.1 (1.0)	-0.6 (2.0)	-3.4 (3.4)	-0.1 (1.1)	-1.1 (2.0)	-5.6 (4.2)
Trail Making Test–part A	-0.3 (1.1)	-0.4 (1.6)	-3.4 (3.1)	-0.1 (0.8)	-0.5 (2.0)	-4.4 (3.6)	0.3 (0.8)	0.1 (0.7)	-2.1 (2.3)
D-KEFS CWIT–mean of color and word naming	-0.4 (1.2)	-0.5 (1.3)	-4.1 (3.3)	0.0 (0.9)	-0.2 (1.2)	-3.4 (3.6)	0.1 (1.1)	-0.2 (1.1)	-2.5 (2.4)
Digit Symbol test	-0.3 (0.9)	-0.3 (1.1)	-2.4 (1.0)	-0.0 (0.9)	-0.6 (1.3)	-2.4 (1.1)	0.2 (0.9)	-0.1 (1.1)	-1.6 (1.1)
Digit span forward	-0.0 (1.0)	0.0 (0.9)	-1.1 (1.2)	0.1 (1.0)	-0.2 (1.3)	-1.3 (1.4)	0.1 (1.2)	-0.2 (1.2)	0.2 (1.1)
Category fluency	-0.2 (1.0)	-0.4 (0.9)	-2.1 (0.9)	0.1 (0.8)	-0.3 (1.0)	-2.1 (0.9)	-0.1 (0.9)	-0.4 (0.6)	-1.7 (1.3)
Phonemic fluency	-0.4 (0.9)	-0.3 (1.1)	-1.8 (0.9)	0.0 (1.0)	0.2 (1.3)	-1.9 (1.0)	-0.1 (1.0)	-0.0 (1.1)	-1.2 (1.1)
Trail Making test–part B	-0.4 (1.6)	-0.8 (2.1)	-4.3 (2.9)	0.0 (0.8)	-0.9 (2.4)	-5.3 (2.9)	0.2 (0.7)	-0.2 (1.2)	-3.4 (3.1)
D-KEFS CWIT–ink naming	-0.8 (2.0)	-0.9 (1.5)	-6.1 (4.5)	-0.1 (1.3)	-1.5 (4.0)	-5.9 (6.4)	0.1 (1.5)	-0.1 (1.2)	-3.2 (3.1)
Digit span backward	-0.0 (1.0)	0.2 (1.2)	-1.4 (1.0)	-0.1 (1.0)	-0.3 (1.1)	-1.6 (1.2)	0.1 (1.0)	-0.3 (1.0)	-0.4 (1.3)
FCSRT immediate free recall	-0.5 (1.1)	-0.8 (1.2)	-2.6 (1.3)	-0.1 (0.9)	-0.4 (1.3)	-2.7 (1.8)	-0.0 (1.0)	-0.4 (1.4)	-2.8 (1.5)
FCSRT immediate total recall	-0.5 (1.8)	-0.8 (2.3)	-3.3 (4.0)	0.1 (0.7)	-0.7 (2.3)	-5.7 (5.5)	0.0 (1.1)	-0.9 (2.6)	-5.2 (4.0)
FCSRT delayed free recall	-0.5 (1.2)	-0.5 (1.0)	-2.8 (1.4)	-0.0 (1.0)	-0.7 (1.4)	-2.6 (1.8)	-0.0 (1.2)	-0.3 (1.6)	-2.9 (1.8)
FCSRT delayed total recall	-0.4 (1.4)	-0.4 (1.9)	-3.6 (4.4)	0.0 (0.7)	-0.6 (2.5)	-4.7 (5.8)	-0.2 (1.4)	-0.9 (3.1)	-4.7 (4.4)
Benson Figure recall	-0.2 (1.0)	0.1 (1.0)	-2.0 (1.7)	-0.1 (1.0)	-0.4 (1.2)	-2.2 (1.7)	-0.0 (1.0)	-0.6 (1.8)	-2.6 (2.0)
Facial Emotion Recognition Test	-0.1 (1.0)	-0.7 (1.3)	-3.1 (2.2)	0.1 (1.1)	-0.7 (1.4)	-2.8 (1.9)	0.1 (0.8)	-0.5 (1.2)	-2.2 (2.1)
Benson Figure copy	-0.1 (1.2)	-0.2 (1.6)	-2.3 (2.9)	0.2 (0.8)	0.2 (1.0)	-1.9 (3.2)	-0.2 (0.9)	-0.2 (0.9)	-1.3 (2.7)

Values are represented as mean Z-score compared to controls (standard deviation). Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration; y = years; MMSE = Mini-Mental State Examination; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test.

Supplementary file 2: example output

Results: Language domain model

Model specification using lmer function in R:

```
mod_3way <- lmer( domain_language ~ time_years + cdr_cats + gene_gp + cdr_cats:gene_gp:mc +
        time_years:cdr_cats:mc +
        time_years:gene_gp +
        time_years:gene_gp:cdr_cats:mc + Baseline_age + Education +
        (1|family/id), data = dataset )
```

1. Joint tests for interaction terms

Term	Chi-squared statistic	Degrees of freedom	p-value
Time (years)	4.534122	1	0.03
CDR categories	357.0388	2	<0.01
Gene group	11.76297	3	0.01
Baseline age (years)	28.14819	1	<0.01
Education	47.87221	1	<0.01
Time by gene group	74.03938	3	<0.01
CDR category by gene group (pathogenic variant carriers only)	8.731389	4	0.07
CDR category by CDR category (pathogenic variant carriers only)	70.76203	2	<0.01
CDR category by gene group by CDR category (pathogenic carriers only)	19.74931	4	<0.01

2. Full model output

	Domain language (z-score)		
Predictors	*Estimates*	*CI*	*p*
(Intercept)	-0.54	-1.17 – 0.08	0.089
time_years	0.03	-0.02 – 0.08	0.227
cdr_cats [0.5]	-0.35	-1.13 – 0.43	0.377
cdr_cats [1]	-3.49	-4.16 – -2.83	**<0.001**
gene_gp [C9]	0.93	0.19 – 1.67	**0.014**
gene_gp [GRN]	1.00	0.23 – 1.77	**0.011**
gene_gp [MAPT]	-0.31	-0.74 – 0.12	0.153
Baseline_age	-0.02	-0.03 – -0.01	**<0.001**
Education	0.10	0.07 – 0.13	**<0.001**
time_years * gene_gp [C9]	-0.36	-0.52 – -0.21	**<0.001**
time_years * gene_gp [GRN]	-0.88	-1.08 – -0.68	**<0.001**
time_years * gene_gp [MAPT]	-0.31	-0.52 – -0.10	**0.004**
cdr_cats0 * gene_gp [C9] * mc	-1.08	-1.85 – -0.32	**0.005**
cdr_cats [0.5] * gene_gp [C9] * mc	-0.76	-1.78 – 0.27	0.147
cdr_cats0 * gene_gp [GRN] * mc	-0.92	-1.70 – -0.14	**0.021**
cdr_cats [0.5] * gene_gp [GRN] * mc	-1.02	-2.06 – 0.03	0.056
time_years * cdr_cats0 * mc	0.31	0.09 – 0.54	**0.007**
time_years * cdr_cats [0.5] * mc	0.09	-0.22 – 0.40	0.577
time_years * cdr_cats0 * gene_gp [C9] * mc	0.01	-0.27 – 0.30	0.918
time_years * cdr_cats [0.5] * gene_gp [C9] * mc	0.22	-0.20 – 0.65	0.297
time_years * cdr_cats0 * gene_gp [GRN] * mc	0.54	0.23 – 0.84	**0.001**
time_years * cdr_cats [0.5] * gene_gp [GRN] * mc	0.68	0.25 – 1.11	**0.002**
Random Effects			
σ^2	0.31		
$\tau_{00\ id:family}$	1.08		
$\tau_{00\ family}$	0.51		
ICC	0.84		
N_{id}	769		
N_{family}	345		
Observations	1532		
Marginal R^2 / Conditional R^2	0.490 / 0.916		

3. Pairwise comparisons

(a) Intercepts – difference with control

Gene group	CDR category	Estimated difference with control	Std error	Statistic	p-value
C9	0	-0.15617	0.153821	-1.01529	0.31
C9	0.5	-0.17974	0.25242	-0.71206	0.48
C9	1	-2.56677	0.201894	-12.7134	0.00
GRN	0	0.080445	0.14006	0.574361	0.57
GRN	0.5	-0.36613	0.252077	-1.45247	0.15
GRN	1	-2.49597	0.224901	-11.0981	0.00
MAPT	0	-0.31005	0.216886	-1.42954	0.15
MAPT	0.5	-0.65989	0.360704	-1.82944	0.07
MAPT	1	-3.80474	0.294486	-12.9199	0.00

(b) Slopes – difference with control

Gene group	CDR category	Estimated difference with control	Std error	Statistic	p-value
C9	0.5	-0.05	0.13	-0.40	0.69
C9	1	-0.36	0.08	-4.62	0.00
GRN	0.5	-0.11	0.12	-0.93	0.35
GRN	1	-0.88	0.10	-8.56	0.00
MAPT	0.5	-0.22	0.12	-1.80	0.07
MAPT	1	-0.31	0.11	-2.88	0.00

(c) Pairwise differences in slopes

CDR category	Contrast	Estimate	SE	df	t.ratio	p-value
0	control 0–C9 1	0.04	0.05	827.70	0.74	0.46
0	control 0–GRN 1	0.03	0.04	828.11	0.66	0.51
0	control 0–MAPT 1	0.00	0.06	806.35	-0.08	0.94
0	C9 1–GRN 1	-0.01	0.05	822.46	-0.17	0.86
0	C9 1–MAPT 1	-0.04	0.07	809.71	-0.62	0.53
0	GRN 1–MAPT 1	-0.03	0.06	804.35	-0.53	0.60
0.5	C9 1–GRN 1	0.06	0.17	841.11	0.33	0.74
0.5	C9 1–MAPT 1	0.17	0.17	831.53	0.97	0.33
0.5	GRN 1–MAPT 1	0.11	0.16	812.53	0.68	0.50
1	C9 1–GRN 1	0.51	0.12	850.15	4.15	0.00
1	C9 1–MAPT 1	-0.06	0.13	838.88	-0.44	0.66
1	GRN 1–MAPT 1	-0.57	0.14	842.10	-3.98	0.00

CHAPTER 3

New sensitive cognitive instruments in the frontotemporal dementia spectrum

CHAPTER 3.1

Exploring abstract semantic associations in the frontotemporal dementia spectrum in a Dutch population

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Abstract

Objective: To investigate the differential ability of the 'Test Relaties Abstracte Concepten' (TRACE), a Dutch test for abstract semantic knowledge, in frontotemporal dementia (FTD).

Methods: The TRACE was administered in patients with behavioural variant FTD (bvFTD; n=16), non-fluent variant (nfvPPA; n=10), logopenic variant (lvPPA; n=10), and semantic variant primary progressive aphasia (svPPA; n=9), and controls (n=59). We examined group differences, performed correlational analyses with other neuropsychological tests and investigated discriminative ability. We compared the TRACE with a semantic association test for concrete stimuli (SAT).

Results: All patient groups, except nfvPPA, performed worse on the TRACE than controls (p<0.01). svPPA patients performed worse than the other patient groups (p<0.05). The TRACE discriminated well between patient groups, except nfvPPA, versus controls (all p<0.01) and between svPPA versus other patient groups with high sensitivity (75-100%) and specificity (86%-92%). In bvFTD and nfvPPA the TRACE correlated with language tests (ρ>0.6), while in svPPA the concrete task correlated (ρ≥0.75) with language tests. Patients with bvFTD, nfvPPA and lvPPA performed lower on the TRACE than the SAT (p<0.05), whereas patients with svPPA were equally impaired on both tasks (p=0.2).

Discussion: We demonstrated impaired abstract semantic knowledge in patients with bvFTD, lvPPA, and svPPA, but not nfvPPA, with svPPA patients performing worse than the other subtypes. The TRACE was a good classifier between each patient group versus controls and between svPPA versus other patient groups. This highlights the value of incorporating semantic tests with abstract stimuli into standard neuropsychological assessment for early differential diagnosis of FTD subtypes.

Introduction

Semantic memory refers to a long-term memory system for the storage of lexical, concept and object knowledge, that is essential for the ability to generalize information[1]. Degradation of semantic memory can have devastating effects on daily living, as is apparent in patients with temporal lobe degeneration, most notably in patients with subtypes of frontotemporal dementia (FTD)[1]. FTD constitutes a spectrum of clinically and pathologically heterogeneous diseases, with patients typically presenting with primarily behavioural and executive functioning impairments (behavioural variant FTD (bvFTD)) or language impairments (primary progressive aphasia (PPA))[2-5]. Three subtypes of PPA are distinguished: semantic variant PPA (svPPA), non-fluent variant PPA (nfvPPA) and logopenic variant PPA (lvPPA)[2], with the latter also manifesting as a result of Alzheimer's disease (AD) pathology[6]. Degradation of semantic memory is the main deficit in svPPA[2, 7, 8-1], but can occur in other clinical FTD subtypes as well. For example, semantic deficits are often seen in patients with bvFTD and can be present in combination with other core symptoms of nfvPPA, lvPPA or mixed subtypes of PPA[11-19]. This clinical overlap complicates the differential diagnosis in these patient populations, and together with the subtlety of symptoms in the early stages of the disease misdiagnosis and/or diagnostic delay may occur. Yet, early diagnosis is crucial for proper patient management and early treatment planning.

Standard diagnostic neuropsychological evaluation in FTD syndromes often includes semantic memory tests that focus on concrete stimuli, such as the Pyramid and Palm Trees test[20]. Concrete nouns refer to entities that are tangible, exist in the real world and can be experienced through our senses, e.g., 'umbrella'[1]. In contrast, abstract nouns have minimal physical or tangible qualities, and primarily refer to entities that only exist within language and thought, and are therefore less dependent on sensory information, but rely more on contextual and linguistic information, e.g., ' honour'[1]. In general, individuals are better at identifying and remembering concrete than abstract words, a phenomenon which is referred to as *the concreteness effect* [21, 22]. This effect typically becomes even stronger after brain damage, e.g., aphasia after stroke[23, 24]. As a result, semantic tests focusing on concrete concepts are often not sensitive enough to detect subtle semantic deficits in the early stages of the disease. Fundamental studies using experimental materials have indeed shown a specific degradation of abstract semantic concepts in patients with bvFTD[1, 25], whereas a reversal of this concreteness effect is seen in patients with svPPA, that is, patients are better at identifying abstract than concrete words [1, 22, 25-29]. Yet, clinically validated tests to measure the understanding of abstract words are currently lacking. The Dutch 'Test Relaties Abstracte Concepten' (free translation from Dutch: Test of the relations between abstract concepts (TRACE)') was specifically developed for this purpose and has been validated in Dutch-speaking patients with Alzheimer's disease (AD), patients with aphasia after stroke and cognitively healthy individuals in different age categories[30]. In these validation studies, the

TRACE discriminated between patient groups and control participants, and all three groups performed significantly worse on the TRACE as compared to a Dutch task that uses concrete stimuli. The TRACE has not been investigated in the FTD spectrum yet, and it is unknown how patients with nfvPPA and lvPPA perform on semantic tests for the understanding of abstract words. However, results from previous studies indicate that a test for abstract semantic knowledge, *complementary* to traditional semantic tests with more concrete stimuli could provide important additional diagnostic information about subtle semantic impairments in the early stages of the disease as well as help in the differential diagnosis between FTD subtypes in the early stages.

The aim of the current study was therefore to investigate the differential ability of the TRACE in the FTD spectrum. We compared Dutch-speaking patients with bvFTD, PPA subtypes (svPPA, nfvPPA and lvPPA) and cognitively healthy controls and investigated discriminative ability, sensitivity and specificity of the TRACE. In addition, we investigated correlations with other relevant neuropsychological tests, and more specifically compared the TRACE with the verbal Semantic Association Test (SAT)[32], the concrete counterpart of the TRACE.

Methods

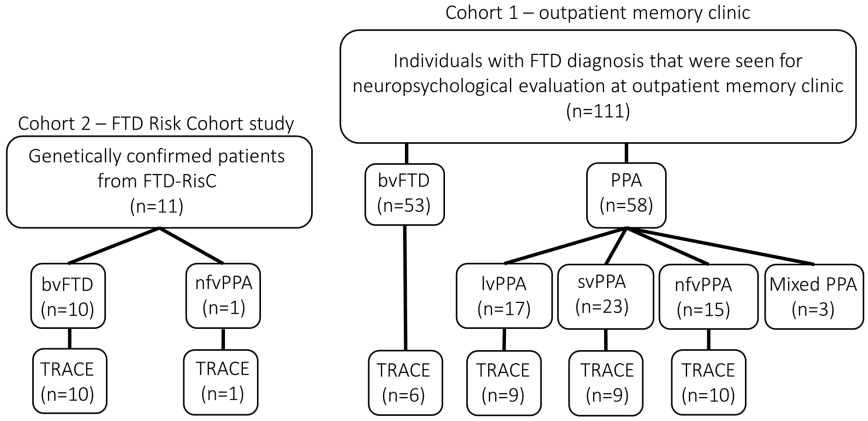
Participants

Data for this study was retrospectively collected via two different ways; the outpatient clinic of the Erasmus MC University Medical Center (cohort 1) and an ongoing cohort study of Dutch genetic FTD families (the FTD Risk cohort, FTD-RisC)[33, 34] (cohort 2). A STROBE participant flowchart can be seen in Figure 1.

Cohort 1: In total, 111 individuals were seen for diagnostic neuropsychological evaluation at the outpatient clinic of the Erasmus MC University Medical Center between January 2017 and March 2020, and received a dementia diagnosis in the FTLD spectrum (bvFTD: n=53; PPA: n=58). From this group, six patients with bvFTD, 9 patients with nfvPPA, 10 patients with lvPPA and 9 patients with svPPA performed the TRACE and were included in this study. Patients with a mixed type of PPA (n=3) were excluded. Based on the referral question and clinical suspicion of PPA, the TRACE was administered as part of the diagnostic neuropsychological evaluation according to the judgment of experienced neuropsychologists (LCJ, EvB, SF, JvH). Reasons for not administering the TRACE were for example when patients were too cognitively impaired to perform the task or if the concerning neuropsychologist not deemed it necessary/relevant to answer the referral question (e.g. other cognitive tests had priority).

Cohort 2: 11 genetically confirmed patients (bvFTD: n=10; nfvPPA: n=1) carrying FTD mutations were recruited via FTD-RisC[33, 34] in which the TRACE is a standard part of the

Figure 1. STROBE participant flowchart.



Abbreviations: FTD = Frontotemporal dementia ; FTD-RisC = Frontotemporal dementia risk cohort; bvFTD = behavioural variant frontotemporal dementia; PPA = primary progressive aphasia; nfvPPA = non-fluent variant primary progressive aphasia ; lvPPA = logopenic variant primary progressive aphasia ; svPPA = semantic variant primary progressive aphasia ; TRACE = Test Relaties Abstracte Concepten

neuropsychological test protocol. In addition, fifty-nine control participants from the FTD-RisC study were used as a reference group (matched for age, education and sex). This control group consists of healthy first-degree family members of genetic FTD patients who tested mutation-negative, upon DNA genotyping (described in more detail in Dopper et al.[33] and Papma et al.[34]).

In all patients, diagnoses were made in a multidisciplinary consensus meeting, involving experienced neurologists, neuropsychologists, (neuro)radiologists, geriatricians, and a care consultant. Patients had a probable (n=31) or definite (n=14) diagnosis according to established diagnostic criteria for bvFTD[4], PPA[2], and FTD-ALS[35]. DNA genotyping was performed as a part of the FTD-RisC study (n=11) or as part of diagnosis setting (n=3). Two patients with bvFTD had concomitant amyotrophic lateral sclerosis (FTD-ALS)[35]. Cerebrospinal fluid (CSF) biomarkers were analyzed as part of the diagnosis setting in 15 patients (lvPPA: n=4; nfvPPA: n=2; svPPA: n=4; bvFTD: n=1; FTD-ALS: n=2) and indicated AD as underlying etiology in four patients with lvPPA[36]. The study was approved by the local Medical and Ethical Review Committee. All patients with dementia that were recruited via the outpatient clinic of the Erasmus MC University Medical Center were part of a local biobank study, for which they provided written informed consent for the use of their anonymized medical and clinical data for research purposes. Participants of the FTD-RisC study provided written informed consent for the use of their anonymized research data.

Procedure

The TRACE was administered as part of a larger standardized neuropsychological assessment protocol for bvFTD and PPA. We administered the Mini-Mental State Examination (MMSE)[37] and Frontal Assessment Battery (FAB)[38] as measures of respectively global and frontal cognitive functioning. Additional tests from the neuropsychological assessment battery that were available in all four patients groups and controls included tests for language (i.e. the Boston Naming Test 60 items (BNT)[31], category fluency[39] and the verbal SAT[32]), attention and executive functioning (i.e. the Trail Making Test (TMT) part A and B[40] and letter fluency[39]), social cognition (i.e. the Emotion Recognition Test (ERT)[41]), and memory (i.e. the Visual Association Test (VAT)[42]).

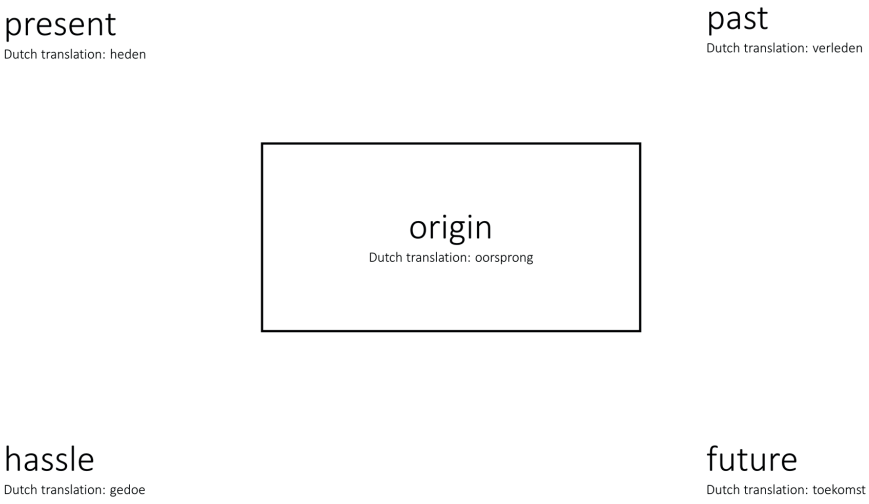
Test Relaties Abstracte Concepten (TRACE)

The TRACE is a Dutch neuropsychological test measuring a patient's understanding of abstract words[30]. The design of the TRACE is analogous to that of the Pyramids and Palm Trees Test[20] where patients have to associate words based on the meaning. The TRACE consists of two practice and 30 test items that are presented visually on successive cards which each shows five abstract words in Dutch: one in the center (target) and four (one correct answer and three distractors) in each corner. An example item from the TRACE, including English translations, can be seen in Figure 2. Two distractors on each card are semantically related to the correct answer, while one distractor is semantically unrelated to both the target and the correct answer. Participants have to choose the item that relates best to the target on an abstract semantic level[30]. Typical administration time of the TRACE is 20-30 minutes. Performance on the TRACE is defined by the number of correct items (maximum = 30). Information regarding the development, administration, validity and reliability of the TRACE as provided in the Dutch test manual[30] is described in the following two paragraphs.

There is a thematic relation between the target and correct answer, which means that the words can be used in a syntagmatic association (i.e., a linear relationship between elements that are able to precede or follow each other in a sentence, e.g. target = 'origin' , correct answer = 'past')[43, 44] and that the target and correct answer do not belong to the same semantic category. The semantic distractors were chosen from the same semantic category as the correct answer with a paradigmatic relation to the correct answer (i.e. a vertical relation between elements that can be substituted for each other, e.g. 'past' could be replaced by 'present' or 'future')[43, 44]. The most important factor in item-selection was imageability of the words, as it is assumed to underlie the abstractness of a word[30, 45]. Only words with low imageability (i.e. imageability score of ≤ 3.5 on a 7-point scale) were selected from an inventory of imagery values of Dutch words[46]. Items from different semantic categories were used and the use of synonyms was avoided as much as possible. Factors such as typical acquisition age, word length and word frequency were taken into account and words belonging to multiple parts of speech were not considered (e.g. words that could function as

both a noun and verb). The first set of items (n=57) were rated by twenty healthy individuals. Some items were adjusted when there was a large variation between participants in how the responses were grouped. This procedure was repeated three times which resulted in 35 items with a high level of agreement. The first version of the TRACE was tested in patients with AD and a healthy elderly control group. Five items were removed based on factor analysis and reliability data to correspond the number of items on the SAT (=30).

Figure 2. Example item from the TRACE with Dutch translations.



Reliability and validity of the TRACE was evaluated in patients with aphasia after stroke (n=59), AD (n=23), and control participants (n=164)[30]. There was a high internal consistency for all three groups (Cronbach's alphas of respectively 0.79, 0.84 and 0.86), and the mean corrected item-total correlation was sufficient (respectively 0.30, 0.38 and 0.36). Test-retest reliability was investigated in 11 patients with aphasia and showed a strong association between test moments (r=0.8, p=0.003; ρ=0.83, p=0.002). Construct validity was determined by investigating the distribution of scores per item and the correlation between the TRACE and demographic factors, and other cognitive tests. There were no items with a ceiling effect, but there were five items that had a possible floor effect which was mediated by education level. There was no significant effect of sex on TRACE performance, but there was a strong correlation between the TRACE and age (r= -0.5, p<0.0001, ρ=-0.51, p<0.0001), as well as a significant effect of education level in control participants (p<0.0001). There were strong correlations between the TRACE and SAT (r=0.64; ρ=0.72, p<0.0001), between the TRACE and abbreviated Token Test[47] (r=0.56, p<0.0001; ρ=0.51, p<0.0001) and between the TRACE and the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) -49 task[48] (r=0.7; ρ=0.68) (all p<0.0001). All groups performed significantly lower on the TRACE than the SAT and the PALPA-49 task (p<0.0001). There was no association between the TRACE and the repetition subtest of the Aachen Aphasia Test (AAT[49]). Criterion validity was determined

by receiver operating characteristic (ROC) analysis which showed a 90% sensitivity and 40% specificity in patients with aphasia after stroke and 96% sensitivity and 44% specificity in patients with AD, with a cut-off of 27 compared to controls. Norms are available in the test manual of the TRACE[30]. A detailed description as well as psychometric properties of the SAT can be found in Supplementary file 1. There was no SAT data available in the control group.

Statistical Analysis

Statistical analyses were performed using STATA version 16 (Texas, USA). The significance level was set at $p<0.05$ (two-tailed) across all comparisons. Statistical assumptions were checked by visually inspecting the data as well as statistical tests (Shapiro-Wilk and Levene's Test). We compared age (one-way ANOVA), sex (chi square test), education level (Kruskal-Wallis and Wilcoxon Rank Sum Test) and disease duration (Kruskal-Wallis and Wilcoxon Rank Sum Test) between groups.

Performance in controls was assessed by calculating the cumulative frequency of test scores (and therefore percentile scores) as well as investigating the effect of sex (Wilcoxon Rank Sum Test), age (Spearman rank correlation) and education level (Spearman rank correlation).

Mean differences between patient groups and control participants on total number of correct TRACE items were analyzed with one-way analyses of covariance (ANCOVA) with resampling by means of bootstrapping (1000s repetitions) as the assumption of homoscedasticity and normality were violated. Age and education level[50] were added as covariates. A separate ANCOVA including disease duration as covariate was performed to compare TRACE performance between patient groups. Bootstrapped 95% confidence intervals are reported. All post-hoc pairwise comparisons were Bonferroni corrected.

We performed logistic regression analyses and determined sensitivity and specificity by the area under the curve (AUC) by nonparametric ROC analyses to investigate classification abilities of the TRACE between patient groups and controls, and between patient groups. Optimal cut-off levels were given by the highest Youden's index[51].

To compare the TRACE with the SAT across the different patient groups, we performed a 2x4 repeated measures ANOVA with test (i.e. TRACE and SAT) as a within-subjects factor and patient group (i.e. bvFTD, nfvPPA, lvPPA, svPPA) as between-subjects factor. Post-hoc paired sample t-tests were performed to investigate the difference in TRACE and SAT performance in each group. Statistical assumptions for repeated measures ANOVA and paired sample t-tests were not violated (i.e. the difference score between the SAT and TRACE was normally distributed and there was no heteroscedasticity).

Due to small sample sizes we ran nonparametric equivalents for all ANOVAs in this study but results remained largely (>90%) similar. For reasons of clarity we present only the results from the parametric set of analyses.

Spearman rank correlations were performed to investigate the association between the TRACE total number of correct items and the other neuropsychological tests in each patient group. For the VAT, the percentage correct was calculated due to different versions and therefore different maximum scores depending on age (12-item for persons ≥65 years old vs. 24-item for persons <65 years old). The TMT scores were truncated to 300 s for patients that exceeded the time limit or were unable to complete the test due to cognitive disabilities (n=10). In addition, we investigated the association between SAT and other language tests (i.e. BNT, animal and letter fluency) with Spearman rank correlations in the PPA patient groups (as there were only 2 bvFTD patients with a SAT in combination with BNT or verbal fluency measures).

Results

Demographic data

Demographic, clinical and neuropsychological data are shown in Table 1. Patients with nfvPPA and lvPPA were older than control participants (nfvPPA: Beta=13.0, 95%CI 2.9 – 23.1, $p<0.01$; lvPPA: Beta=18.8, 95%CI 8.7 – 28.9, $p<0.01$), and patients with lvPPA were older than patients with bvFTD (Beta=16.0, 95%CI 4.1 – 27.9, $p<0.01$). There were no differences between patient groups in education level ($H(4)=3.7$, $p=0.5$), disease duration ($H(3)=5.9$, $p=0.1$) or sex ($X^2(4)=4.8$, $p=0.3$), but there was a significant main effect of group on MMSE ($H(4)=30.6$, $p<0.01$) and FAB ($H(4)=37.9$, $p<0.01$). Post-hoc pairwise comparisons revealed that all patient groups, except nfvPPA, performed worse on the MMSE than control participants (bvFTD: $z=3.4$, $p<0.01$; lvPPA: $z=4.1$, $p<0.01$; svPPA: $z=3.2$, $p<0.01$). All patient groups, except svPPA, performed worse on the FAB than control participants (bvFTD: $z=4.4$, $p<0.01$; nfvPPA: $z=3.9$, $p<0.01$; lvPPA: $z=4.2$, $p<0.01$).

Table 1. Demographic and neuropsychological data.

	bvFTD	nfvPPA	lvPPA	svPPA	controls
			Demographics		
n	16	10	10	9	59
Sex f:m	8:8	6:4	3:7	2:7	31:28
Age, y	56.8±8.8	67.0±8.9	72.8±9.0	60.8±7.4	54.0± 11.4
[Range]	[39-73]	[55-81]	[57-83]	[52-72]	[32-78]
Education level[a]	5.4±0.8	4.7±1.0	5.3±1.3	5.2±1.4	5.4±1.0
Disease duration, y	5.1±3.5	3.1±1.6	3.3±1.8	5.5±2.8	-
[Range]	[1.5-13.3]	[1.1-6.2]	[0.5-6.7]	[2.2-8.9]	-
			Neuropsychological data		
MMSE [max=30]	26.8±2.8	26.3±3.4	25.7±2.1	24.8±4.4	28.9±1.4
FAB [max=18]	13.9±2.6	13.2±4.0	12.1±3.6	14.8±3.5	16.8±1.7
BNT 60 [max=60]	46.9±7.6	51.9±5.6	42.7±10.0	12.6±11.3	54.4±5.2
Animal fluency	15.5±5.6	14.9±6.8	12.3±4.1	7.1±5.5	24.6±4.7
Letter fluency	20.7±12.9	17.9±9.4	20.5±12.1	19.2±13.3	39.0±12.2
TMT A [max=300]	43.5±17.2	73.3±82.0	89.9±57.4	41.4±16.6	28.8±15.1
TMT B [max=300]	138.2±80.3	167.6±87.9	229.8±88.1	155.4±100.4	66.7±43.2
ERT total [max=96]	41.4±12.0	39.8±16.9	40.0±8.4	40.5±13.7	55.5±9.1
SAT [max=30]	24.0±6.2	27.0±2.3	26.6±2.4	18.6±7.8	-
VAT %[b]	92.3±22.9	91.7±13.7	73.8±29.1	62.5±31.8	100.0±0.0
			TRACE data		
TRACE total score	21.9±4.7	22.1±6.0	21.7±3.1	13.9±6.5	27.0±2.3
Range	13-30	14-29	19-28	19-28	20-30
Skewness[c]	-0.04	-0.32	0.96	-0.18	-1.07

Values are: raw mean ± standard deviation or n unless otherwise specified. Abbreviations: bvFTD = behavioural variant frontotemporal dementia; nfvPPA = non fluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; MMSE = Mini-Mental State Examination; FAB = Frontal Assessment Battery; BNT 60 = Boston Naming Test 60 items; TMT = Trail Making Test; ERT = Emotion Recognition Test; SAT = Semantic Association Test; VAT = Visual Associatoin Test; TRACE = Test Relaties Abstracte Concepten.aLevel of education was recorded using seven categories in accordance with the Dutch educational system (1=less than 6 years of primary education to 7 = academic schooling)50.bFor the VAT, the percentage correct was calculated due to different maximum scores depending on age (12-item for persons ≥65 years old vs. 24-item for persons <65 years old). cSkewness values are a representation of the extent to which a given distribution varies from a normal distribution, where a perfect normal distribution has a skew of zero[52]

Normative data in the control population

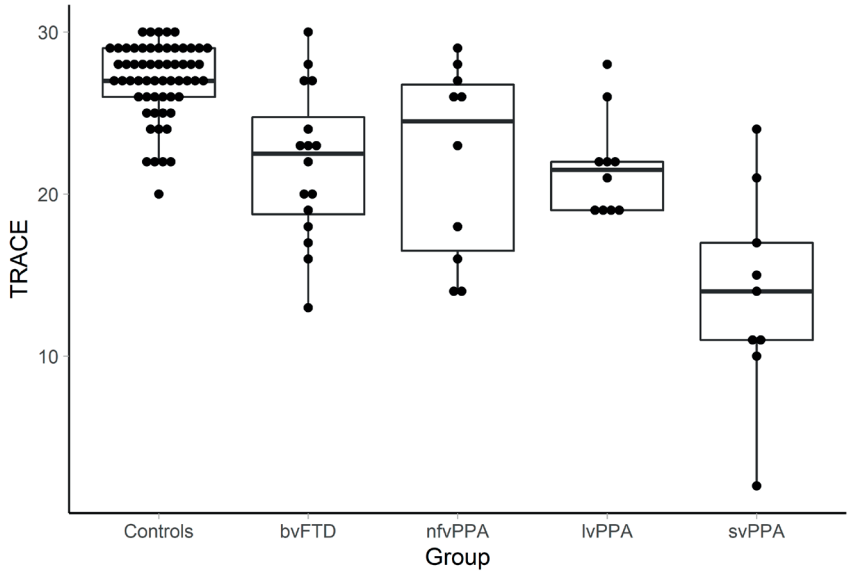
Cumulative frequencies (Supplementary Table 1), percentile scores (Supplementary Table 2) and mean performance on the TRACE stratified by age group, sex, and education level for control participants (Supplementary Tables 3 and 4) can be found in Supplementary file 2. Overall, control participants scored between 20 and 30 out of a total possible score of 30 and the 5th percentile score is 22. There was a weak negative correlation between TRACE performance and age (ρ=-0.2, p=0.03), and a moderate positive correlation between

TRACE performance and education level (ρ=0.5, p<0.05) in control participants. There was no significant difference between males and females on the TRACE (z=-1.5, p=0.14).

Group differences TRACE

Means, standard deviations and ranges of TRACE scores can be found in Table 1 and Figure 3. There was a significant main effect of group (F(4, 97)=22.8, p<0.01, η^2=0.53). All patient groups, except nfvPPA patients, performed worse on the TRACE than control participants (bvFTD: Beta=-5.1, 95%CI -8.4 to -1.9, p<0.01; nfvPPA: Beta=-4.1, 95%CI -9.1 to 1.0, p=0.2; lvPPA: Beta=-5.1, 95%CI -9.2 to -1.0, p<0.01; svPPA: Beta=-12.9, 95%CI -19.4 to -6.4, p<0.01). There was also a significant main effect of group in the analysis comparing patient groups with disease duration as covariate (F(3, 38)=3.2, p<0.01, η^2=0.30). Patients with svPPA performed worse than patients with bvFTD (Beta=-7.9, 95%CI -15.2 to -0.6, p=0.03), nfvPPA (Beta=-8.6, 95%CI -16.4 to -0.8, p=0.02) and lvPPA (Beta=-7.5, 95%CI -14.5 to -0.4, p=0.03). After removing one outlier (total TRACE = 2/30, Figure 3) from the group with svPPA, results remained largely similar. The difference between bvFTD and svPPA became non-significant, although a trend remained visible (Beta=-6.2, 95%CI -12.6 – 0.1, p=0.05).

Figure 3. TRACE total scores in each patient group.



Abbreviations: TRACE = Test Relaties Abstracte Concepten; bvFTD = behavioural variant frontotemporal dementia; nfvPPA = non-fluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia.

Classification abilities of the TRACE

The classification abilities of the TRACE can be found in Table 2. The TRACE significantly differentiated between control participants and patients with bvFTD (X^2(1)=24.6, p<0.01),

nfvPPA (X^2(1)=13.5, p<0.01), lvPPA (X^2(1)=24.4, p<0.01) and svPPA (X^2(1)=40.7, p<0.01). In addition, the TRACE had significant discriminative ability between patients with svPPA and bvFTD (X^2(1)=10.5, p<0.01), nfvPPA (X^2(1)=7.2, p<0.01) and lvPPA (X^2(1)=10.3, p<01).

Table 2. Classification abilities of the TRACE.

	Odds ratio	Wald chi square	SE	AUC	95% CI AUC	Cut-off	Sensitivity (%)	Specificity (%)
bvFTD vs. controls	1.54	3.91	0.17	0.83	0.68-0.87	24	75	86
nfvPPA vs. controls	1.39	3.15	0.14	0.76	0.57-0.94	23	50	92
lvPPA vs. controls	1.84	3.75	0.30	0.90	0.78-1.00	22	80	92
svPPA vs. controls	2.11	2.57	0.61	0.96	0.96-1.00	24	100	86
bvFTD vs. nfvPPA	0.99	-0.11	0.08	0.48	0.22-0.74	16	30	88
bvFTD vs. lvPPA	1.01	0.11	0.10	0.54	0.31-0.77	23	80	31
bvFTD vs. svPPA	1.33	2.42	0.16	0.84	0.66-1.00	15	67	94
nfvPPA vs. lvPPA	1.02	0.84	0.10	0.54	0.23-0.84	22	80	60
nfvPPA vs. svPPA	1.24	2.16	0.13	0.83	0.65-1.00	21	89	60
lvPPA vs. svPPA	1.50	2.10	0.30	0.86	0.67-1.00	17	78	100

Abbreviations: bvFTD = behavioural variant frontotemporal dementia; nfvPPA = non fluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; SE = standard error; AUC = area under the curve; CI = confidence interval.

Correlations with other neuropsychological tests

Spearman rank correlation coefficients between TRACE and neuropsychological tests, and TRACE and language tests can be found in respectively Tables 3 and 4. In patients with bvFTD and nfvPPA, the TRACE had a significant positive correlation with the BNT (ρ>0.60), letter fluency (ρ≥0.65) and ERT (ρ≥0.66), with the latter group also having a significant correlation with animal fluency (ρ=0.85). There were no significant correlations between the TRACE and other neuropsychological tests in lvPPA and svPPA, though there was a trend between the TRACE and ERT (ρ≥0.66). Interestingly, in patients with nfvPPA there were no significant correlations between the SAT and other language tests (ρ≤0.26), whereas there were significant positive correlations between the SAT and other language tests (i.e. BNT, verbal fluency measures) in patients with svPPA (ρ≥0.75).

Differences between the TRACE and SAT

There were significant main effects of group (F(1,35)=11.4, p<0.01, η^2=0.39), and test (F(1,35)=7.7, p<0.05, η^2=0.46), but there was no significant interaction effect (F(1,35)=1.6, p=0.2) (Table 1), indicating that all patients performed worse on the TRACE than on the SAT. Additional paired sample t-tests showed that patients with bvFTD (t(3)=-3.4, p=0.02, Cohen's d=1.70), nfvPPA (t(7)=-2.1, p=0.04, Cohen's d=0.74) and lvPPA (t(8)=-3.2, p<0.01, Cohen's

d=1.07) performed significantly worse on the TRACE than on the SAT, but patients with svPPA were equally impaired on the TRACE and SAT (*t*(6)=-1.1, *p*=0.2).

Table 3. Spearman rank correlation coefficients between TRACE and other neuropsychological tests.

Tests	**bvFTD**			**nfvPPA**			**lvPPA**			**svPPA**		
	n	***r***	***p***	**n**	***r***	***p***	**n**	***r***	***p***	**n**	***r***	***p***
BNT 60	14	**0.63**	0.02	10	**0.75**	0.01	10	0.38	0.28	9	0.48	0.19
Animal fluency	14	0.45	0.11	10	**0.85**	0.00	10	0.40	0.25	9	0.56	0.12
TMT A	12	-0.03	0.94	10	-0.30	0.40	10	0.08	0.82	8	-0.23	0.59
TMT B	12	-0.33	0.30	10	-0.60	0.07	10	0.19	0.61	8	-0.20	0.64
Letter fluency	14	**0.65**	0.01	10	**0.67**	0.04	10	0.58	0.08	9	0.45	0.22
ERT total score	14	**0.66**	0.01	8	**0.79**	0.02	5	0.72	0.17	6	0.66	0.16
SAT	4	0.50	0.50	8	0.45	0.26	9	0.14	0.71	7	0.56	0.19
VAT %[1]	13	0.29	0.33	9	0.41	0.27	10	-0.49	0.16	7	0.27	0.60

Abbreviations: bvFTD = behavioural variant frontotemporal dementia; nfvPPA = non fluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; BNT 60 = Boston Naming Test 60 items; TMT = Trail Making Test; ERT = Emotion Recognition Test; SAT = Semantic Association Test; VAT = Visual Association Test. [1] For the VAT, the percentage correct was calculated due to different maximum scores depending on age (12-item for persons ≥65 years old vs. 24-item for persons <65 years old).

Table 4. Spearman rank correlation coefficients between SAT-verbal, TRACE and other language tests.

Tests	**nfvPPA**						**lvPPA**						**svPPA**					
	SAT			TRACE			SAT			TRACE			SAT			TRACE		
	n	*r*	*p*	n	*r*	*p*	n	*r*	*p*	*n*	*r*	p	n	*r*	*p*	n	*r*	*p*
BNT 60	8	0.17	0.70	10	**0.75**	0.01	9	-0.04	0.93	10	0.38	0.28	7	**0.96**	0.00	9	0.48	0.19
Animal fluency	8	0.26	0.54	10	**0.85**	0.00	9	0.54	0.14	10	0.40	0.25	7	**0.84**	0.02	9	0.66	0.12
Letter fluency	8	0.23	0.58	10	**0.67**	0.04	9	0.33	0.40	10	0.58	0.08	7	**0.75**	0.05	9	0.45	0.22

Abbreviations: bvFTD = behavioural variant frontotemporal dementia; nfvPPA = non fluent variant primary progressive aphasia; lvPPA = logopenic variant primary progressive aphasia; svPPA = semantic variant primary progressive aphasia; BNT 60 = Boston Naming Test 60 items; SAT = Semantic Association Test; TRACE = Test Relaties Abstracte Concepten.

Discussion

This study examined the diagnostic utility of the TRACE, a test for abstract semantic concept knowledge, in the FTD spectrum by comparing Dutch-speaking patients with bvFTD, PPA, and control participants. Patients with bvFTD, lvPPA and svPPA, but not nfvPPA, had lower TRACE scores than control participants and patients with svPPA performed worse than the other patient groups. The TRACE discriminated well between patient groups, except nfvPPA, and controls and between svPPA and other patient groups with high sensitivity and specificity. Patients with bvFTD, nfvPPA and lvPPA performed worse on the TRACE than SAT, but patients

with svPPA were equally impaired on the TRACE and SAT. There were strong correlations between the TRACE and language tests (i.e. BNT, verbal fluency) in patients with bvFTD and nfvPPA, whereas in patients with svPPA the SAT had strong correlations with other language tests. These results indicate that the TRACE is sensitive to detect subtle semantic deficits in bvFTD and lvPPA and can differentiate between FTD subtypes in Dutch-speaking patients, and therefore could be a valuable addition to the standard neuropsychological protocol in Dutch memory clinics.

Patients with bvFTD were significantly impaired on the TRACE and 75% of patients and controls were correctly classified. Furthermore, they had more difficulty with identifying abstract than concrete semantic concepts. Recent studies from Cousins and colleagues[1, 25] have indeed shown that patients with bvFTD are impaired on both the comprehension and production of abstract nouns. It is thought that due to the multiple meanings of abstract nouns, there are typically more competing interpretations than for concrete nouns, and abstract nouns therefore rely more on executive functioning to select the correct meaning and process the word efficiently[25]. This is further corroborated by neuroimaging studies that related abstract noun processing and production to atrophy of the left inferior frontal gyrus, an area known to be important in executive processes such as semantic control/selection[53-56]. In line with this, our results showed significant positive correlations with tests for executive functioning (i.e. letter fluency), social cognition (i.e. emotion recognition) and language (i.e. naming), which are cognitive constructs known to deteriorate progressively in bvFTD. Thus, this semantic deficit in bvFTD is likely due to the relative difficulty of abstract words, which is typically not observed with more traditional tests for semantic knowledge that use concrete stimuli such as Pyramids and Palm Trees test and SAT.

Patients with svPPA performed worse on the TRACE than the other patient groups and 100% of cases and controls were correctly classified. This is not a surprising finding given that atrophy in svPPA tends to be most severe in the left anterior and ventral temporal lobes, causing the clinical profile to be typically characterized by a global impairment in verbal and non-verbal semantic memory[1]. Several studies have indeed shown a superior performance on concrete as compared to abstract verbs, nouns, associates and synonyms in patients with svPPA[55, 57]. Yet, numerous other studies have demonstrated a reversal of the concreteness effect and relative sparing of abstract noun comprehension compared to concrete nouns in svPPA[1, 22, 25-29, 58]. Additional analyses from our study demonstrate an equal impairment on the abstract and concrete task in patients with svPPA. Thus, the amplified concreteness effect that is usually seen in patients with bvFTD, lvPPA and nfvPPA is not present in patients with svPPA. Furthermore, we found strong positive correlations in svPPA between the SAT and other language tests that call upon concrete knowledge (i.e. BNT and verbal fluency), but not between the TRACE and these language tests, suggesting that the SAT and TRACE have different underlying representations and measure different aspects of semantic memory

that can be differentially affected. Together, these results imply that the combination of an abstract and concrete semantic test is most useful in differentiating svPPA from other clinical subtypes in a Dutch sample.

Possible factors that have been raised before and might also explain the discrepancy between prior study findings and our findings are differences between study population and more specifically variance in the trajectory, severity and disease stage of study samples[25, 58]. For example, Cousins et al.[25] argue that semantic impairment in svPPA might be initially non-specific (and thus include impairment in both concrete and abstract concepts), but as the disease spreads through the ventrolateral temporal lobe, words with rich visual features (i.e. concrete) are becoming increasingly impaired. Vice versa it might be that early atrophy in the visual association cortex may lead to an initial impairment in the understanding of concrete words, but as the disease progresses towards other brain regions, a multimodal semantic deficit may arise[59, 60]. Thus, individual variation in the extent and precise distribution of atrophy in the temporal lobe might determine how semantic impairment evolves in svPPA patients[9]. Differences in characteristics of the experimental materials such as comprehension vs. production or high vs. low frequency words or the use of verbs/nouns/synonyms and variation in education/occupational experience might also explain, in part, the contradictory findings between studies[55]. In addition, patients with svPPA often have difficulty reading and may exhibit surface dyslexia[2], which may have led to lower TRACE scores than for the other subtypes. Although patients are initially asked to read aloud the words themselves, instructions for test administration include reading the words to the patient if there are visual impairments or reading difficulties. The TRACE starts with two practice items to test whether the patient understood the instructions and check for possible visual or reading difficulties. The effect of possible surface dyslexia is therefore believed to be minimal.

Patients with lvPPA, but not nfvPPA, performed worse than control participants. For patients with lvPPA and controls 80% were correctly classified, but for nfvPPA and controls only 50% were correctly classified. The clinical profile of lvPPA is characterized by impaired lexical retrieval in conversational speech and impaired repetition of sentences, and that of nfvPPA by effortful, nonfluent speech that is associated with highly simplified grammatical structures and a deficit in understanding grammatically complex utterances[8]. Since semantic impairments are not considered as core features in lvPPA and nfvPPA, relatively few studies have focused on investigating semantic knowledge in these subtypes. The few studies that have been carried out showed that semantic knowledge is indeed relatively intact in patients with lvPPA and nfvPPA[61, 62], though there are studies that show atypical presentations of lvPPA with semantic memory deficits [6, 11, 63]. Furthermore, neuroimaging studies have demonstrated that, as the disease progresses, the anterior temporal lobe becomes more involved in lvPPA and thus semantic impairment, similar to svPPA, can be expected[64]. Longitudinal studies confirm that semantic memory degrades over time in this group, though not as severe as in svPPA[61]. The

significant difference between the concrete and abstract task indicates that more traditional semantic tests with concrete stimuli are not sensitive enough to detect semantic impairment in the beginning stages of lvPPA whereas a test for abstract semantic concepts, such as the TRACE, is.

Strengths of the current study are the inclusion of and direct comparison between patients with bvFTD and all three forms of PPA, as they are rare diseases. The relatively small numbers of PPA patients that we included, may have influenced statistical power, but is inherent to the low-base rate of these disorders. Studies on the epidemiology of FTD syndromes have shown a range in prevalence between 10-22/100.000 and incidence between 1.6-4.1/100.000[65, 66]. This underlines the uniqueness of a single-center study including 45 patients with different clinical subtypes, but warrants replication in other cohorts and in different languages. Furthermore, the use of a well-validated cognitive test to investigate abstract semantic knowledge rather than (new) experimental materials and/or designs, allows for the investigation of the utility of the TRACE as a clinical tool. However, as the TRACE is currently only available in Dutch, this may have repercussions for external validity. Another disadvantage of the study was that the neuropsychological assessment was part of the clinical evaluation with which diagnoses were determined. As such, the TRACE may have confounded the diagnostic classification of cases resulting in possible circular reasoning. However, diagnosis did not solely depend on the neuropsychological assessment as, in our multidisciplinary meeting, international consensus criteria for bvFTD[4] and PPA[2] were followed using all available clinical information, including MR imaging of the brain, anamnestic and heteroanamnestic information as well as behavioural and neuropsychiatric questionnaires. Another limitation to consider is the heterogeneity within and between patient groups as it remains difficult to match groups on disease severity and duration. Furthermore, results from the correlational analysis should be interpreted cautiously as they are exploratory in nature rather than hypothesis driven and we did not statistically compare correlation coefficients due to small sample sizes. Directions for future research entail correlating TRACE performance with neuroimaging findings in a larger sample size, investigating decline over time with longitudinal follow-up and translating the test to English and other languages to investigate the psychometric properties of the TRACE in non-Dutch speaking samples enabling replication of our results in other, larger FTD cohorts.

Our study demonstrates the presence of deficits in abstract semantic knowledge by means of the TRACE in Dutch-speaking patients with bvFTD, svPPA and lvPPA, but not in patients with nfvPPA. Patients with svPPA performed worse than the other groups. The TRACE proved a good classifier between patient groups, except nfvPPA, and controls as well as between svPPA and other FTD subtypes. We demonstrate a significant concreteness effect in patients with bvFTD, lvPPA and nfvPPA, whereas this concreteness effect was not present in patients with svPPA–indicating equally impaired performance for both abstract and concrete words in those patients. The TRACE had strong associations with language tests in patients with bvFTD and

nfvPPA, whereas the SAT had strong associations with language tests in patients with svPPA. Together, these results suggest that the degradation of abstract word knowledge is more specific to patients with bvFTD and lvPPA whereas a test for concrete semantic knowledge is more sensitive to identify svPPA. In conclusion, the TRACE is able to detect subtle semantic deficits, differentiate between FTD subtypes in Dutch-speaking patients and provides, in combination with tests for concrete semantic concepts, new relevant information that can significantly help in the differential diagnosis between FTD subtypes.

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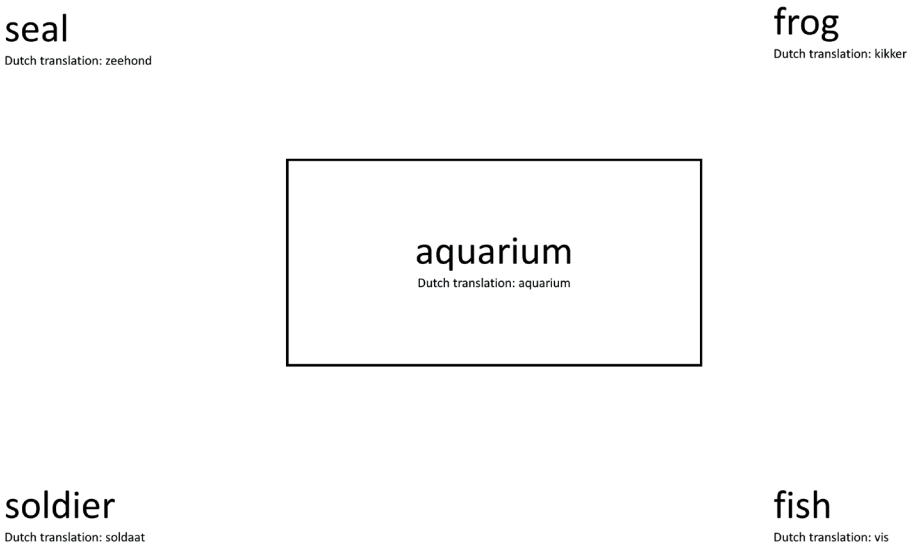
Supplementary file 1: description of the Semantic Association Test–Verbal

The Semantic Association Test (SAT) is a Dutch neuropsychological test for verbal semantic processing analogous the Pyramids and Palm Trees Test[1]. The test consists of 30 items that are presented visually on successive cards showing five Dutch words: one in the center (target) and four (one correct answer and three distractors) in each corner. An example item, including English translations, can be seen in Supplementary Figure 1. Two distractors on each card are semantically related to the correct answer, while one distractor is semantically unrelated to both the target and the correct answer. Participants have to choose the item that relates best to the target word based on their meaning. There is a thematic relation between the target word and responses, which means that the responses are not from the same semantic category as the target word and that they can be used in a syntagmatic association (i.e. a linear relationship between elements that are able to precede or follow each other in a sentence) and a paradigmatic relationship between the correct response and the two semantic distractors (a vertical relation between elements that can be substituted for each other)[2, 3]. Half of the target items concern living objects, whereas the other half are non-living objects. Performance on the SAT is reflected by the number of correct items, with a maximum of 30. The manual of the SAT[4] describes several factors that were considered in selecting the items of the SAT. Culture-specific items and objects that were too similar in shape were avoided. The first set of items (n=60) were rated by twenty healthy individuals. The possible responses per item were grouped according to semantic association to the target word. Some items were adjusted when there was a large variation between participants in how the responses were grouped. This procedure was repeated three times with different research participants which resulted in 30 items with a high level of agreement. The first version of the SAT was tested in Dutch-speaking healthy individuals (n=56) and patients with aphasia (n=7) after which several items were again adjusted. Psychometric properties of the SAT were established by testing Dutch-speaking healthy individuals (n=96), patients with aphasia due to injury to the left-hemisphere (n=78), patients without aphasia with injury to the right-hemisphere (n=10), and patients with Alzheimer's Disease (AD) (n=52). There was a high internal consistency for patients with aphasia and AD (respectively Cronbach's alpha of 0.84 and 0.85). There was a significant correlation between the SAT and Token Test ($p<0.05$), but not between the SAT and subtests of the Dutch version of the Akense Afasie Test (AAT)[5]. Patients with injury to the left-hemisphere and aphasia performed significantly worse than patients with right-sided hemisphere injury and control participants ($p<0.01$). Males performed significantly better on the SAT than females, but there was no effect of age or education level on performance in both patients with aphasia and AD. Criterion validity was determined by ROC analysis which showed a 79% sensitivity and 94% specificity with a cut-off of 26 in patients with aphasia and 54% sensitivity and 88% specificity with a cut-off of 23 in patients with AD[4].

Supplementary Figure 1. Example item from the SAT with Dutch translations.



Supplementary file 2: Tables

Supplementary Table 1. Cumulative frequency of the TRACE in control participants.

Score	N	Cumulative frequency (%)
20	1	1.69
21	0	1.69
22	4	8.47
23	0	8.47
24	3	13.56
25	4	20.34
26	6	30.51
27	12	50.85
28	11	69.45
29	13	91.53
30	5	100

Abbreviation: TRACE = Test Relaties Abstracte Concepten.

Supplementary Table 2. Percentile TRACE scores in control participants.

Percentile	TRACE
5	22
10	24
20	25
30	26
40	27
50	27
60	28
70	29
80	29
90	29

Abbreviation: TRACE = Test Relaties Abstracte Concepten.

Supplementary Table 3. Mean and standard deviation of the TRACE in control participants stratified by age group and sex.

	all			females			males		
Age group	n	mean	SD	n	mean	SD	n	mean	SD
30.0-39.9	5	27.8	2.28	2	26	2.83	3	29	1
40.0-49.9	18	27.56	1.42	7	27	2.39	11	27.91	1.45
50.0-59.9	17	26.88	2.39	11	26.55	2.62	6	27.5	1.98
60.0-69.9	16	26.81	2.97	10	26.9	2.69	6	26.67	3.67
>70	3	24.67	0.58	1	24	-	2	25	0

Abbreviation: TRACE = Test Relaties Abstracte Concepten; SD = standard deviation.

Supplementary Table 4. Mean and standard deviation of the TRACE in control participants stratified by age group and educational level.

	Education level								
	low			medium			high		
Age group	n	mean	SD	n	mean	SD	n	mean	SD
<40	0	-	-	2	27	4.24	3	28.33	0.58
40-60	0	-	-	17	26.47	1.7	17	27.94	2.01
>60	3	23	3.61	9	26.78	2.05	7	27.57	2.57

Education level was according to the Dutch educational system categorized into levels from 1 = less than 6 years of primary education to 7 = academic schooling (ref); low = <4; medium = 4><6; high = >6. Abbreviation: TRACE = Test Relaties Abstracte Concepten; SD = standard deviation.

CHAPTER 3.2
A cognitive composite for genetic frontotemporal dementia: GENFI-Cog

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Abstract

Background: Clinical endpoints for upcoming therapeutic trials in frontotemporal dementia (FTD) are increasingly urgent. Cognitive composite scores are often used as endpoints but are lacking in genetic FTD. We aimed to create cognitive composite scores for genetic frontotemporal dementia (FTD) as well as recommendations for recruitment and duration in clinical trial design.

Methods: A standardized neuropsychological test battery covering six cognitive domains was completed by 69 *C9orf72*, 41 *GRN*, and 28 *MAPT* mutation carriers with CDR® plus NACC-FTLD≥0.5 and 275 controls. Logistic regression was used to identify the combination of tests that distinguished best between each mutation carrier group and controls. The composite scores were calculated from the weighted averages of test scores in the models based on the regression coefficients. Sample size estimates were calculated for individual cognitive tests and composites in a theoretical trial aimed at preventing progression from a prodromal stage (CDR® plus NACC-FTLD 0.5) to a fully symptomatic stage (CDR® plus NACC-FTLD ≥1). Time-to-event analysis was performed to determine how quickly mutation carriers progressed from CDR® plus NACC-FTLD=0.5 to ≥1 (and therefore how long a trial would need to be).

Results: Results from the logistic regression analyses resulted in different composite scores for each mutation carrier group (i.e. *C9orf72, GRN* and *MAPT*). The estimated sample size to detect a treatment effect was lower for composite scores than for most individual tests. A Kaplan-Meier curve showed that after three years ~50% of individuals had converted from CDR® plus NACC-FTLD 0.5 to ≥1, which means that the estimated effect size needs to be halved in sample size calculations as only half of the mutation carriers would be expected to progress from CDR® plus NACC FTLD 0.5 to ≥1 without treatment over that time period.

Discussion: We created gene-specific cognitive composite scores for *C9orf72, GRN* and *MAPT* mutation carriers, which resulted in substantially lower estimated sample sizes to detect a treatment effect than the individual cognitive tests. The GENFI-Cog composites have potential as cognitive endpoints for upcoming clinical trials. The results from this study provide recommendations for estimating sample size and trial duration.

Background

Frontotemporal dementia (FTD) encompasses a heterogeneous group of early onset neurodegenerative disorders caused by prominent frontal and/or temporal lobe degeneration with a wide range of overlapping clinical features[1]. The two main phenotypes are behavioural variant FTD (bvFTD), with prominent behavioural changes and executive dysfunction[2], and primary progressive aphasia (PPA), with impairment in language comprehension and/or production[3]. FTD is a highly heritable disease, with 20-30% of cases having an autosomal dominant pattern of inheritance[4]. The most common causes of genetic FTD are mutations in the microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), and chromosome 9 open reading frame 72 (*C9orf72*) genes[4].

Clinical trials testing disease-modifying treatments for FTD are now underway and clinical endpoints to monitor treatment response are therefore urgently needed. It is believed that interventions may have the most profound effect if initiated in the earliest stages of the disease, however, a major challenge facing these clinical trials is the lack of outcome measures that are sensitive enough to track the effect of treatment in the early stages of the disease[5-7].

Traditional outcomes such as progression to clinical diagnosis or cognitive measures developed for other forms of dementia such as Alzheimer's disease (AD) might not be well-suited to serve as endpoints for early-stage FTD treatment trials because of the large sample size and long trial duration that would be required to measure possible treatment effects or due to the psychometric properties of the tests themselves[8-10]. Sensitive outcome measures in patients with clinically diagnosed AD, such as the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-Cog), might not be sensitive to decline in patients with FTD[10, 11]. Multiple genetic FTD cohort studies have investigated a wide range of cognitive instruments and found gene-specific cognitive impairment and/or decline in language, executive function, social cognition, attention/processing speed and memory, in symptomatic and presymptomatic stages[12-27]. However, due to the subtlety of cognitive decline in the early stages of the disease, using individual tests as outcome measures might not be sensitive enough to detect a treatment effect. Furthermore, an individual cognitive test is limited to measuring only one specific symptom and due to the heterogeneity of clinical features between FTD patients, tests from multiple cognitive domains would need to be included. A selection of the most sensitive tests for each genetic group would enable shortening of the neuropsychological test battery thereby significantly minimizing time and other resource costs compared to using a broad range of individual cognitive tests[28].

Composite scores are often used in clinical trials to reduce the number of variables used as outcome measures[8]. A composite score is any measure which combines the results of multiple cognitive and clinical assessments into a single summary score[29]. As a result, it provides a

measure of multiple domains but can serve as a single primary endpoint in clinical trials[8]. Such composites have been developed for several neurodegenerative disorders, such as AD (e.g. the ADAS-Cog (11)), Parkinson's disease (PD) (e.g. the Unified Parkinson's Disease Rating Scale (UPDRS[30])), and Huntington's disease (HD) (e.g. the Unified Huntington's Disease Rating Scale (UHDRS[29])), but are, as of yet, lacking in FTD.

Therefore, the aim of this study was to create gene-specific cognitive composite scores for *MAPT*, *GRN* and *C9orf72* mutation carriers in the early symptomatic stage by empirically determining the combination of neuropsychological tests most sensitive to differentiate mutation carriers from non-carriers. Data was collected within the Genetic FTD Initiative (GENFI), an international genetic FTD cohort study aimed at developing novel markers of disease onset and progression[14]. To evaluate their performance we compared sample size requirements between each of the proposed composites and individual cognitive tests for a theoretical trial aimed at preventing progression from a prodromal stage (CDR® plus NACC-FTLD[31]=0.5) to a fully symptomatic stage (CDR® plus NACC-FTLD≥1). Lastly, we performed time-to-event analyses to determine how many people progressed from a CDR® plus NACC FTLD 0.5 to ≥1, to provide recommendations on the duration of such clinical trials.

Methods

Participants

Data was included from the fifth GENFI data freeze in which participants from confirmed genetic FTD families were recruited between 30th January 2012 and 31th May 2019 in 24 centres across Europe and Canada. A total of 69 *C9orf72*, 41 *GRN* and 28 *MAPT* mutation carriers with a CDR® plus NACC FTLD≥0.5 and 275 mutation negative controls (i.e. family members who tested negative for the mutation) were included in this study. Of the mutation carrier group, 41 *C9orf72*, 17 *GRN* and 16 *MAPT* mutation carriers fulfilled diagnostic criteria for bvFTD[2] (*C9orf72*=36, *GRN*=11, *MAPT*=16), PPA[3] (*GRN*=6) or FTD with amyotrophic lateral sclerosis (FTD-ALS)[32](*C9orf72*=5). Participant characteristics are summarized in Table 1 and number of participants included in each of the statistical analysis steps can be found in Supplementary Figure 1.

Procedure

All participants completed a comprehensive neuropsychological test battery covering six cognitive domains: language (modified Camel and Cactus Test[33]; Boston Naming Test (BNT, short 30 item version)[34]; category fluency (animals)[35]), attention/processing speed and executive function (WMS-R Digit span[34]; Trail Making Test (TMT)[36]; WAIS-R Digit Symbol test[34]; D-KEFS Color-Word Interference Test (CWIT)[37]; phonemic fluency[35]); verbal and visuospatial memory (Free and Cued Selective Reminding Test (FCSRT)[20]; Benson Figure recall), social

cognition (Facial Emotion Recognition test[38]), and visuoconstruction (Benson Figure copy). The Mini-Mental State Examination (MMSE[39]) was administered to measure global cognitive functioning and clinical status was determined by means of a structured clinical interview, including the CDR® plus NACC FTLD[31].

Statistical methods

Statistical analyses were performed using Stata version 14 and R version 3.6.2. We compared continuous demographic data between mutation carrier groups with Kruskal-Wallis and post-hoc Mann-Whitney tests. A chi-square test was used to compare sex between groups.

All neuropsychological data were converted to Z-scores corrected for age, education and sex compared to the control group collected within GENFI (i.e. mutation negative participants). The FCSRT and letter fluency scores were also corrected for language as the test stimuli differed by language across the different GENFI sites. The control data available in each language can be found in Supplementary Table 1. Z-scores for tests with reaction times (i.e. TMT and D-KEFS CWIT) were inversed so that lower Z scores indicated worse performance on all tests. A detailed description of how the corrected Z-scores were calculated can be found in Supplementary file 2.

Creating the composite scores

Least absolute shrinkage and selection operator (LASSO)[40] logistic regression models with 10-fold cross validation were used to identify the combination of neuropsychological tests that discriminated best between each mutation carrier group and controls. Participants with missing data were excluded from this analysis. A separate model was fitted for each genetic group with carrier status as the outcome and the neuropsychological tests as the predictors. A detailed description of the statistical methods can be found in Supplementary file 2. The glmnet package in R was used to fit the LASSO models and carry out the cross-validation.

From the resulting model two different cognitive composite scores were calculated: (1) an average of the scores for all cognitive tests that were selected in the model; and (2) a weighted average of the scores for all cognitive tests that were selected in the model, using the regression coefficients to determine the weights.

Sample size calculation

For each outcome the sample size was calculated for a hypothetical two arm study with 1:1 randomization to placebo versus active drug with 80% power to detect a treatment effect at a 5% significance level[41]. The focus of future studies is likely to be on treating people with very early symptomatic disease and so we focused on calculating sample sizes for a trial of prodromal mutation carriers (i.e. CDR® plus NACC FTLD=0.5) where the therapeutic drug had an effect on the progression to being fully symptomatic (i.e. CDR® plus NACC FTLD=1).

We therefore calculated sample sizes for a 10%, 20% and 40% effect size where a 100% treatment effect would be the difference in mean between the CDR® plus NACC FTLD 0.5 and 1 groups. Choosing the effect size in this way assumes that the hypothetical treatment will prevent a given proportion of the decline in cognitive scores seen between these two groups. For example, a 20% treatment effect assumes that the untreated group will experience the change seen between CDR® plus NACC FTLD 0.5 and 1 groups but the treated group will only experience 80% of this change (i.e. 20% less). See Supplementary files 1 and 2 for more details on the sample size calculations and the parameters used (Supplementary Table 2)[41].

Time-to-event analysis

To provide recommendations on the timeline for the hypothesized trial we present Kaplan-Meier curves showing the cumulative proportion of participants who progressed from a CDR® plus NACC FTLD 0.5 to ≥1 within the GENFI cohort over time. In this analysis the censoring date was the date of conversion or the date of last follow-up. As this is an ongoing prospective cohort study, not all mutation carriers completed all study visits which resulted in missing data. There were 62 mutation carriers (19 *C9orf72*, 27 *GRN* and 16 *MAPT*) that had a CDR® plus NACC FTLD of 0.5 and one or multiple follow-up visits and were included in the time to event analysis (Supplementary Table 4 and Figure 1). A log rank test was performed to compare the rate of progression between genetic groups.

Results

Demographics

Participant characteristics for all mutation carriers are summarized in Table 1. Overall, the number of males to females differed between groups (p=0.020). *C9orf72*, *GRN* and *MAPT* mutation carriers were older, had lower MMSE and higher CDR® plus NACC FTLD sum of boxes scores than controls (all p<0.010). In addition, *C9orf72* mutation carriers had higher CDR® plus NACC FTLD sum of boxes scores than *GRN* mutation carriers (p=0.007). There were no differences between groups in years of education (p=0.290). The characteristics of participants when individually stratified by CDR® plus NACC FTLD global score (i.e. in 0.5, 1, 2 and 3 groups) can be found in Supplementary Table 3.

Logistic regression analyses

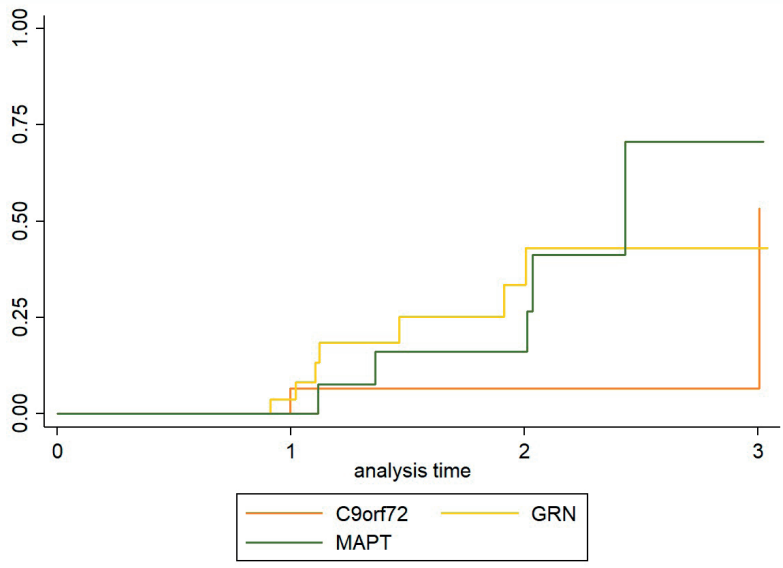
Results from the logistic regression model can be seen in Table 2. A combination of category fluency, D-KEFS CWIT – color, word and ink naming, TMT – part B, the Benson Figure copy, FCSRT free recall and the Facial Emotion Recognition Test was most sensitive to discriminate *C9orf72* repeat expansion carriers from controls. For *GRN* mutation carriers a combination of the Camel and Cactus Test, TMT – part B, D-KEFS CWIT – ink naming, Benson Figure recall, FCSRT total and delayed free recall and the Facial Emotion Recognition Test was most

Table 1. Participant characteristics and neuropsychological test results.

	C9orf72	*GRN*	*MAPT*	Controls
Number of participants	69	41	28	275
Sex f:m	30:39	20:21	14:14	160:115
Age	55 (12.0)	53.0 (11.4)	51.1 (12.6)	45.8 (12.7)
Education	13.7 (3.1)	14.0 (3.5)	14.3 (3.4)	14.6 (3.4)
MMSE	27.1 (3.2)	26.6 (7.0)	27.5 (3.0)	29.3 (2.1)
CDR® plus NACC FTLD sob	5.9 (5.5)	3.4 (4.8)	4.8 (5.0)	0.2 (0.6)
Language				
Camel and Cactus Test	-1.81 (2.81)	-0.57 (1.36)	-2.10 (3.08)	-
Boston Naming Test	-1.77 (3.32)	-0.68 (1.62)	-2.63 (3.16)	-
Category fluency	-1.20 (1.05)	-0.54 (1.04)	-0.84 (1.14)	-
Attention and mental processing speed				
Digit span forward	-0.39 (1.19)	-0.08 (1.26)	0.13 (1.23)	-
Trail Making Test–part A	-1.37 (2.17)	-0.69 (1.63)	-0.72 (1.54)	-
Digit Symbol	-1.18 (1.30)	-0.62 (1.23)	-0.67 (1.31)	-
D-KEFS CWIT–color naming	-2.85 (3.58)	-0.52 (1.85)	-1.30 (2.17)	-
D-KEFS CWIT–word naming	-1.86 (3.11)	-0.02 (1.46)	-0.54 (1.47)	-
Executive function				
Digit span backward	-0.53 (1.23)	-0.49 (1.23)	-0.19 (0.98)	-
Trail Making Test–part B	-2.44 (2.95)	-1.81 (3.06)	-1.37 (2.58)	-
D-KEFS CWIT–ink naming	-3.46 (3.91)	-1.13 (2.21)	-1.16 (2.54)	-
Phonemic fluency	-1.18 (1.18)	-0.08 (1.33)	-0.64 (1.28)	-
Visuoconstruction				
Benson Figure copy	-0.90 (1.90)	-0.06 (1.16)	-0.46 (1.39)	-
Memory				
Benson Figure recall	-0.72 (1.57)	-0.75 (1.46)	-1.27 (1.91)	-
FCSRT free recall	-1.68 (1.36)	-0.72 (1.49)	-1.71 (1.80)	-
FCSRT total recall	-2.20 (3.56)	-1.42 (3.05)	-2.86 (3.62)	-
FCSRT delayed free recall	-1.59 (1.59)	-0.97 (1.58)	-1.72 (2.04)	-
FCSRT delayed total recall	-2.10 (3.81)	-1.13 (3.09)	-2.82 (4.02)	-
Social cognition				
Facial Emotion Recognition Test	-1.67 (1.87)	-1.00 (1.47)	-1.04 (1.59)	-

Values are mean Z-scores (raw score – mean score controls/standard deviation of controls) corrected for age, years of education and sex, with standard deviation in parentheses unless otherwise specified. For the FCSRT and letter fluency an additional correction was made for language as stimuli differed between languages. Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; MMSE = Mini-Mental State Examination; CDR® plus NACC FTLD sob= Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration sum of boxes; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test.

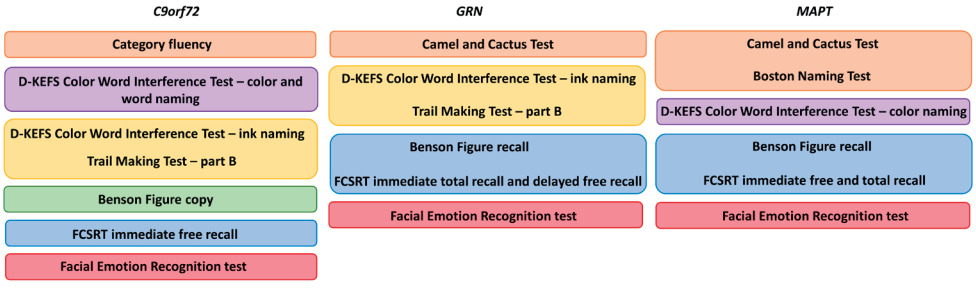
Figure 1. Kaplan-Meier estimates of mutation carriers that converted from CDR® plus NACC FTLD 0.5 to ≥1.



Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration.

sensitive. In *MAPT* mutation carriers, a combination of the Camel and Cactus Test, BNT, D-KEFS CWIT – color naming, Benson Figure recall, FCSRT free, total and delayed free recall, and the Facial Emotion Recognition Test was most sensitive to differentiate from controls. For each mutation carrier group, the average and weighted composite scores were calculated, including the tests with a negative coefficient in Table 2. A summary of the included tests that were included in each GENFI-Cog per gene group can be seen in Figure 2.

Figure 2. Overview of the neuropsychological tests included in the GENFI-Cog scores per cognitive domain.



Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau

Table 2. Regression coefficients and corresponding weights.

	C9orf72		*GRN*		*MAPT*	
Language						
	Coef.	**Weight**	**Coef.**	**Weight**	**Coef.**	**Weight**
Camel and Cactus Test			-0.004	0.003	-0.04	0.04
Boston Naming Test					-0.39	0.40
Category fluency	-0.13	0.09				
Attention and mental processing speed						
Digit span forward						
Trail Making Test–part A						
Digit Symbol						
D-KEFS CWIT–color naming	-0.06	0.04			-0.09	0.09
D-KEFS CWIT–word naming	-0.04	0.03	0.09*			
Executive function						
Digit span backward						
Trail Making Test–part B	-0.07	0.05	-0.28	0.23		
D-KEFS CWIT–ink naming	-0.29	0.20	-0.24	0.20		
Phonemic fluency			0.24*			
Visuoconstruction						
Benson Figure copy	-0.09	0.06				
Memory						
Benson Figure recall			-0.06	0.05	-0.01	0.01
FCSRT free recall	-0.50	0.35			-0.06	0.06
FCSRT total recall			-0.05	0.04	-0.30	0.31
FCSRT delayed free recall			-0.16	0.13	-0.01	0.01
FCSRT delayed total recall						
Social cognition						
Facial Emotion Recognition Test	-0.26	0.18	-0.42	0.35	-0.08	0.08

Data are presented as coefficients and weights. Coefficient gives the change in log odds of being a mutation carrier for each Z score increase in the score on the cognitive test. Weight gives the weighting used when calculating the weighted cognitive composite score. Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test. *Positive coefficients indicate better performance in mutation carriers compared to controls and were not included in the composite score.

Sample size calculation

Sample size estimates can be observed in Table 3. In *C9orf72* repeat expansion carriers, both the average and weighted composite score resulted in lower sample sizes than most individual cognitive tests. The only test that resulted in a lower sample size than the composite score was the D-KEFS CWIT – ink naming, with the Digit Symbol test also resulting in a lower sample size than the average but not the weighted composite score. In *GRN* mutation carriers, again both composite scores resulted in lower sample sizes than for most individual cognitive tests except the TMT – part B. The TMT – part A also resulted in a lower sample size than

the weighted composite, but not the average composite. In addition, the D-KEFS CWIT – ink naming resulted in a sample size of less than 100, albeit not lower than the composites. In *MAPT* mutation carriers, both composites resulted in estimated samples sizes smaller than 130 with an effect size of 0.1, but the TMT – part A, Digit Symbol test, D-KEFS CWIT – color and ink naming resulted in even lower sample sizes (n<100). In *C9orf72* and *MAPT* mutation carriers, the weighted composite score resulted in a lower estimated sample size than the average composite, whereas in *GRN* mutation carriers the average composite resulted in a lower sample size. For *GRN* (all n<60) and *MAPT* (all n<125) mutation carriers lower sample sizes would be necessary to detect a treatment effect than for *C9orf72* repeat expansion carriers (all n≤306).

Time-to-event analysis

Kaplan-Meier curves can be seen in Figure 1 and details on the sample included in the time-to-event analysis are reported in Supplementary Table 4. For *C9orf72* repeat expansion carriers, the probability of converting to a CDR® plus NACC FTLD of ≥1 increases from 6% after two years (SE=0.06, 95% CI 0.01 – 0.39) to 53% after three years (SE=0.33, 95% CI 0.12 – 0.99). In *GRN* mutation carriers, the probability of converting to a CDR® plus NACC FTLD of ≥1 increased from 4% after one year (SE=0.04, 95% CI 0.01 – 0.24) to 43% after three years (SE=0.14, 95% CI 0.22 – 0.72). In *MAPT* mutation carriers, the probability of converting to a global score of ≥1 increased from 10% after one year (SE=0.10, 95% CI 0.01 – 0.49) to 42% during the second year (SE=0.20, 95% CI 0.14 – 0.85). The Kaplan-Meier curve for *MAPT* mutation increased to 100% after three years in Figure 1 because only one mutation carrier had follow-up up to this point and this individual progressed to a CDR® plus NACC FTLD of ≥1. There was no significant difference between the progression rates of different genetic groups ($X^2(2) = 1.18$, $p = 0.55$). In the total group of mutation carriers, the probability of converting to a CDR® plus NACC FTLD of ≥1 was 21% after two years (SE=0.03, 95% CI 0.11 – 0.40) and 52% after three years (SE=0.16, 95% CI 0.26 – 0.83). This means that for a three year trial where drug treatment is assumed to have 20% effect (i.e. only 80% of the treated group will experience the change seen between CDR® plus NACC FTLD 0.5 and 1 groups) the sample size corresponding to a 10% effect in Table 3 needs to be included in order to demonstrate a treatment effect, because only ~50% of mutation carriers would be expected to progress from CDR® plus NACC FTLD 0.5 to 1 without treatment (i.e. effect size needs to be divided by 2).

Discussion

We have empirically developed gene-specific cognitive composite scores in *MAPT*, *GRN* and *C9orf72* mutation carriers (GENFI-Cog) and demonstrated that that they provide feasible sample sizes for clinical trials to evaluate the effect of treatment on clinical progression from the prodromal to the fully symptomatic stage. Time-to-event analyses revealed that

Table 3. Sample size per arm for a hypothetical clinical trial using different cognitive outcome measures.

Outcome measures	*C9orf72*			*GRN*			*MAPT*		
	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%	ES 10%	ES 20%	ES 40%
Cognitive composite scores									
Average composite	306	76	19	27	7	2	124	31	8
Weighted composite	214	53	13	53	13	3	90	23	6
Language									
Camel and Cactus Test	4946	1237	309	292	73	18	357	89	22
Boston Naming Test	1109	277	69	213	53	13	223	56	14
Category fluency	1584	396	99	781	195	49	400	100	25
Attention and mental processing speed									
Digit span forward	130210	32553	8138	2677	669	167	17773	4443	1111
Trail Making Test–part A	2272	568	142	45	11	3	69	17	4
Digit Symbol	254	64	16	925	231	58	80	20	5
D-KEFS CWIT–color naming	866	216	54	502	126	31	66	17	4
D-KEFS CWIT–word naming	19224	4806	1202	3310	828	207	150	37	9
Executive functioning									
Digit span backward	1724	431	108	840	210	52	26218	6555	1639
Trail Making Test–part B	1275	319	80	25	6	2	81	20	5
D-KEFS CWIT–ink naming	61	15	4	70	17	4	26	7	2
Phonemic fluency	558	139	35	2229	557	139	161	40	10
Visuoconstruction									
Benson Figure copy	5911	1478	369	2119	530	132	6282036	1570509	392627
Memory									
Benson Figure recall	1044	261	65	657	164	41	7611	1903	476
FCSRT free recall	1302	326	81	294	74	18	521	130	33
FCSRT total recall	1020	255	64	477	119	30	524	131	33
FCSRT delayed free recall	606	152	38	767	192	48	261	65	16
FCSRT delayed total recall	358	89	22	193	48	12	681	170	43
Social cognition									
Facial Emotion Recognition Test	7570	1892	473	7805	1951	488	147	37	9

Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; ES = effect size as a proportion of the difference between the outcome in the CDR® plus NACC-FTLD 0.5 group and the outcome in the CDR® plus NACC-FTLD 1 group; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test. The sample size per arm was estimated as: n=(1-ρ^2)(2σ^2)/δ^2 f(α,β). Where, ρ is the correlation between baseline and follow-up measures of the outcome, σ is the standard deviation of the outcome in the CDR® plus NACC-FTLD 0.5 group, δ is the treatment effect (effect size multiplied by difference in mean between CDR® plus NACC-FTLD 0.5 and 1 group), α is the significance level (0.05), 1- β is the power to detect a treatment effect (80%).

roughly 50% of the patients with a CDR® plus NACC FTLD of 0.5 progress to 1 or higher after a period of three years. The results from this study show that GENFI-Cog has potential as a cognitive endpoint in upcoming clinical trials and provide important guidelines on sample size recruitment and clinical trial duration.

The GENFI-Cog composites can be regarded as attractive clinical outcome measures because they produce substantially lower sample size estimates than most individual neuropsychological tests. Depending on the effect size (40% to 10%), sample size estimates ranged between 13-214 for *C9orf72*, 3-53 for *GRN* and 6-90 for *MAPT* per study arm for the weighted GENFI-Cog. A practical problem in trial design for FTD spectrum disorders is recruiting enough patients to test candidate therapeutics as FTD is much less common than AD, with an estimated prevalence of 15/100,000 and approximately 10-20% of cases being caused by mutations in *C9orf72, GRN* and *MAPT* genes[4, 7, 42]. It is therefore unlikely that a trial would be able to include many hundreds of patients per study arm, which our results showed would be necessary for most individual neuropsychological tests. There were some individual neuropsychological tests that required reasonable sample sizes similar to that of GENFI-Cog, e.g. TMT and D-KEFS CWIT. These tests are typically included in clinical trials such as the current AL001 study of *GRN*-related FTD[7]. Yet, due to the heterogeneity in cognitive symptoms between patients even with the same genetic mutation, individually examining each cognitive test might not provide a sensitive and clinically meaningful primary outcome measure. Using GENFI-Cog will allow a single cognitive outcome to be used when analyzing treatment effect, although validation in other large cohorts is warranted.

The CDR® plus NACC FTLD is currently often used as an inclusion criterion for clinical trials as well as for tracking disease progression. Results showed that roughly 50% of the patients with a CDR® plus NACC FTLD 0.5 progress to 1 or higher after a period of three years. This indicates that for trials with duration of three years around 50% of patients with CDR® plus NACC FTLD of 0.5 on entry to the trial would be expected to progress to CDR® plus NACC FTLD of 1 in the absence of effective disease modifying treatment. This means that if a treatment is expected to have a 20% effect the sample size corresponding to a 10% effect needs to be included per study arm to be able to demonstrate a treatment effect, because only half of the mutation carriers would be expected to progress from CDR® plus NACC FTLD 0.5 to 1 without treatment. This is important to consider when planning trial duration and recruitment with the currently available clinical measures.

The optimal gene-specific cognitive composite score incorporated tests from different cognitive domains. For *GRN* mutation carriers, tests for executive function and social cognition contributed the most to the composite score, with the addition of tests for memory and language. In *MAPT* mutation carriers, there was a strong focus on semantic and episodic memory tests in the composite score with the addition of tests for attention and mental

processing speed. A combination of tests from all cognitive domains was most sensitive in *C9orf72* mutation carriers, with the strongest contribution from tests within the domains of executive function, social cognition and memory. These results complement recent studies showing cognitive decline in the early stages of FTD with widespread cognitive impairment covering multiple domains in *C9orf72*[22, 43], dysexecutive functioning as the key feature in *GRN*[13, 22] and a specific impairment in episodic and semantic memory in *MAPT*-associated FTD[13, 20, 22]. Impairment of social cognition appears to be a key feature in all three genetic groups[38], which was probably due to the high number of bvFTD cases in the sample. Neuroimaging studies have indeed shown that the neurodegenerative process in *C9orf72* mutation carriers typically is reflected by widespread degeneration in frontal, temporal as well as cerebellar and subcortical structures[43], whereas focal atrophy of the anteromedial temporal lobe, an area important for memory and semantic functioning, is often seen in *MAPT*-associated FTD[44]. In *GRN* mutation carriers the typical pattern of degeneration includes the inferior frontal regions as well as the cingulate cortex, areas known to be critical in executive function[44]. Thus, although the GENFI-Cog was empirically derived, the selected tests are clinically meaningful and in line with a theoretically driven approach where the composite would be constructed a priori from cognitive tests that are known to decline in the early stages of each genetic group.

This is to our knowledge the first study that has created cognitive composites for genetic forms of FTD by selecting the most sensitive combinations of cognitive variables based on systematic comparisons with controls. A major strength of this study is the use of a large cohort of genetic FTD mutation carriers allowing gene-specific analyses, but also the use of a matched control group of mutation negative family members. Another strength is the use of LASSO with cross-validation to avoid overfitting bias to ensure that results have generalizability[41].

Limitations

There are some limitations to the present study however. Results from the logistic regression analysis revealed two neuropsychological tests in *GRN* mutation carriers with a positive coefficient, indicating better performance compared to controls, and were excluded from the composite scores. Development of GENFI-Cog was constrained by the neuropsychological test battery that is used in the GENFI cohort[14], which made validation in an independent sample not possible and limits the generalizability of the findings. Validation in other cohorts (such as ALLFTD[45] or DINAD) is therefore recommended. Although the LASSO model with 10-fold cross validation included an internal cross-validation step to select the penalization term for selection of the cognitive tests, findings were not externally validated in an independent sample thereby limiting the generalizability of GENFI-Cog. Future collaborations within the FTD Prevention Initiative (FPI) could be a starting point to cross-validate our findings. The sample size estimates serve as a guide on the sensitivity and power of GENFI-Cog compared to

individual cognitive tests and should be interpreted with caution as they were calculated from the cross-sectional difference between a small number of patients with CDR® plus NACC FTLD 0.5 and 1, assuming that the difference between these groups is representative of the change over time that would be seen in longitudinal scores in a clinical trial as patients progress from a score of 0.5 to 1 i.e. prodromal to fully symptomatic. Future research using longitudinal data and larger sample sizes is necessary to examine the validity of this assumption and to examine if the cognitive composites presented in the current study are similar to those derived using longitudinal change in scores. Importantly, it is essential for future clinical trials of FTD to also include other biomarkers such as neuroimaging, neurofilament light chain or other fluid protein levels as endpoints. As such, it would be interesting to include such biomarkers in addition to GENFI-Cog within a future longitudinal multimodal analysis. Lastly, as GENFI is a prospective cohort study with ongoing recruitment not all participants completed the same number of visits contributing to low sample sizes at later visits in the time-to-event analysis. The time-to-event analysis was performed to provide insight on the possible duration required for a clinical trial, but validation with larger sample sizes where all participants have completed the same number of visits is warranted.

Conclusions

In summary, we examined cognitive data from the GENFI cohort and conducted a search for the combination of cognitive assessments most sensitive to differentiate *MAPT*, *GRN* and *C9orf72* mutation carriers from non-carriers. As a result, we created three gene-specific cognitive composite scores, GENFI-Cog, that were sensitive to track progression on the clinical progression of the CDR® plus NACC FTLD 0.5 to 1 stage as it resulted in smaller sample sizes than most individual neuropsychological tests. To conclude, GENFI-Cog has the potential to be a primary cognitive outcome measure in upcoming clinical trials for *C9orf72, GRN* and *MAPT* mutation carriers.

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Supplementary file 1: Tables and Figures

Supplementary Table 1. Number of control data available in each language per cognitive test.

	English	Dutch	Spanish	French	Italian	Swedish	Portugese	German
Camel and Cactus Test	78	62	38	39	39	15	14	8
Boston Naming Test	78	79	38	39	38	15	14	7
Category fluency	78	79	38	39	38	14	14	8
Digit span forward	78	80	38	39	40	15	14	8
Trail Making Test–part A	77	79	38	39	39	15	14	8
Digit Symbol	78	65	38	39	38	15	14	8
D-KEFS CWIT–color naming	78	77	38	39	37	15	14	8
D-KEFS CWIT–word naming	78	77	38	39	37	15	14	8
Digit span backward	78	80	38	39	40	15	14	8
Trail Making Test–part B	77	79	38	37	38	15	14	8
D-KEFS CWIT–ink naming	78	77	38	39	37	15	14	8
Phonemic fluency	77	62	38	39	38	15	13	8
Benson Figure copy	78	65	38	39	40	15	14	8
Benson Figure recall	78	65	38	39	40	15	14	8
FCSRT free recall	77	62	38	39	38	15	13	8
FCSRT total recall	77	62	38	39	38	15	13	8
FCSRT delayed free recall	77	62	38	39	38	15	13	8
FCSRT delayed total recall	77	62	38	39	38	15	13	8
Facial Emotion Recognition Test	78	61	38	39	38	15	14	8

Abbreviations: D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test.

Supplementary Table 2. Parameters included in the sample size calculations.

	C9orf72			*GRN*			*MAPT*		
	MD	σ	ρ	MD	σ	ρ	MD	σ	ρ
Cognitive composite scores									
Average	-1.01	0.83	0.76	-1.44	0.42	0.92	-1.67	1.29	0.83
Weighted	-1.13	0.74	0.77	-1.70	0.66	0.85	-2.12	1.87	0.86
Language									
Camel and Cactus Test	-0.71	2.87	0.45	-0.94	0.69	0.76	-1.47	2.28	0.72
Boston Naming Test	-1.36	3.49	0.63	-1.49	0.57	0.47	-1.91	2.88	0.82
Category fluency	-0.75	0.80	0.29	-0.97	0.70	0.33	-0.66	0.36	0.69
Attention and mental processing speed									
Digit span forward	-0.07	0.93	0.57	-0.68	1.34	0.41	0.22	1.36	0.61
Trail Making Test–part A	-0.58	1.88	0.74	-1.80	0.58	0.84	-1.05	0.38	0.87
Digit Symbol	-1.17	1.11	0.80	-1.13	1.14	0.34	-1.26	1.08	0.93
D-KEFS CWIT–color naming	-1.24	3.06	0.72	-1.49	1.06	0.32	-1.99	0.79	0.79
D-KEFS CWIT–word naming	-0.26	1.83	0.56	-0.52	0.83	0.32	-0.87	0.41	0.82
Executive function									
Digit span backward	-0.85	1.46	0.46	-1.06	1.03	0.42	-0.17	0.77	0.38
Trail Making Test–part B	-1.43	4.14	0.60	-3.51	2.30	0.92	-2.07	0.75	0.70
D-KEFS CWIT–ink naming	-2.31	1.52	0.86	-2.84	0.87	0.59	-1.94	0.47	0.86
Phonemic fluency	-0.80	1.25	0.82	-0.54	0.85	0.51	-1.22	0.88	0.83
Visuoconstruction									
Benson Figure copy	-0.71	2.71	0.30	-0.64	0.57	0.03	-0.02	0.95	0.00
Memory									
Benson Figure recall	-0.74	0.87	0.58	1.38	1.22	0.35	-0.77	2.93	0.01
FCSRT free recall	-0.93	1.15	0.38	-0.87	0.92	0.85	-1.68	2.20	0.58
FCSRT total recall	-1.80	4.57	0.54	-0.72	0.96	0.83	-3.11	5.98	0.46
FCSRT delayed free recall	-1.10	1.19	0.61	-0.81	1.42	0.77	-1.86	2.39	0.76
FCSRT delayed total recall	-2.07	2.99	0.67	-0.60	1.28	0.97	-3.02	8.38	0.53
Social cognition									
Facial Emotion Recognition Test	-0.47	1.66	0.37	-0.41	1.55	0.47	-1.68	1.42	0.81

MD is the mean difference between the CDR® plus NACC-FTLD 0.5 and 1 group; σ is the standard deviation of the outcome in the CDR® plus NACC-FTLD 0.5 group; ρ is the correlation between baseline and follow-up measures of the outcome. Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test.

Supplementary Table 3. Participants characteristics and neuropsychological test results per CDR® plus NACC FTLD global score.

	C9orf72				*GRN*				*MAPT*			
CDR® plus NACC FTLD global score	0.5	1	2	3	0.5	1	2	3	0.5	1	2	3
Number of participants	28	14	18	9	25	10	3	3	13	7	5	3
Sex f:m	17:11	4:10	5:13	4:5	13:12	6:4	1:2	0:3	9:4	3:4	0:5	2:1
Age	47.26 (11.31)	56.99 (11.32)	62.33 (8.91)	61.31 (5.87)	48.24 (11.39)	58.63 (6.62)	66.36 (4.97)	61.02 (0.63)	44.28 (11.84)	52.62 (12.72)	59.62 (7.46)	62.81 (3.10)
Education	14.43 (2.64)	13.57 (3.57)	13.72 (2.93)	11.56 (3.13)	14.92 (3.41)	13.00 (4.00)	12.33 (3.06)	12.00 (1.73)	13.77 (2.31)	14.71 (3.50)	12.40 (4.51)	18.67 (2.31)
MMSE	28.79 (2.01)	27.57 (1.87)	25.56 (2.57)	24.25 (5.57)	28.08 (6.16)	24.50 (9.37)	26.0 (3.0)	19.50 (0.71)	28.50 (2.15)	27.83 (2.56)	25.60 (4.51)	25.67 (2.89)
CDR® plus NACC FTLD sum of boxes	1.07 (0.75)	4.14 (1.60)	9.78 (2.61)	16.06 (2.08)	0.82 (0.64)	3.50 (0.91)	11.17 (3.01)	16.83 (1.26)	1.08 (0.76)	3.57 (1.37)	9.80 (0.76)	15.17 (2.57)
Language												
Camel and Cactus Test	-0.58 (1.70)	-1.30 (2.25)	-3.14 (2.44)	-3.79 (4.73)	-0.16 (0.83)	-1.11 (1.82)	-1.10 (2.58)	-1.69 (1.08)	-0.45 (1.51)	-1.92 (2.91)	-4.77 (2.83)	-5.26 (4.70)
Boston Naming Test	-0.23 (1.87)	-1.58 (3.49)	-2.88 (2.29)	-4.64 (5.54)	-0.05 (0.75)	-1.44 (1.61)	-1.24 (1.44)	-2.84 (4.10)	-0.76 (1.70)	-2.66 (2.45)	-4.16 (2.83)	-8.11 (3.10)
Category fluency	-0.46 (0.90)	-1.21 (0.81)	-1.96 (0.75)	-1.97 (0.74)	-0.04 (0.84)	-1.01 (0.64)	-1.21 (0.74)	-2.46 (0.61)	-0.23 (0.60)	-0.89 (1.33)	-1.57 (0.91)	-2.14 (1.47)
Attention and mental processing speed												
Digit span forward	0.06 (0.96)	-0.01 (1.10)	-1.01 (1.20)	-1.16 (1.16)	0.16 (1.16)	-0.52 (1.46)	0.06 (0.70)	-0.80 (1.68)	-0.02 (1.17)	0.20 (1.02)	0.04 (1.64)	0.75 (1.73)
Trail Making Test–part A	-0.45 (1.37)	-1.03 (2.12)	-2.31 (1.96)	-2.87 (3.25)	0.03 (0.76)	-1.83 (1.99)	-3.48 (1.40)	-0.11 (1.01)	0.25 (0.62)	-1.30 (1.35)	-1.06 (1.36)	-3.02 (2.28)
Digit Symbol	-0.23 (1.05)	-1.40 (1.02)	-2.11 (0.89)	-1.97 (1.16)	-0.17 (1.07)	-1.30 (1.41)	-1.50 (0.60)	-1.19 (0.81)	0.02 (1.04)	-1.23 (1.61)	-0.76 (0.40)	-2.21 (0.94)
D-KEFS CWIT–color naming	-0.70 (1.75)	-1.94 (1.95)	-5.46 (4.01)	-5.74 (3.96)	-0.04 (1.03)	-1.53 (3.13)	-0.18 (1.05)	-1.53 (0.99)	-0.14 (0.89)	-2.13 (2.65)	-2.95 (2.54)	-1.62 (2.57)
D-KEFS CWIT–word naming	-0.42 (1.35)	-0.67 (1.59)	-3.60 (3.42)	-4.73 (4.59)	0.36 (0.91)	-0.87 (2.40)	0.43 (0.45)	-0.22 (1.01)	0.27 (0.64)	-1.15 (1.75)	-1.14 (1.31)	-1.63 (2.41)
Executive function												
Digit span backward	0.19 (1.21)	-0.67 (1.18)	-1.12 (0.85)	-1.40 (0.85)	-0.01 (1.01)	-1.07 (1.44)	-1.31 (0.09)	-1.77 (0.92)	-0.22 (0.88)	-0.39 (0.97)	0.34 (1.41)	-0.46 (0.80)
Trail Making Test–part B	-0.70 (2.04)	-2.13 (2.70)	-4.86 (2.58)	-3.47 (2.94)	-0.27 (1.52)	-3.78 (3.50)	-5.05 (3.35)	-4.85 (3.82)	0.11 (0.87)	-2.18 (3.01)	-2.34 (2.71)	-4.25 (3.48)
D-KEFS CWIT- ink naming	-0.75 (1.23)	-3.06 (3.77)	-6.46 (3.38)	-6.49 (4.60)	-0.28 (0.94)	-3.12 (3.56)	-1.81 (0.61)	-0.86 (0.47)	0.27 (0.68)	-2.21 (3.40)	-2.36 (2.73)	-2.88 (3.05)
Phonemic fluency	-0.45 (1.12)	-1.25 (0.97)	-2.00 (0.79)	-1.70 (1.07)	0.54 (0.92)	-0.97 (1.54)	-0.80 (0.48)	-1.58 (1.16)	0.08 (0.94)	-1.14 (1.19)	-0.85 (1.29)	-2.26 (0.97)
Visuoconstruction												
Benson Figure copy	-0.29 (1.65)	-0.99 (1.43)	-1.38 (2.14)	-1.68 (2.45)	0.30 (0.75)	-0.34 (1.17)	-0.49 (0.27)	-1.73 (2.77)	-0.22 (0.98)	-0.24 (1.19)	-0.68 (1.86)	-1.61 (2.60)

Supplementary Table 3 continued

	C9orf72				*GRN*				*MAPT*			
Memory												
Benson Figure recall	0.18 (0.93)	-0.57 (1.36)	-1.67 (1.50)	-1.85 (1.98)	-0.28 (1.11)	-1.09 (1.14)	-1.70 (2.21)	-2.51 (2.83)	-0.69 (1.71)	-1.46 (2.12)	-1.34 (2.06)	-3.18 (1.34)
FCSRT free recall	-0.87 (1.07)	-1.80 (1.14)	-2.29 (1.21)	-2.77 (1.44)	-0.13 (0.96)	-1.00 (1.30)	-2.43 (1.82)	-2.96 (2.40)	-0.60 (1.48)	-2.28 (1.65)	-2.60 (1.20)	-3.70 (1.53)
FCSRT total recall	-0.73 (2.14)	-2.53 (3.37)	-3.31 (3.97)	-4.03 (5.12)	-0.32 (0.98)	-1.05 (1.85)	-5.30 (5.12)	-7.97 (5.55)	-0.92 (2.45)	-4.03 (2.88)	-4.29 (2.80)	-6.17 (7.09)
FCSRT delayed free recall	-0.52 (1.09)	-1.63 (1.43)	-2.47 (1.37)	-3.08 (1.34)	-0.43 (1.19)	-1.24 (1.54)	-2.65 (1.59)	-2.89 (2.45)	-0.45 (1.55)	-2.31 (1.85)	-2.65 (1.64)	-4.32 (1.53)
FCSRT delayed total recall	-0.34 (1.73)	-2.41 (3.69)	-3.36 (4.30)	-4.59 (5.49)	-0.19 (1.3)	-0.79 (1.84)	-3.40 (5.95)	-7.79 (6.27)	-0.98 (2.89)	-4.00 (4.13)	-4.16 (3.12)	-5.88 (7.20)
Social cognition												
Facial Emotion Recognition Test	-0.81 (1.29)	-1.27 (1.11)	-2.49 (1.45)	-3.35 (3.19)	-0.55 (1.24)	-0.96 (1.06)	-2.53 (0.89)	-3.41 (1.99)	-0.56 (1.19)	-1.10 (1.85)	-1.69 (2.27)	-1.88 (1.07)

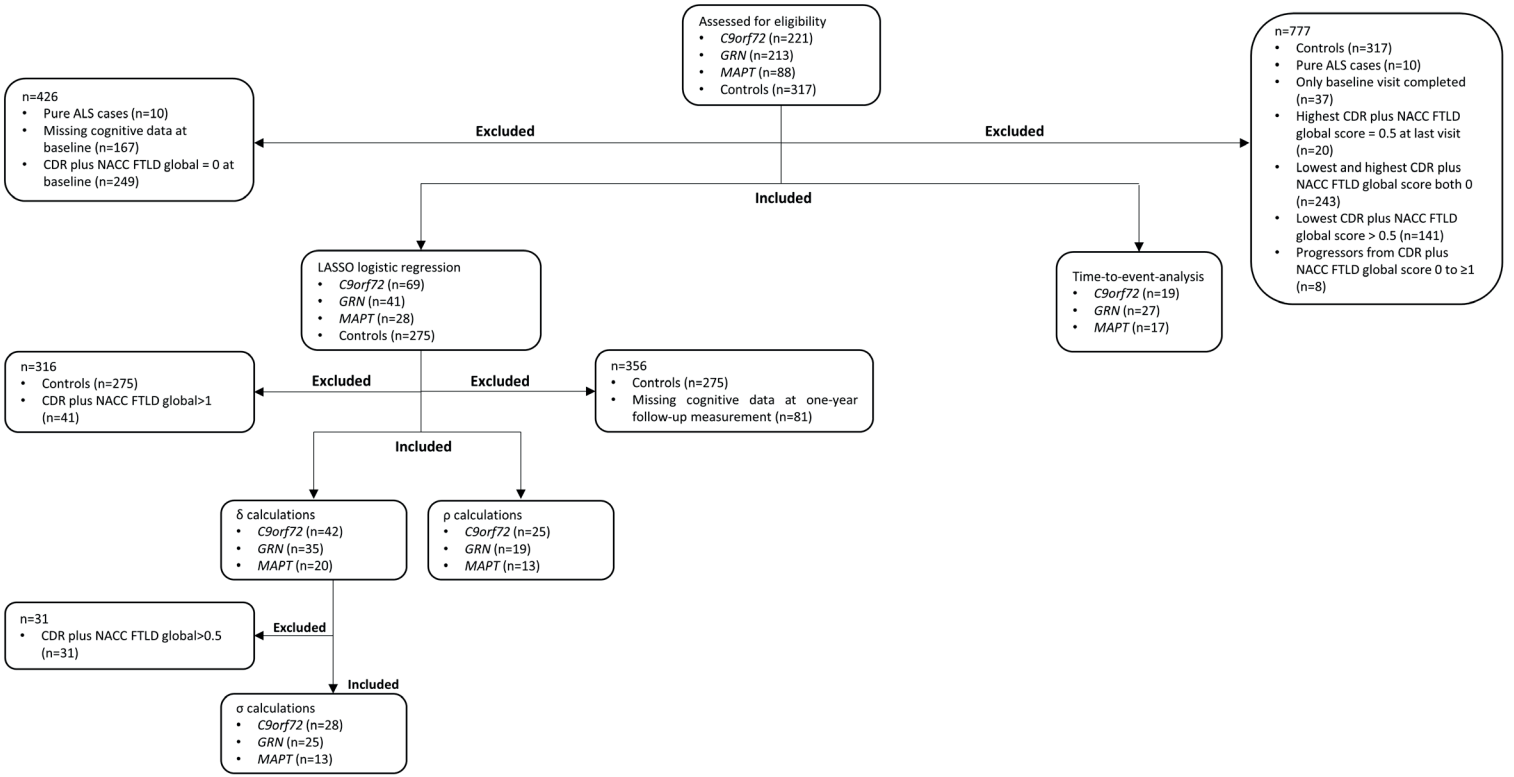
Values are: mean Z-scores (raw score – mean score controls/standard deviation of controls) corrected for age, years of education and sex, with standard deviation between parentheses unless otherwise specified. For the FCSRT and letter fluency an additional correction was made for language as stimuli differed between languages. Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration; D-KEFS CWIT = Delis-Kaplan Executive Function System Color-Word Interference Test; FCSRT = Free and Cued Selective Reminding Test.

Supplementary Table 4. Number of mutation carriers that progressed on the CDR® plus NACC FTLD.

		Number that did not progress to CDR® plus NACC FTLD > 0.5	Number that progressed to CDR® plus NACC FTLD > 0.5	Number that did not complete visit*
C9orf72	Year 0	21	0	0
	Year 1	16	1	4
	Year 2	3	0	11
	Year 3	2	1	2
GRN	Year 0	27	0	0
	Year 1	23	1	3
	Year 2	7	5	11
	Year 3	1	1	6
MAPT	Year 0	16	0	0
	Year 1	14	0	2
	Year 2	7	1	6
	Year 3	0	3	4

Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration. *Refers to participants that dropped out of GENFI and participants that had not completed the visit for this study yet. As the data concerns an ongoing prospective cohort study not all participants completed a second, third or fourth visit yet.

Supplementary Figure 1. STROBE flowchart



Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; LASSO = least absolute shrinkage and selection operator; CDR plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration. ρ, σ and δ are used for the sample size calculations where, ρ is the correlation between baseline and follow-up measures of the outcome, σ is the standard deviation of the outcome in the CDR® plus NACC-FTLD 0.5 group, δ is the treatment effect (effect size multiplied by difference in mean between CDR® plus NACC-FTLD 0.5 and 1 group).

Supplementary file 2: Description of statistical analysis

Calculating the Z-scores corrected for covariates

Raw data of each cognitive outcome was converted to a Z-score corrected for age, education and sex (and language for the Free and Cued Selective Reminding Test) compared to 312 healthy controls as collected within GENFI (i.e. mutation negative participants). The formula for this calculation is:

Corrected Z-score = [(raw score – predicted score)/standard deviation of the residuals in control group]

A linear regression with all covariates was performed in the control group to calculate the residuals and the coefficients of each covariate. The predicted scores were calculated with the coefficients from the model according to the following formula:

Predicted score = (a) + (b*age) + (c*education) + (d*sex) + (e*language)

Developing the cognitive composite score

Logistic regression models were used to identify the combination of neuropsychological tests that discriminated best between each mutation carrier group and controls, where mutation carrier status was the outcome and the cognitive tests the predictors of interest. Due to relatively small sample sizes least absolute shrinkage and selection operator (LASSO) regularisation was used in the logistic regression model. This approach adds a penalization term (λ) to the log-likelihood function which forces the sum of the absolute value of the regression coefficients to be less than the fixed value. This has the effect of shrinking all coefficients towards zero (James, Witten, Hastie and Tibshirani, 2013), and can therefore be used to perform variable selection. If λ=0 the results are the same as those from a standard logistic regression model, but as λ is increased, fewer tests are selected in the final model and their coefficients are shrunk towards zero. The optimal size for λ was specified by using 10-fold cross validation to find the value that had the smallest error in prediction of mutation carrier status. This approach divides the data into 10 “folds” of equal size, fits the LASSO logistic regression model using only 9 of the 10 folds, and calculates the prediction error on the remaining “fold” not used in fitting the model. This is repeated excluding each of the 10 folds one at a time and the average prediction error across the 10 folds gives a measure of cross-validated performance. This process was repeated for λ between 0.001 to 100. The final λ was selected as the one which showed minimum cross-validation error in prediction of mutation carrier status (i.e. one which had the most parsimonious model but achieved an

error of within 1 standard error of the minimum value). The package glmnet in R was used to fit the LASSO models and perform the cross-validation.

From the resulting model two different cognitive composite scores were calculated: (1) average of the scores for all cognitive tests that were selected in the model; and (2) weighted average of the scores for all cognitive tests that were selected in the model, using the regression coefficients to determine the weights (i.e. individual regression coefficient/ sum of coefficients). For example:

Average composite:

$$Score1 = \frac{x_1 + x_2 + x_3}{3}$$

Weighted composite:

$$core2 = \frac{0.25x_1 + 0.15x_2 + 0.10x_3}{0.25 + 0.15 + 0.10}$$

Sample size calculation

To evaluate performance of the cognitive composites and all the individual cognitive tests, sample sizes were calculated for a hypothetical clinical trial of a disease modifying treatment. The sample size for a hypothetical two arm study with 1:1 randomization to placebo versus active to have 80% power to detect a treatment effect at 5% significance level was calculated as:

$$n = (1 - \rho^2)\frac{2\sigma^2}{\delta^2}\left(Z_{\alpha/2} + Z_{\beta}\right)^2$$

Where,

ρ is the correlation between baseline and one year follow-up measures of the outcome of interest at baseline in each mutation carrier group. There were 25 *C9orf72*, 19 *GRN* and 13 *MAPT* mutation carriers that had a complete follow-up visit after one year. Pearson correlation analysis was used to estimate the correlation between baseline and follow-up.

σ is the standard deviation of the outcome of interest in the group with CDR® plus NACC FTLD 0.5 at baseline (*C9orf72*: n=28, *GRN*: n=25, *MAPT*: n=13).

δ is the treatment effect as defined below.

α is the type I error rate (significance level) for the two-sided test comparing active treatment to control

β is the type II error rate (100%-power) for the two-sided test comparing active treatment to control

$Z_{\alpha/2}$ is the value of the standard normal distribution above which the proportion of the distribution is equal to α/2

Z_{β} is the value of the standard normal distribution above which the proportion of the distribution is equal to β

For 80% power to detect a treatment effect at 5% significance level:

$$\left(Z_{\alpha/2} + Z_{\beta}\right)^2 = (1.960 + 0.842)^2 = 7.85$$

Sample sizes were calculated for three hypothesized treatment effects (δ), which were each a proportion (10%, 20% and 40%) of the difference in mean between the CDR® plus NACC FTLD 0.5 and 1 group (*C9orf72*: n=28 and n=14, *GRN*: n=25 and n=10, *MAPT*: n=13 and n=7).

CHAPTER 3.3

Emotion recognition of morphed facial expressions in presymptomatic and symptomatic frontotemporal dementia, and Alzheimer's dementia

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Abstract

Background: The Emotion Recognition Task (ERT) was developed to overcome shortcomings of static emotion recognition paradigms, by identifying more subtle deficits in emotion recognition across different intensity levels. In this study, we used the ERT to investigate emotion recognition deficits across the frontotemporal (FTD) and Alzheimer's Dementia (AD) spectrum.

Methods: With the ERT, we assessed the recognition of facial emotional expressions (anger-disgust-fear-happiness-sadness-surprise) across four intensities (40-60-80-100%) in patients with behavioural variant FTD (bvFTD; n=32), and AD (n=32), presymptomatic FTD mutation carriers (n=47) and controls (n=49). We examined group differences using multilevel linear regression with age, sex and education level as covariates, and performed post-hoc analyses on presymptomatic (*MAPT*, *GRN* and *C9orf72*) mutation carriers. Classification abilities were investigated by means of logistic regression.

Results: Lowest ERT total scores were found in patients with bvFTD and AD, whereas equal highest performance was found in presymptomatic mutation carriers and controls. For all emotions, significantly lower subscores were found in patients with bvFTD than in presymptomatic mutation carriers and in controls (highest p-value = 0.025). Patients with bvFTD performed lower than patients with AD on anger (p=0.005) and a trend towards significance was found for a lower performance on happiness (p=0.065). Task performance increased with higher emotional intensity, and classification was better at the lowest than at the highest intensity. *C9orf72* mutation carriers performed worse on recognizing anger at the lowest intensity than *GRN* mutation carriers (p=0.047) and controls (p=0.038). The ERT differentiated between patients with bvFTD and controls, and between patients with AD and controls (both $p<0.001$).

Discussion: Our results demonstrate emotion recognition deficits in both bvFTD and AD, and suggest the presence of subtle emotion recognition changes in presymptomatic *C9orf72*-FTD. This highlights the importance of incorporating emotion recognition paradigms into standard neuropsychological assessment for early differential diagnosis, and as clinical endpoints in upcoming therapeutic trials.

Introduction

Frontotemporal dementia (FTD) and Alzheimer's Dementia (AD) are the two most prevalent early-onset types of dementia. The clinical profile of FTD is typically characterized by behavioural and language disturbances, with cognitive deficits in executive function and relative sparing of memory and visuospatial abilities[1, 2], whereas the first symptoms of AD are usually episodic memory and visuospatial impairments[3]. Differential diagnosis in a young-onset population is complicated by frequent atypical presentations and clinical overlap between the two entities, with significant memory deficits in FTD[4], and predominant 'frontal' (dysexecutive and behavioural) and language variants of AD being described[5], often leading to misdiagnosis and/or diagnostic delay. Early diagnosis is, however, essential for proper patient and caregiver management and planning, non-pharmacological symptomatic treatment, and patient stratification in upcoming clinical trials[6].

As marked behavioural and emotional changes may already occur in the early disease stages of both FTD and AD, an increasing number of studies emphasize the importance of social-cognitive assessments to improve early diagnosis of dementia[7]. Social cognition refers to a broad and complex cognitive concept encompassing the psychobiological processes needed to comprehend and socially interact with other people, often conceptualized along three hierarchical levels, ranging from perception and automatic attribution (e.g., emotion recognition), understanding and interpretation of social information, to reasoning and regulation[8]. Recent meta-analyses have shown consistent deficits across all three levels of social cognition in FTD[7] and mild cognitive impairment (MCI)[9], often the prodromal phase of AD. Special emphasis is often put on deficits in facial emotion recognition, as they are thought to lie at the base of social cue misinterpretation leading to difficulties with social conduct[10]. Meta-analyses of emotion recognition abilities have shown significant deficits in behavioural (bvFTD[10]) and language variants of FTD (primary progressive aphasia, or PPA[7]), as well as MCI[9] and AD[10], but with large variability across studies depending on the specific tasks used. Prodromal FTD studies are lacking thus far, with only one study showing subtle decline over time in presymptomatic FTD mutation carriers[11].

The question is whether traditional measures of social cognition are able to identify the subtle and slowly emerging deficits in the earliest stages of dementia. The Ekman 60 Faces test[12], one of the most often used paradigms, for instance employs static photographs of actors mimicking full-blown emotions. More subtle emotion recognition deficits can therefore be missed, as full-blown emotions often do not resemble facial expression in everyday communication. Static images also take natural movement and dynamic development of facial expressions less into account. Moreover, (near) ceiling effects for the emotion happiness are often found, as happy faces are generally more easily recognised in the absence of other

positive emotions as possible distractors. This could reduce the test's sensitivity (i.e. the proportion of patients identified as being impaired), hampering its use in clinical practice[13].

To overcome the shortcomings of the Ekman Faces, the Emotion Recognition Task (ERT)[13, 14] was developed. It presents dynamically morphed facial expressions of the same six basis emotions (happiness, anger, disgust, surprise, sadness and fear), but across different levels of intensity. In that way, the ERT might be more sensitive to detect subtle deficits in the early stages of dementia than the static images used in the Ekman Faces Test. The ERT has been validated in a wide range of neurological diseases, including Huntington's disease[15], multiple sclerosis[16], traumatic brain injury[17], stroke[18], Korsakoff's syndrome[19], and Parkinson's disease[20]. With respect to research into the ERT in the dementia field, a study in a small convenience sample of bvFTD patients demonstrated specific impairments in the recognition of the emotions anger and surprise[14], however no studies have been performed in presymptomatic FTD yet. The ERT has only been used in one study on MCI and AD[21], but no direct comparisons with bvFTD have been made so far. The aim of the present study is therefore to investigate emotion recognition deficits across the different emotions and emotional intensities as well as classification abilities of the ERT in patients with bvFTD and compare them to patients with AD, presymptomatic FTD mutation carriers, and cognitively unimpaired controls, that can be used to improve early differential diagnosis in dementia.

Methods

Participants

In this retrospective study, we included data from 32 patients with bvFTD via the outpatient memory clinics of the Erasmus Medical Center (n=22) and Radboud University Medical Center (n=10), the Netherlands. Six bvFTD patients were carrying a pathogenic FTD mutation (chromosome 9 open reading frame 72 repeat expansion (*C9orf72*), all other patients were sporadic. Five other bvFTD patients had concomitant amyotrophic lateral sclerosis (bvFTD-ALS). We included data from 32 patients with AD, who were either assessed at the outpatient memory clinic of the Erasmus Medical Center (n=3) or participated in a previous study for which they were recruited via the outpatient memory clinic of the Zorg Groep Twente (ZGT) hospital in Almelo and Hengelo[29], the Netherlands[21]. Diagnoses were made in a multidisciplinary consensus meeting, using established diagnostic criteria for probable bvFTD (n=28) and bvFTD with definite FTLD pathology (n=4)[1], ALS[22], and probable AD[23]. Furthermore, we enrolled 101 participants of the FTD Risk Cohort (FTD-RisC) from the Erasmus Medical Center, in which first-degree family members patients with FTD due to a pathogenic mutation are followed longitudinally[24]. DNA genotyping assigned these participants to either the mutation carrier (n=47) or non-carrier group (controls; n=49). Mutation carriers were from either microtubule-associated protein tau (*MAPT*; n=7), progranulin (*GRN*; n=22) or *C9orf72*

(n=18) families. Mutation carriers were deemed to be presymptomatic when they did not fulfill clinical diagnostic criteria for bvFTD[1], PPA[2] or FTD-ALS[22], and had CDR® plus Behaviour and Language domains from the NACC FTLD Module (CDR® plus NACC FTLD)[25] of 0. The investigators and participants were blinded for the genetic status of at-risk participants, except for those that underwent predictive testing at their own request.

All patients with dementia from the outpatient clinic of the Erasmus Medical Center were part of a local biobank study, for which they provided written informed consent for the use of their anonymized medical and clinical data for research purposes. Participants of the FTD-RisC study provided written informed consent for the use of their anonymized research data. The data from the Radboud University Medical Center were collected as part of routine neuropsychological assessments, and stored and analyzed in anonymized form in accordance with the General Data Protection Regulation. Patients provided written informed consent concerning their storage and use. The data from the ZGT hospital were collected as part of another study[21], for which written informed consent was obtained in all patients according to the declaration of Helsinki and the Institutional Review Board of the ZGT hospital gave approval. The Erasmus Medical Center ethics committee gave approval for both the local biobank and the FTD-RisC study.

Procedure

The ERT was administered as part of the neuropsychological assessment performed during the memory clinic work-up (patients) or study visit (FTD-RisC participants). The Mini-Mental State Examination (MMSE)[26] was administered as measure of global cognitive functioning. The Clinical Dementia Rating scale (CDR)[27] was used as a measure of disease severity in patients with AD, while patients with bvFTD from the Erasmus Medical Center as well as FTD-RisC participants were assessed about functional changes in behaviour, neuropsychiatric symptoms, cognition and language by means of the CDR® plus NACC FTLD[25] during the study visit or afterwards in a telephone interview.

Emotion recognition task (ERT)

Emotion recognition abilities were assessed with the ERT. The ERT is a computerized neuropsychological test, available via the *DiagnoseIS* neuropsychological assessment system (www.diagnoseis.com). It enables a real-time interactive morphing between two endpoint facial expressions (0% = neutral, and 100% = full-blown emotion)[13, 14]. Each morph was created from 21 images between 0% and 100% intensity, generating video clips in which the degree of emotional expression was increased by 20% steps, starting at 40% intensity. The video clips were presented starting at the lowest intensities (i.e., neutral morphed into 40% intensity to neutral morphed into 100% intensity – see Figure 1). The duration of the video clips was one (40% intensity) to three (100% intensity) seconds. The ERT starts with a screen presenting the task instructions to the participant in her/his native language. Simultaneously, the examiner

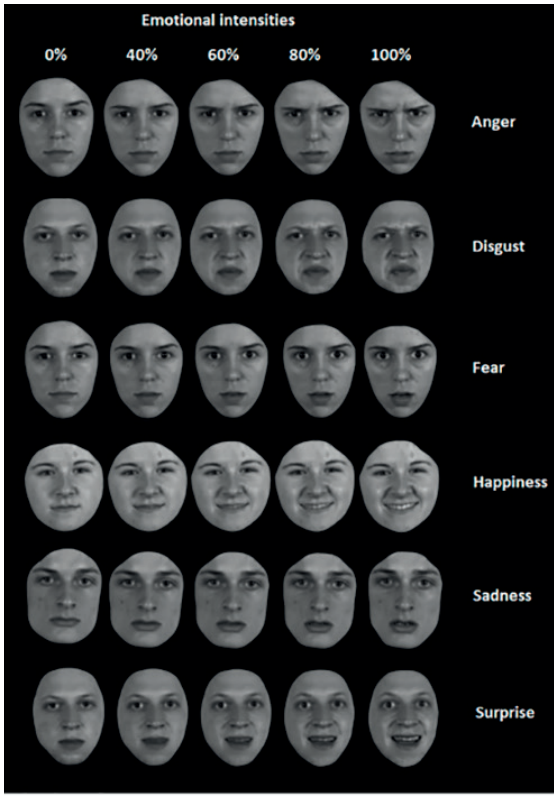
reads these instructions aloud to the participant, thereby ensuring minimal variation in the administration procedure. Following the instructions, three practice stimuli are presented, showing respectively an angry, a happy, and a disgusted expression that were not part of the final test set. The instructions and practice trials were repeated if the participant did not understand the instructions. Responses were made by mouse click. If participants were unsure how to or unable to operate the computer mouse, the examiner assisted by asking which label he or she deemed the most appropriate (and clicked the given response if needed). The test was discontinued in case the participant still did not understand the test instructions or did not know how to respond after repeating the instructions. In the real test, all emotions of the same emotional intensity were presented in pseudo-random but fixed order to control for possible order effects of previously encountered emotions. In each trial, the participants had to label the facial emotional expression by using a six-alternative forced choice (i.e., anger, disgust, fear, happiness, sadness and surprise). Performance was calculated as the number of correctly labelled expressions per emotion and intensity (maximum = 4). Across the four intensities, the maximum score of each emotion was 16, to a total of 96 for the entire test. Administration time was approximately 10 minutes.

Statistical analysis

We performed statistical analyses using SPSS Statistics 25.0 (IBM Corp., Armonk, NY). Alpha was set at 0.05 across all comparisons, unless otherwise specified, and two-tailed analyses were performed. We compared continuous demographic data between groups by means of one-way ANOVA for normally distributed data, or Kruskal-Wallis tests in case of non-normally distributed data. We performed post hoc comparisons with Bonferroni (parametric data) or Mann-Whitney U (nonparametric data) tests. Between-group differences in sex distribution were analysed using Pearson X^2 tests. We examined group differences in ERT total and emotion subscores using by means of one-way ANCOVA for normally distributed data, or Quade's rank analysis of covariance for non-normally distributed data – using age, sex and education level as covariates. To investigate differences between emotions across emotional intensities we used multilevel linear regression modeling, with group as between-subject variable and emotion and emotional intensity as within-subject variables – using raw scores for normally distributed data and, in case of non-normally distributed data, using rank-transformed data. Again, analyses were corrected for age, sex and education level. In post hoc analyses we explored differences between patients with sporadic bvFTD, *C9orf72*-associated bvFTD, and patients with concomitant ALS, as well as between pathogenic mutations amongst presymptomatic mutation carriers (*MAPT*, *GRN* and *C9orf72*) and controls. We performed multinomial logistic regression analyses, and determined sensitivity and specificity by the area under the curve (AUC) by receiver operating characteristic (ROC) analyses to investigate the classification abilities of the ERT between the subgroups. We first checked for non-linearity, dependence of errors and multicollinearity. All analyses were adjusted for age, sex and education level. Optimal cut-off levels were given by the highest Youden's index[28].

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). Goodness of fit was evaluated with the HL X2 test. Nagelkerke R2 is reported as measure of effect size. To correct for the potential influence of our data coming from different cohorts, we reran all analyses using centre as a covariate.

Figure 1. The Emotion Recognition Task. Displayed are examples of facial expressions of six universal emotions (anger, disgust, fear, happiness, sadness, and surprise). The ERT is a computerized test, that enables a real-time interactive morphing between two endpoint facial expressions (0%, i.e. neutral, and 40, 60, 80 or 100% intensity). Adapted with permission from Kessels et al.[13]



Results

Demographics data

Demographic and clinical data of patients with bvFTD and AD, presymptomatic mutation carriers, and controls are shown in Table 1. Patients with AD were significantly older than patients with bvFTD (U = 135.5, p<0.001), presymptomatic mutation carriers (U = 29, p<0.001) and controls (U = 61, p<0.001), and patients with bvFTD were significantly

older than presymptomatic mutation carriers (U = 278, p<0.001) and controls (U = 421, p<0.001). The patients with AD had a lower education level than mutation carriers and controls (p<0.001), and patients with bvFTD (p=0.039). MMSE scores were highest in the presymptomatic mutation carriers and controls, being significantly higher than in patients with bvFTD (bvFTD vs. presymptomatic mutation carriers: U = 145.5, p<0.001; bvFTD vs. controls: U = 179, p<0.001). MMSE scores were lower in patients with AD than in all other subgroups (AD vs. bvFTD: U = 146.5, p<0.001; AD vs. presymptomatic mutation carriers: U = 14, p<0.001; AD vs. controls: U = 19, p<0.001). There were no significant differences in sex between groups (X(4) = 3.08, p=0.38). Disease duration (U = 44, p=0.85) and stage (CDR® / CDR® plus NACC FTLD scores) did not differ between patients with bvFTD and AD (Table 1). There were no significant differences regarding demographic or clinical data between the presymptomatic mutation carriers and controls. There was, however, a significant age difference between presymptomatic mutation carrier groups [H(2) = 7.31, p<0.026], with *C9orf72* mutation carriers being younger than *GRN* mutation carriers (U = 105, p=0.011).

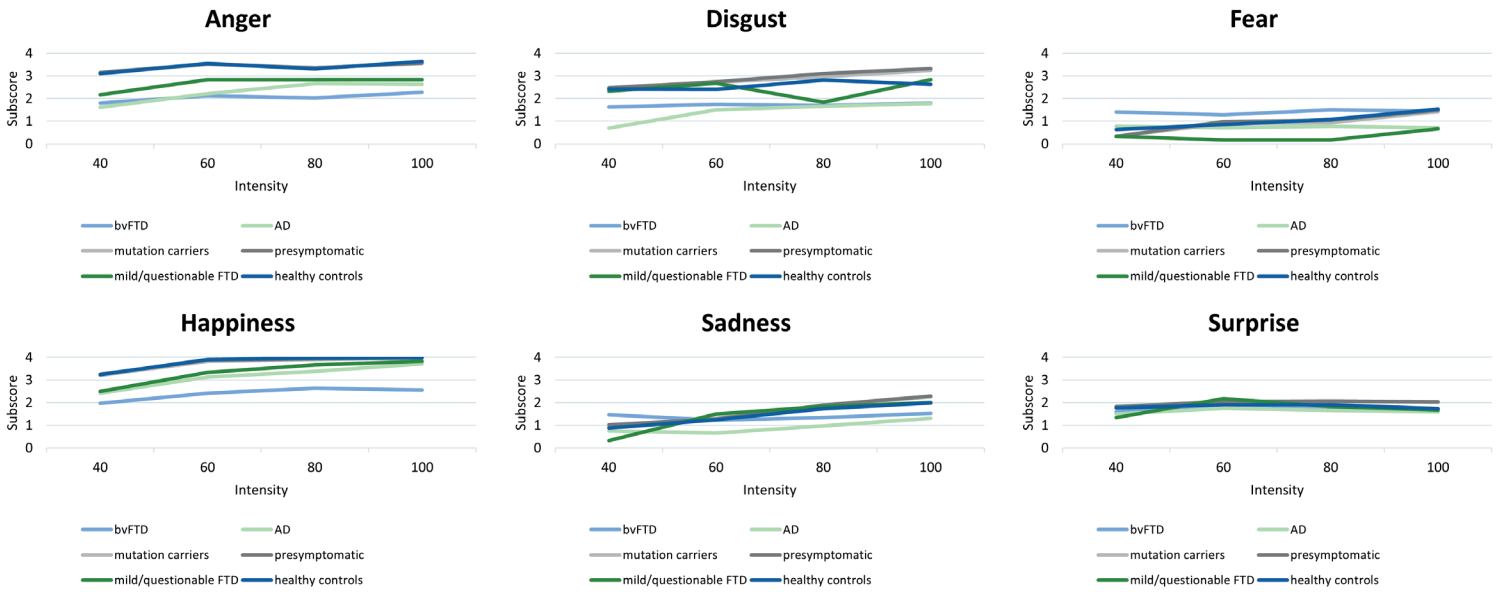


Figure 2. Mean performance (y-axis, number correctly identified emotions = max 4) of patients with bvFTD (light blue), patients with AD (light green), presymptomatic mutation carriers (dark grey), and cognitively unimpaired controls (dark blue) for the six different emotions across the emotional intensities (x-axis).

Table 1. Demographic and clinical data per subgroup.

	bvFTD patients (n=32)	AD patients (n=32)	Presymptomatic mutation carriers (n=47)	Controls (n=49)
Age, y [range]	63.0 ± 9.9 [35.8 – 79.8]	76.0 ± 6.8 [62.1 – 87.0]	48.7 ± 12.6 [23.4 – 76.1]	52.4 ± 13.3 [34.8 – 74.5]
Female (%)	14 (43.8)	19 (59.4)	29 (61.7)	25 (51.0)
Gene in family	*MAPT* n=0 *GRN* n=0 *C9orf72* n=4	n/a	*MAPT* n=7 *GRN* n=22 *C9orf72* n=18	*MAPT* n=10 *GRN* n=26 *C9orf72* n=13
Education (level)*	4.7 ± 1.3	3.9 ± 1.3	5.5 ± 1.0	5.5 ± 0.9
Disease duration, y [range]	4.3 ± 2.8 [0.7 – 11.3]	5.2 ± 6.0 [0.7 – 12.0]	n/a	n/a
MMSE (max. 30)	25.6 ± 4.0	19.4 ± 4.7	29.4 ± 0.8	29.3 ± 0.9
CDR© (plus NACC FTLD), range†	0.5-2.0	1.0-2.0	0	0
ERT total score (max. 96)	42.9 ± 14.3	40.6 ± 9.8	58.6 ± 7.2	51.0 ± 12.4
Anger subscore (max. 16)	8.3 ± 3.8	9.1 ± 3.6	13.6 ± 2.1	13.6 ± 2.4
Disgust subscore (max. 16)	6.9 ± 4.4	5.6 ± 3.4	116 ± 3.0	10.3 ± 3.7
Fear subscore (max. 16)	5.6 ± 5.5	3.0 ± 2.1	3.9 ± 2.9	4.1 ± 3.4
Happiness subscore (max. 16)	9.6 ± 5.6	12.6 ± 2.3	15.0 ± 1.1	15.1 ± 1.2
Sadness subscore (max. 16)	5.6 ± 4.5	3.7 ± 2.6	6.5 ± 3.2	5.8 ± 2.8
Surprise subscore (max. 16)	7.0 ± 4.10	6.5 ± 2.9	8.0 ± 2.6	7.3 ± 2.4

Values indicate mean ± SD or n (%). Abbreviations: bvFTD = behavioural variant frontotemporal dementia; AD = Alzheimer's Dementia; MMSE = Mini-Mental State Examination; CDR = clinical dementia rating; NACC = National Alzheimer's Coordinating Center; FTLD = frontotemporal lobar degeneration; ERT = Emotion Recognition Test. * Dutch educational system categorized into levels from 1 = less than 6 years of primary education to 7 = academic schooling[51]. †The CDR weighted score was used for patients with AD, whereas the CDR© plus NACC FTLD weighted score was used for patients with bvFTD, presymptomatic mutation carriers and controls; CDR© plus NACC FTLD scores were available for 22/32 bvFTD patients.

Group differences on the ERT

As there were no significant differences in total ERT or ERT subscores between sporadic bvFTD patients, bvFTD patients carrying the *C9orf72* mutation, or bvFTD patients with concomitant ALS (see Supplementary Table 1), we pooled the three subtypes into one bvFTD group. There were significant differences in ERT total score between groups [$F(3,161) = 31.13$, $p<0.001$] (Table 1). Patients with bvFTD had lower scores than patients with AD (p=0.001), presymptomatic mutation carriers ($p<0.001$) and controls ($p<0.001$), and also patients with AD had lower ERT total scores than presymptomatic mutation carriers ($p<0.001$) and controls ($p<0.001$). There were no significant differences in ERT total scores between presymptomatic mutation carriers and controls (p=0.250). Apart from fear [$F_{Quade}(3,145) = 1.32$, p=0.270], all ERT subscores showed significant differences between groups ($p\leq0.011$) (Table 1). The lowest scores, regardless of clinical status, were found for the identification of the emotions fear and sadness, followed by surprise and disgust (Figure 2). Patients with bvFTD performed lower than patients with AD on the emotions anger (p=0.005) and a trend towards significance was found for happiness (p=0.065) (Table 1, Figure 2). For all emotions,

significantly lower subscores were found in patients with bvFTD than in presymptomatic mutation carriers and controls (highest p-value = 0.025). Patients with AD had lower disgust scores than presymptomatic mutation carriers (p=0.013), but did neither differ regarding other subscores, nor from controls. For all emotions, performance was almost identical in the presymptomatic mutation carriers and controls (p=1.00; Figure 2). All emotions, irrespective of clinical status, showed a similar pattern of increasing performance with higher emotional intensity [F(3,460) = 3.80, p=0.01]. Differences between groups were the largest at the lowest intensity (40%) than at the highest intensity (100%) for the emotions disgust (p=0.028), fear (p=0.006), and sadness (p=0.03). Rerunning our analyses using centre as additional covariate did not change aforementioned results.

ERT total scores did not differ between the presymptomatic *MAPT*, *GRN* and *C9orf72* mutation carriers and the controls [F(3,92) = 1.19, p=0.320]. Again, main effects were found for emotion [F(4,445) = 193.07, p<0.001] and intensity [F(3,93) = 92.90, p<0.001] – with the highest scores for happiness and anger, and higher performance with increasing emotional intensity (Supplementary Figure 1). *C9orf72* mutation carriers performed worse in recognizing anger at the lowest (40%) emotional intensity than controls (p=0.038), and *GRN* mutation carriers (p=0.047), but no other interaction effects were found between mutation carriers and controls [F(38,1292) = 1.18, p=0.22]. For happiness, group differences were larger at the lowest intensity (40%) than at the highest intensity (100%) (trend; p=0.082), whereas for sadness group differences showed an opposite pattern (p=0.021).

Classification abilities of the ERT

The classification abilities of the ERT total scores and emotion subscores can be found in Table 2. The ERT total score differentiated well between subgroups (X^2(138) = 213.072, p<0.001), with significant discriminative ability between patients with bvFTD and presymptomatic mutation carriers (X^2(1) = 19.752, p<0.001), patients with bvFTD and controls (X^2(1) = 16.308, p<0.001), patients with AD and presymptomatic mutation carriers (X^2(1) = 22.325, p<0.001), patients with AD and controls (X^2(1) = 20.352, p<0.001), but neither between patients with bvFTD and AD (X^2(1) = 0.574, p=0.449), nor between the presymptomatic mutation carriers and controls (X^2(1) = 2.185, p=0.139). A model consisting of the emotions anger, fear, happiness and surprise correctly classified 93.7% of patients with bvFTD and presymptomatic mutation carriers (X^2(1) = 9.680, p=0.002). The model with anger and happiness differentiated best (87.7% correctly classified) between patients with bvFTD and controls (X^2(1) = 11.327, p=0.001). The classification accuracy between patients with bvFTD and AD was low, just above chance level (59.4% correct), with only the emotion happiness being a significant predictor of the presenting phenotype (X^2(1) = 5.368, p=0.021). The ERT classified well (87.3% correctly classified) between patients with AD and presymptomatic mutation carriers with anger, disgust, and happiness as predictors (X^2(1) = 13.211, p<0.001). A similar model classified best (87.7% correct) between patients with AD and controls X^2(1) = 16.155, p<0.001). As

can be expected from similar scores on the ERT, discriminative ability was low between presymptomatic mutation carriers and controls (64.6% correct), with only disgust being a significant classifier between groups (Table 2). Rerunning our analyses using centre as additional covariate did not change our results significantly.

Table 2. Classification abilities of the ERT per subgroup.

	AUC	95% CI	p-value	Optimal cut-off	Sensitivity (%)	Specificity (%)
bvFTD vs. AD						
Total score	0.52	0.34-0.63	0.830	-	-	-
Anger	0.55	0.40-0.67	0.532	-	-	-
Disgust	0.57	0.29-0.57	0.320	-	-	-
Fear	0.58	0.27-0.56	0.245	-	-	-
Happiness	0.63	0.49-0.77	0.086	-	-	-
Sadness	0.59	0.26-0.55	0.197	-	-	-
Surprise	0.51	0.34-0.63	0.856	-	-	-
bvFTD vs. presymptomatic carriers						
Total score	0.83	0.72-0.95	<0.001	50.5	89.4	78.1
Anger	0.89	0.82-0.96	<0.001	12.5	74.5	90.6
Disgust	0.81	0.71-0.91	<0.001	9.5	85.1	68.8
Fear	0.54	0.32-0.60	0.566	-	-	-
Happiness	0.87	0.79-0.96	<0.001	14.5	78.7	84.4
Sadness	0.59	0.45-0.73	0.176	-	-	-
Surprise	0.62	0.48-0.75	0.069	-	-	-
bvFTD vs. controls						
Total score	0.81	0.69-0.92	<0.001	43.5	95.9	62.5
Anger	0.88	0.81-0.95	<0.001	12.5	73.5	90.6
Disgust	0.72	0.61-0.84	<0.001	7.5	77.6	59.4
Fear	0.54	0.41-0.68	0.517	-	-	-
Happiness	0.88	0.80-0.97	<0.001	14.5	85.7	84.4
Sadness	0.57	0.43-0.72	0.277	-	-	-
Surprise	0.57	0.43-0.71	0.273	-	-	-
Presymptomatic carriers vs. controls						
Total score	0.59	0.48-0.71	0.111	-	-	-
Anger	0.52	0.40-0.63	0.764	-	-	-
Disgust	0.62	0.50-0.73	0.045	11.5	63.3	66.0
Fear	0.51	0.39-0.62	0.918	-	-	-
Happiness	0.50	0.39-0.62	0.947	-	-	-
Sadness	0.56	0.44-0.68	0.317	-	-	-
Surprise	0.58	0.47-0.70	0.174	-	-	-
AD vs. controls						
Total score	0.90	0.82-0.98	<0.001	48.5	83.7	90.6
Anger	0.84	0.75-0.93	<0.001	12.5	73.5	81.2
Disgust	0.82	0.73-0.91	<0.001	9.5	61.2	90.6
Fear	0.57	0.45-0.70	0.284	-	-	-
Happiness	0.87	0.78-0.95	<0.001	14.5	85.7	84.4
Sadness	0.73	0.61-0.84	0.001	4.5	65.3	71.9
Surprise	0.59	0.46-0.73	0.153	-	-	-

Abbreviations: ERT = Emotion Recognition Task; AUC = area under the curve; CI = confidence interval; bvFTD = behavioural variant frontotemporal dementia; AD = Alzheimer's Dementia.

Discussion

This study is the first to examine emotion recognition abilities of dynamically morphed facial expressions in a large cohort of patients with bvFTD and AD, presymptomatic mutation carriers, and cognitively unimpaired control subjects, by means of the ERT. Across all emotions and intensities, patients with bvFTD and AD performed the worst, whereas highest scores were found in the total group of presymptomatic mutation carriers and controls, in which performance did not differ. Overall test performance was highest for anger and happiness, on which patients with bvFTD performed significantly worse than patients with AD. Presymptomatic *C9orf72* mutation carriers performed worse than presymptomatic *GRN* mutation carriers and controls on the 40% intensity level of the emotion disgust. The ERT classified well between patients with bvFTD and controls, patients with AD and controls, but could neither discriminate bvFTD from AD patients, nor presymptomatic mutation carriers from controls. A model that included anger, fear, happiness and surprise correctly classified 93.7% of patients with bvFTD and presymptomatic mutation carriers.

Our finding that patients with bvFTD perform low across all emotions of the ERT is in line with a large number of studies showing significant impairments in emotion recognition in bvFTD (e.g. [10, 14, 29, 30]). Neuroimaging studies have demonstrated a key role for the anterior temporal, orbitofrontal and insular cortex and a number of subcortical areas in emotional processing[31, 32], brain regions known to be heavily affected early in the disease process of bvFTD[33, 34]. Although there is general consensus that emotion recognition is impaired in bvFTD, the literature about the range to which (diffuse vs. selective) and the types of emotions (positive vs. negative) are affected shows mixed findings[35]. In line with, for instance, Keane et al.[36] and Kessels et al.[14], we found evidence for the presence of specific impairments in the recognition of anger, disgust and happiness in our bvFTD patient sample. Regarding the latter, contradicting findings have been found for positive emotions, with some studies showing preservation (e.g.[10, 14, 37, 38]) and others showing deficits (e.g. [36, 39]) in the identification of happy facial expressions. Regardless of relative higher performance in comparison to the other emotions, no ceiling effects for happiness were found in our study – an explanation brought forward by previous studies for the relative preservation of recognition of happiness[10]. We can infer from our findings that atrophy in bvFTD is likely not specific to brain regions involved in negative emotions[10], but also affects brain regions involved in positive emotion processing, explaining global emotion recognition impairments in our bvFTD sample. This notion is in line with previous studies suggesting two different subtypes of bvFTD: a temporal variant with selective deficits in the recognition of negative emotions, and a frontal variant with both impairments in the recognition of negative *and* positive emotions[30, 36, 40]. One explanation for our findings is that our bvFTD patients had a predominant frontal or mixed frontotemporal pattern of atrophy – unfortunately MRI scanning was only performed in a subset of patients, and therefore we could not include neuroimaging data in the present study.

Emotion recognition deficits were also found in our AD group, wherein patients scored lower than presymptomatic mutation carriers and controls on the ERT total score and lower disgust scores than presymptomatic mutation carriers, resulting in overall good classification accuracy between the two groups. These findings are consistent with previous studies demonstrating significant emotion recognition impairments in patients with AD[15, 41, 42], thereby contrasting the notion that impairment of emotion recognition is relatively unique for the frontotemporal dementia spectrum[10]. As the brain areas involved in emotion recognition also tend to be affected in patients with AD[40], this is not a surprising finding. It might explain that, although patients with bvFTD performed worse on the emotions anger and happiness than patients with AD, the differences were smaller than previously reported[10]. Another potential explanation can be found in the commonly atypical presentations of patients with AD we see in our outpatient memory clinic, such as 'frontal' (dysexecutive and behavioural) variants, in which there is potentially more clinical overlap with bvFTD. As most clinical diagnoses were not pathologically confirmed (e.g., using AD biomarkers in CSF), the small possibility remains that patients with frontal AD presentations have been diagnosed as bvFTD, and bvFTD patients with prominent memory deficits as patients with AD, thereby decreasing classification accuracy between the two groups in our study.

The presymptomatic mutation carrier group as a whole did not differ significantly from cognitively unimpaired controls on the ERT total score and emotion subscores. Prior research in presymptomatic familial FTD so far has been scarce, with only a few studies investigating social cognition in *MAPT*[11, 43, 44] and *GRN*[11, 43] mutation carriers. In our previous study in the FTD-RisC cohort, we demonstrated longitudinal presymptomatic decline in emotion recognition (by means of the Ekman Faces test) in *MAPT* mutation carriers and in theory of mind (by means of the Happé cartoons test) in *GRN* mutation carriers[11]. Direct comparison to this study is – however – complicated, as different statistical methods (e.g., a cross-sectional approach in this study vs. longitudinal modelling, and using estimated years to symptom onset (EYO) in the previous study) and instruments were used. The same goes for the study by Cheran et al.[44], in which mostly observer-based measures of social cognition were employed. As a next step, it will be interesting to explore the potential of the ERT in mutation carriers closer to overt disease ('converters')[45] than the presymptomatic mutation carriers investigated in this study, allowing us to further explore emotion recognition deficits in early-stage FTD. Our study is the first to demonstrate emotion recognition deficits at the lowest emotional intensity in presymptomatic *C9orf72* mutation carriers. It could be hypothesized that this is related to early changes in socio-emotional cognition linked to the selective vulnerability and loss of von Economo neurons, which is specifically characteristic of bvFTD due to *C9orf72*[46]. We did not find differences on the ERT between bvFTD patients carrying the *C9orf72* mutation and sporadic or concomitant ALS bvFTD patients. This is in line with previous research, demonstrating that – although there can be some clinical heterogeneity – the cognitive profiles between respectively *C9orf72*-bvFTD and sporadic bvFTD[47, 48] and between sporadic

bvFTD and FTD-ALS[49] are remarkably similar. This strengthens our idea of bvFTD as a disease spectrum, though with common deficits in social cognition.

We find large differences in emotion subscores regardless of clinical status, with relatively high scores for anger and happiness, low scores for fear, intermediate scores for surprise, and more variable scores for disgust and sadness. The overall high anger and happiness scores, and low fear scores are consistent with the results from Kessels et al.[14], and are most likely the result of task difficulty (i.e. the recognition of fearful expressions is regarded as difficult, even by cognitively unimpaired controls)[13], whereas variability in subscores could be related to the ambiguity of some items (i.e. happiness and anger are more uniformly portrayed than disgust and surprise, specifically at lower intensities). Near-ceiling performances were found for happiness above 60% intensity in presymptomatic mutation carriers and controls. This preservation could stem from the statistical artefact of only having one positive emotion to choose from when using the six basic emotions, whereas the recognition of negative emotions is more difficult as one has more answer choices (e.g., fear, sadness, anger, disgust)[35]. In contrast to studies finding ceiling effects in bvFTD using static emotions[10, 29], use of the ERT which includes presentation of emotional morphs at lower intensities, results in small deficits in the presymptomatic stage of *C9orf72*-FTD, underlining the importance of using more sensitive cognitive tasks to improve early diagnosis. This is further corroborated by our findings of increasing task performance with higher emotional intensity, and better discrimination between groups at the lowest than at the highest emotional intensity, where the latter condition resembles the full-blown intensity used in static paradigms.

Key strengths of our study constitute our large groups of presymptomatic mutation carriers from *MAPT*, *GRN* and *C9orf72* families, patients with bvFTD and AD, and controls. Although the ERT has been investigated in a small convenience sample of bvFTD[14], this study is the first to make the direct comparison between patients with AD and bvFTD, and to investigate the presymptomatic phase of FTD. Our results should be replicated in our own longitudinal as well as larger international cohorts, such as GENFI[50], allowing us to draw firmer conclusions with respect to emotion recognition deficits in early-stage FTD. The use of patient cohorts from three different centres may have potentially introduced some heterogeneity into our patient samples, although rerunning our analyses using centre as additional covariate did not change our results significantly. Directions for future research entail increasing and expanding group samples, and including MCI-AD and PPA patients. Moreover, investigating neuroimaging as well as cognitive correlates could increase our insight into the erosion of neural networks thought to underlie behavioural and emotional changes in early-stage FTD. Lastly, it would be interesting to explore a fuller range of emotions than the basic six investigated here, for instance self-conscious emotions (e.g., embarrassment, shame, guilt, contempt) that are thought to be particularly important for effective social functioning[35], and to investigate more modalities than visual perception alone along higher hierarchical

levels of social cognition, in order to get a full understanding of changes in conversion from presymptomatic to symptomatic stages of FTD.

Conclusion

Our study demonstrates the presence of emotion recognition deficits of morphed facial expressions by means of the ERT in patients with bvFTD and AD, but not in cognitively unimpaired controls or presymptomatic FTD mutation carriers, apart from minor deficits in recognizing anger at the lowest emotional intensity in *C9orf72* mutation carriers. The ERT classified well between patients with bvFTD and controls/presymptomatic mutation carriers, patients with AD and controls/presymptomatic mutation carriers, but not between patients with bvFTD and AD nor presymptomatic mutation carriers and controls. Our results demonstrate clear emotion recognition deficits in bvFTD and AD patients, and points towards the presence of subtle changes in facial emotion recognition in presymptomatic FTD due to the *C9orf72* mutation. This highlights the importance of incorporating dynamic emotion recognition paradigms such as the ERT into the standard neuropsychological assessment for early differential diagnosis in dementia and as potential clinical endpoints in upcoming therapeutic trials for FTD and AD.

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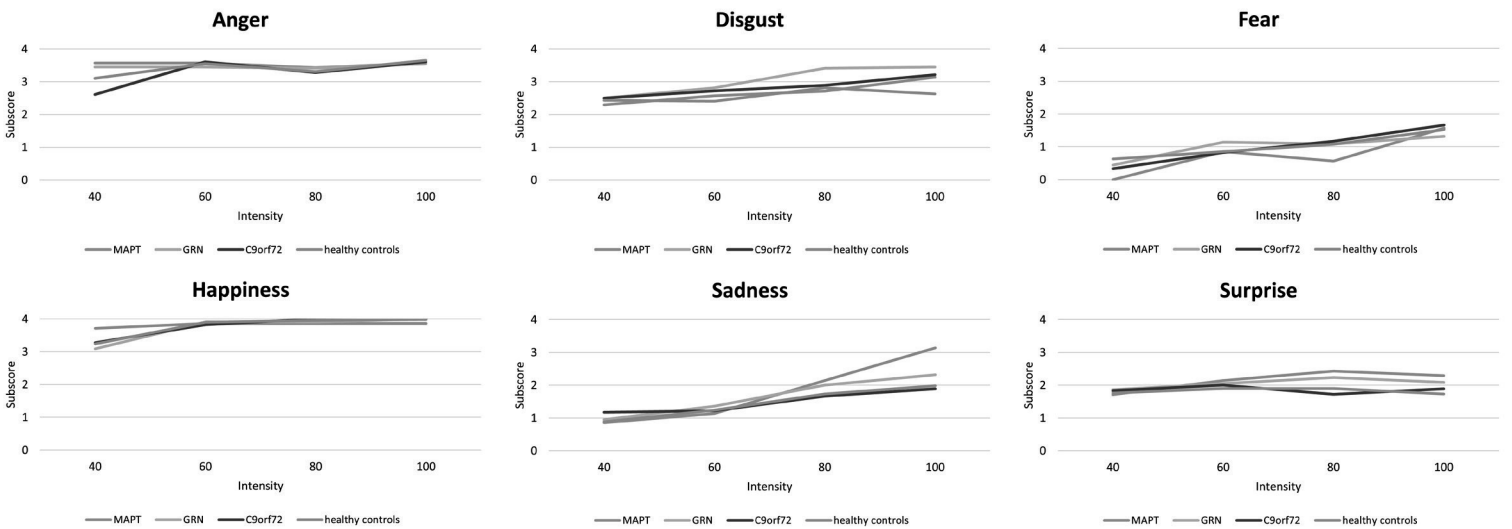
Supplementary file 1: Tables and Figures

Supplementary Table 1. ERT total and subscores of sporadic bvFTD patients, bvFTD patients carrying the *C9orf72* mutation, and bvFTD patients with concomitant ALS.

	Sporadic bvFTD (n=21)	*C9orf72*-bvFTD (n=6)	bvFTD with concomitant ALS (n=5)	Test statistics	
Total score	36.9 ± 7.9	38.5 ± 10.2	31.6 ± 3.6	F(2,0.588) = 3.14	p=0.567
Anger	8.3 ± 3.6	7.7 ± 6.0	8.6 ± 3.0	H(2) = 0.018	p=0.991
Disgust	7.8 ± 4.5	6.2 ± 2.7	3.8 ± 4.4	H(2) = 3.832	p=0.147
Fear	7.4 ± 6.0	2.5 ± 1.6	2.0 ± 1.0	H(2) = 4.269	p=0.118
Happiness	8.2 ± 6.1	12.8 ± 1.3	11.2 ± 4.6	H(2) = 1.901	p=0.386
Sadness	7.0 ± 4.8	3.3 ± 2.3	2.4 ± 2.5	H(2) = 4.878	p=0.087
Surprise	8.1 ± 4.3	6.0 ± 2.9	3.6 ± 2.2	H(2) = 5.752	p=0.056

Values indicate: mean ± standard deviation. Abbreviations: ERT = Emotion Recognition Test; bvFTD = behavioural variant frontotemporal dementia; *C9orf72* = Chromosome 9 open reading frame 72; ALS = amyotrophic lateral sclerosis. Data were analysed using one-way analysis of variance (ANOVA) for normally distributed data (F-statistic), or Kruskal-Wallis tests for non-normally (nonparametric) data (H-statistic).

Supplementary Figure 1. Mean performance (y-axis, number correctly identified emotions = max 4) of presymptomatic FTD mutation carriers with an *MAPT* mutation (light blue), *GRN* mutation (light green), or *C9orf72* repeat expansion (dark blue) and cognitively unimpaired controls (grey) for the six different emotions across the emotional intensities (x-axis).



CHAPTER 4

Memory impairment in frontotemporal dementia

CHAPTER 4.1

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

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Abstract

Objective: A meta-analysis of the extent, nature and pattern of memory performance in behavioral variant frontotemporal dementia (bvFTD). Multiple observational studies have challenged the relative sparing of memory in bvFTD as stated in the current diagnostic criteria.

Methods: We performed a meta-analytic review covering the period 1967–February 2017 of case-control studies on episodic memory in bvFTD *versus* control participants (16 studies, 383 patients, 603 control participants), and patients with bvFTD *versus* 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*.

Results: 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.

Conclusions: 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]. Behavioral 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[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 and colleagues[25] showed lower perfusion in the right temporal lobe in amnesic patients with FTD compared to non-amnesic patients with FTD[25]. 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. 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 1 and 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[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 single 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 and colleagues[36] included an Italian and Australian bvFTD

patient sample; these were included as two separate studies. Wicklund and colleagues[37] and Lemos and colleagues[38] reported standard errors instead of standard deviations. We calculated the standard deviations based on the known confidence intervals and degrees of freedom.

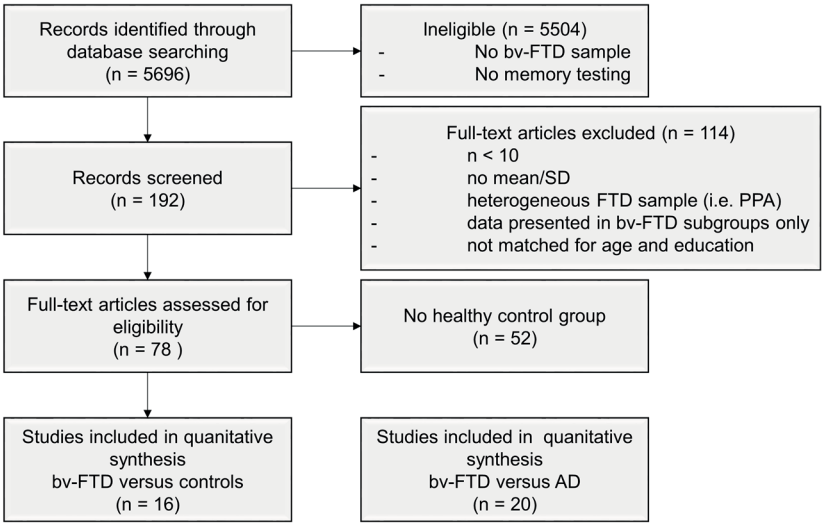
The meta-analysis was performed in four consecutive steps. First, the overall effect size for patients with bvFTD *versus* control participants was calculated. Second, overall effect sizes for the four identified types of memory processes were calculated and compared between patients with bvFTD and controls. Third, the overall effect size for patients with bvFTD *versus* 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.[7] or Neary et al.[39]), and type of diagnosis (possible, probable, definite, mixed or unknown) as categorical moderators. Rascovsky et al.[7] revised the publication of consensus criteria by Neary et al.[39] due to limitations. Among these were the ambiguity of behavioral 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 1). Of these, 10 were included in both analyses as they included both a healthy control group and patients with AD. Tables 1 and 2 display the characteristics of these studies.

Figure 1. Flow chart illustrating the process of inclusion of eligible studies and reasons for exclusion.



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 1). The overall weighed effect size for patients *versus* controls was –1.10 [95% CI –1.23 to –0.95]; % overlap = 41.1 (Figure 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]; % 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]; % 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]; % 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

Table 1. Study characteristics of studies included in the meta-analysis: bvFTD versus control participants.

	n		Age		Gender (% female)		Education (yrs)		MMSE		Dementia diagnosis	Memory measurements
study	F	C	F	C	F	C	F	C	F	C		
Mandelli et al.[40]	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. (2011)	CVLT-SF, RCFT, digit span
Balconi et al.[41]	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)	Neary et al. (1998)	logical memory, RCFT
Hardy et al.[42]	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. (2011)	RMT F/W, digit span
Tu et al.[43]	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. (2011)	RAVLT, RCFT, digit span
Smits et al.[44]	20	112	63 (8)	61 (8)	49	56	5.0 (1.3)*	5.5 (1.1)*	26 (3)	28 (1)	Rascovsky et al. (2011)	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, digit span, 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.[45]	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]–Italian	15	28	65.7 (8.6)	68.5 (6.7)	40	61	10.3 (3.2)	11.4 (2.8)	26.6 (3.4)	N.S.	Neary et al.[39]	RAVLT
Ricci et al.[36]–Australian	11	15	59.8 (9)	60.2 (5.8)	55	60	12.6 (2.4)	13.5 (3.0)	26.5 (2.3)	N.S.	Neary et al.[39]	RAVLT
Stopford et al.[46]	26	26	64 (6)	59 (13.5)	50	69	N.S.	N.S.	23 (6)	N.S.	Neary et al.[39]	logical memory, digit span
Giovagnoli et al.[47]	40	91	61.1 (10.7)	62.3 (10)	38	55	8.9 (4.1)	11.3 (4.4)	N.S	N.S.	Neary et al.[39]	the short story, RCFT, digit span, Corsi cube span
Piolino et al.[48]	13	21	67.2 (7.9)	69.9 (8.6)	N.S.	N.S.	N.S.	N.S.	24.8 (4)	N.S.	Neary et al.[39]	Grober & Buscke Test, digit span
Torralva et al.[49]	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]	logical memory, digit span
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)	N.S.	N.S.	12.4 (1.8)	12.8 (2.2)	27.1 (2.0)	N.S.	Neary et al.[39]	digit span, logical memory, RCFT
Gregory et al.[50]	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)	Neary et al.[39]	digit span, logical memory RCFT

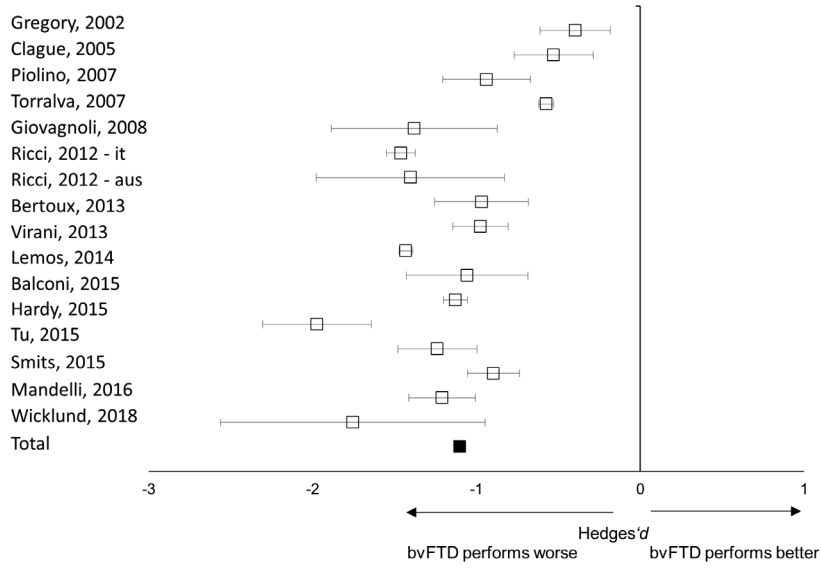
Abbreviations: F = bvFTD; C = control participants; MMSE = Mini Mental State Examination; CVLT-SF = California Verbal Learning Test – Short version; RCFT = Rey Complex Figure Test; RMT F/W = Recognition Memory Test Words/Faces; RAVLT + Rey Auditory Verbal Learning Test; VAT = Visual Association Test; FCSRT = Free and Cued Selective Reminding Test; BVMT-R = Brief Visuospatial Memory Test- Revised; WMS-R = Wechsler Memory Scale – Re vised; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; N.S. = not specified. *According to the Verhage system.

Table 2. Study characteristics of studies included in the meta-analysis: bvFTD versus AD.

	n		Age		Gender (% female)		Education (yrs)		MMSE		Dementia diagnosis		Memory measurements
study	F	A	F	A	F	A	F	A	F	A	F	A	
Balconi et al.[41]	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	logical memory, RCFT
Smits et al.[44]	20	199	63 (8)	65 (8)	49	44	5.0 (1.3)*	4.9 (1.2)*	26 (3)	22 (4)	Rascovsky et al.[7]	NINCDS-ADRDA	RAVLT, VAT
Tu et al.[43]	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, digit span
Barsuglia et al.[56]	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	Digit span, logical memory 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, digit span, BVMT-R
Perri et al.[51]	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]	N.S.	FCSRT
Ricci et al.[36]–Italian	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]–Australian	11	17	59.8 (9)	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.[52]	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]	N.S.	digit span, CERAD
Giovagnoli et al.[47]	40	77	61.1 (10.7)	65.5 (9.9)	38	63	8.9 (4.1)	8.9 (4.9)	N.S.	N.S.	Neary et al. [39]	NINCDS-ADRDA	the short story, RCFT, digit span, Corsi cube span
Heidler-Gary et al.[53]	25	30	64.8 (9.9)	72.6 (8.8)	N.S.	N.S.	N.S.	N.S.	N.S.	18.9 (5.4)	Neary et al. [39]	NINCDS-ADRDA	RAVLT
Luzzi et al.[54]	11	14	64 (7)	71 (8)	27	50	10 (2)	10(4)	24 (6)	24 (2)	Neary et al. [39]	NINCDS-ADRDA	Digit span, Hopkins test, RAVLT, RCFT
Castiglioni et al.[55]	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)	Neary et al. [39]	NINCDS-ADRDA	Story memory, RCFT, Corsi span, digit span
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)	Neary et al. [39]	NINCDS-ADRDA	WMS-R, CERAD
Clague et al.[35]	11	14	60.3 (6.9)	63.8 (6.9)	N.S.	N.S.	12.4 (1.8)	11 (1.2)	27.1 (2.0)	24.5 (2)	Neary et al. [39]	NINCDS-ADRDA	digit span, logical memory, 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
Gregory et al.[50]	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	digit span, logical memory RCFT
Siri et al.[57]	14	14	74.8 (7.3)	69.6 (7.4)	N.S.	N.S.	5.3 (2.8)	7.2 (2.9)	17.8 (4.2)	20.3 (5.8)	Neary et al. [39]	NINCDS-ADRDA	digit span, Corsi block span story memory, RCFT
Binetti et al.[58]	44	121	66.9 (9.2)	70.6 (8.5)	41	62	14.1 (3.5)	13.1 (3.5)	N.S.	N.S.	DSM-IV, ICD-10	N.S.	story memory, figure recall, BVRT
Gregory et al.[12]	12	12	63,6	71.1	N.S.	N.S.	11.7	9,9	25.3	24.1	Neary et al. [39]	NINCDS-ADRDA	Story memory, RCFT, Corsi block span, digit span

Abbreviations: F = bvFTD; A = AD; MMSE = Mini Mental State Examination; CVLT-SF = California Verbal Learning Test – Short version; 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; N.S. = not specified. *According to the Verhage system.

Figure 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 for controls.



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).

Memory performance in patients with bvFTD versus AD

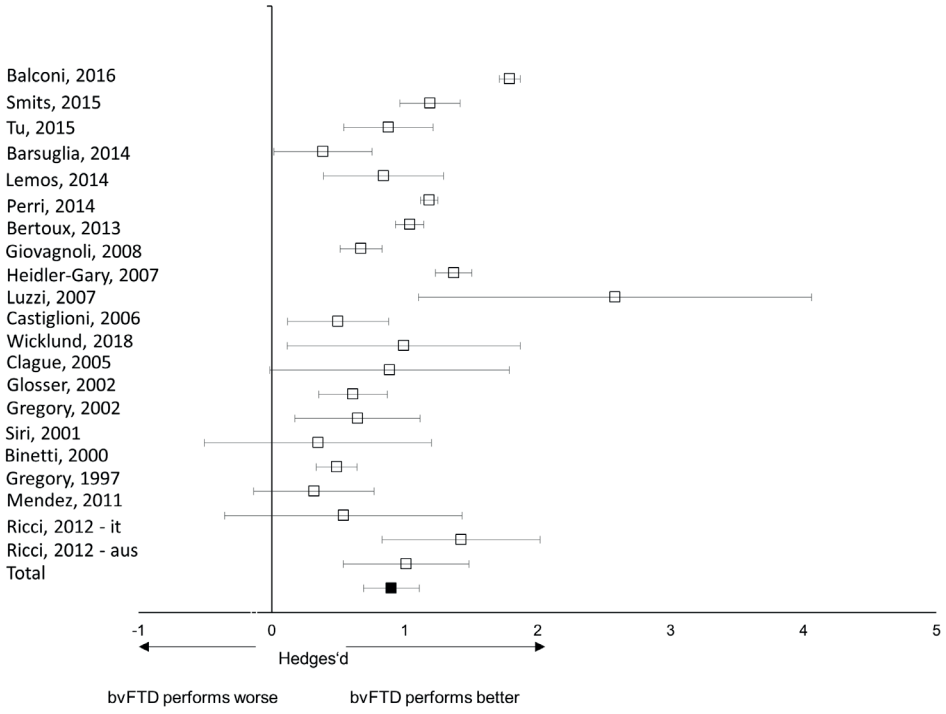
Overall memory performance in bvFTD vs AD

A total of 452 patients with bvFTD and 874 with AD were included in the meta-analysis (Table 2). The overall weighed effect size for bvFTD *versus* 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 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]; % 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

Figure 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.



= 37.8. 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 were 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 versus 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 or Neary et al., 1998) (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 versus 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, Neary et al., 1998 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. [59, 60]), and those showing that patients with AD experience even greater memory problems (e.g. [13, 16, 19, 61-68]) with delayed memory testing being the most discriminative (e.g. [19, 69]). However, our results contrast with those of other studies reporting similar memory impairment in patients with bvFTD and AD (e.g. [10, 70, 71]). 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. [72]). Others theorize a selective retrieval disorder 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, 73]. 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[74]. 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.[75] 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[76-78]. However, Mahoney et al.[79] 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.[80] 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. [81, 82]).

Strengths of our study include the use of a meta-analytical approach that provides a weighted estimate of the magnitude of effects. 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, 83]). 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[84, 85], 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 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 4.2

Episodic memory impairment in genetic frontotemporal dementia: a GENFI study

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Abstract

Introduction: We aimed to assess episodic memory in genetic frontotemporal dementia (FTD) with the Free and Cued Selective Reminding Test (FCSRT).

Methods: The FCSRT was administered in 417 presymptomatic and symptomatic mutation carriers (181 *C9orf72*, 163 *GRN* and 73 *MAPT*) and 290 controls. Group differences and correlations with other neuropsychological tests were examined. We performed voxel-based morphometry to investigate the underlying neural substrates of the FCSRT.

Results: All symptomatic mutation carrier groups and presymptomatic *MAPT* mutation carriers performed significantly worse on all FCSRT scores compared to controls. In the presymptomatic *C9orf72* group, deficits were found on all scores except for the delayed total recall task, whilst no deficits were found in presymptomatic *GRN* mutation carriers. Performance on the FCSRT correlated with executive function, particularly in *C9orf72* mutation carriers, but also with memory and naming tasks in the *MAPT* group. FCSRT performance also correlated with grey matter volumes of frontal, temporal and subcortical regions in *C9orf72* and *GRN*, but mainly temporal areas in *MAPT* mutation carriers.

Discussion: The FCSRT detects presymptomatic deficits in *C9orf72*- and *MAPT*-associated FTD and provides important insight into the underlying cause of memory impairment in different forms of FTD.

Background

Memory deficits are often considered indicative of the onset of Alzheimer's dementia (AD), but an increasing number of studies have reported episodic memory impairment in the frontotemporal dementia (FTD)[1, 2] spectrum as well, even at initial presentation[3]. There is still ongoing discussion on what underlies episodic memory impairment in FTD, with some studies suggesting that it may be a consequence of poor organization and a lack of efficient learning and retrieval strategies (i.e. due to a dysexecutive syndrome caused by (pre)frontal cortical damage) and others suggesting that it is due to "true" consolidation problems, as is the case in AD, as a result of damage to mesiotemporal, including hippocampal, structures of the brain[4-7].

Delineating the contribution of executive/frontal and memory/hippocampal functioning to memory impairment can be performed by using memory tests that separate learning, storage and retrieval processes. The Free and Cued Selective Reminding Test (FCSRT) was designed specifically for this purpose[8]. The FCSRT uses semantic cues to, firstly, test if words were effectively encoded, and, secondly, facilitate subsequent cued recall of words that were not spontaneously retrieved during free recall. Specifically, the performance on cued recall is assumed to provide a measure of "true" memory consolidation, while performance on free recall also relies on executive functioning as it requires people to apply an effective learning and retrieval strategy[5]. Some studies have shown that this paradigm is effective in differentiating behavioural variant FTD (bvFTD) from AD[6, 7, 9-12], while others have failed to show this distinction, or showed that the FTD sample could be split, with approximately half of the patients performing as poorly as patients with AD and the other half performing similarly to healthy controls[6, 11, 13]. Indeed, several neuroimaging studies have shown differences in temporal lobe involvement between amnesic and non-amnesic patients with FTD[4, 11, 14, 15], underlining the pathological and clinical heterogeneity of this disease spectrum.

In approximately 30% of cases, FTD is caused by genetic mutations in progranulin [*GRN*], microtubule-associated protein tau [*MAPT*], and chromosome 9 open reading frame 72 [*C9orf72*][16]. *GRN* mutations often lead to an asymmetrical pattern of atrophy in the frontal, temporal and parietal lobes, whereas *MAPT* mutations show localized temporal lobe involvement[17]. The atrophy associated with the *C9orf72* repeat expansion is rather diffuse with degeneration of the frontal and temporal cortices but also involvement of the subcortical and cerebellar regions[18]. Memory impairment has been described in *GRN*[19, 20] and *C9orf72*[18] mutation carriers as a prominent symptom of later disease stages, whereas in *MAPT* mutation carriers memory decline has been previously described in the presymptomatic stage[21]. A recent study has shown that patients with a *GRN* mutation or *C9orf72* repeat expansion were impaired on immediate recall, whereas *MAPT* mutation carriers were impaired on both immediate and delayed recall. According to the classic view, this suggests a "pure"

memory impairment due to temporal involvement in *MAPT*, whereas the immediate recall impairment in *C9orf72* and *GRN* mutation carriers are potentially a consequence of prefrontal and thus executive dysfunction, with relatively spared delayed recall performance[22]. However, systematic investigations of episodic memory performance using paradigms that can differentiate between primary executive versus true amnestic mechanisms have not been performed in detail in genetic FTD, and in particular, not in the presymptomatic stage. Clinical trials targeting specific pathologies are currently being developed and implemented for both early symptomatic and presymptomatic mutation carriers and it is important to identify gene-specific sensitive outcome measures for signaling disease onset, tracking disease progression and measuring potential treatment effects at an early disease stage.

The aim of this study is therefore to assess memory performance in a large cohort of genetic FTD families by means of the FCSRT and correlate performance with grey matter volume using voxel-based morphometry. We compared both presymptomatic individuals and those with symptomatic FTD with pathogenic mutations in *MAPT*, *GRN* or *C9orf72* to a control group of mutation-negative individuals from the same families. Data was collected within the Genetic FTD Initiative (GENFI), an international genetic FTD cohort study aimed at developing novel markers of disease onset and progression[23].

Methods

Participants

Baseline data was included from the fifth GENFI data freeze in which participants from confirmed genetic FTD families were recruited between 30th January 2012 and 31th May 2019 in 24 centres. The FCSRT was administered in a total of 417 mutation carriers (181 *C9orf72*, 163 *GRN* and 73 *MAPT*) and 290 mutation negative controls. Of the mutation carrier group 96 participants were symptomatic, fulfilling diagnostic criteria for bvFTD[1] (44 *C9orf72*, 19 *GRN*, 17 *MAPT*), non-fluent variant primary progressive aphasia (nfvPPA)[2] (1 *C9orf72*, 8 *GRN*) or FTD with amyotrophic lateral sclerosis (FTD-ALS)[24] (4 *C9orf72*). The presymptomatic mutation carrier group did not fulfill these diagnostic criteria, had a Clinical Dementia Rating Scale plus Behavioral and Language Domains from the National Alzheimer's Coordinating Center (NACC) FTLD module (CDR® plus NACC FTLD) ≤0.5[25] and consisted of 129 *C9orf72* repeat expansion, 136 *GRN* and 56 *MAPT* mutation carriers. There were 352 mutation carriers with an FCSRT at baseline that also had a structural (T1-weighted) MRI brain scan (148 *C9orf72*, 139 *GRN* and 65 *MAPT* mutation carriers). All GENFI sites had local ethical approval for the study and all participants gave written informed consent. The study was in accordance with the Declaration of Helsinki.

Procedure

We administered the Mini-Mental State Examination (MMSE)[26] to measure global cognitive functioning and determined clinical status by means of a structured clinical interview, including the CDR® plus NACC FTLD[25], with the participant and a knowledgeable informant. The FCSRT was administered as part of the GENFI neuropsychological test battery[23]. From this test battery we also collected data on visual episodic memory (Benson figure recall), language (30-item Boston Naming Test (BNT[27]) and category fluency[27]) and executive function tests (Trail Making Test part B (TMT-B[28]) and the Delis–Kaplan Executive Function System Color-Word Interference Test (D-KEFS Color-Word) card III[29]) to correlate with FCSRT performance. The test battery was administered in the same order to all participants and no semantic tests were administered during the delay phase of the FCSRT.

Free and Cued Selective Reminding Test (FCSRT)

The FCSRT consists of 16 words that need to be learned and are presented four at a time on successive cards. Each word belongs to a different semantic category (e.g. herring in the semantic category "fish"). The first presentation is aimed at inducing semantic encoding, for which subjects are asked to read aloud the word corresponding to a specific semantic category (e.g., "what is the name of the fish?"). After all four items are named, the card is removed and the test administrator asks for immediate recall of the four words in response to the semantic cue. This procedure of encoding is repeated a maximum of three times, until the participant is able to recall all four words or has completed the third round, after which the following card is administered and this encoding process is then repeated for the second, third and fourth cards. Subsequently, three successive trials of free recall are administered, where participants are asked to remember as many of the 16 words as possible within two minutes. Each free recall trial is followed by a selective semantic cuing of the words that are not spontaneously recalled. After 20-30 minutes, a delayed free recall and then cued recall of words not spontaneously recalled is administered. This results in four scores to be analyzed: immediate free recall (max. score = 48), immediate total recall (free+cued; max. score = 48), delayed free recall (max. score = 16), delayed total recall (delayed free+cued; max. score = 16). The test was administered across the GENFI centres in 8 different languages: English, Dutch, Swedish, Spanish, Italian, Portuguese, German and French.

Structural brain imaging and voxel-based morphometry

Participants underwent volumetric T1-weighted magnetic resonance imaging (MRI) according to the GENFI imaging protocol on a 3T scanner. Different scanners were used across GENFI sites: Siemens Trio 3T (n=105), Siemens Skyra 3T (n=55), Siemens Prisma 3T (n=57) and Philips Achieva 3T (n=101). All scans underwent extensive visual quality check and those with artefacts or incidental brain abnormalities unrelated to FTD were excluded from analysis. Voxel-based morphometry (VBM) was performed using Statistical Parametric Mapping (SPM) 12 software, version 6225 (www.fil.ion.ucl.ac.uk/spm) running under Matlab R2018a (Mathworks, USA).

T1-weighted images were normalized and segmented into grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) probability maps, by using standard procedures and the fast-diffeomorphic image registration algorithm (DARTEL)30. GM segmentations were affine transformed into the Montreal Neurological Institute (MNI) space, modulated and smoothed using a Gaussian kernel with 6mm full-width at half maximum. Finally, a mask was applied as reported in Ridgway et al, 200931. All segmentations were visually checked at each stage. Total intracranial volume (TIV) (i.e. GM+WM+CSF) was calculated using SPM 1232.

Statistical analysis

Statistical analyses were performed using STATA version 14 (Texas, USA). The significance level was set at $p<0.05$ (2-tailed) across all comparisons. We compared demographic data between groups with linear regression models except for sex which was compared using a chi-square test.

Performance in controls was assessed by calculating the cumulative frequency of test scores (and therefore percentile scores) as well as investigating the effect of age (Spearman rank correlation), years of education (Spearman rank correlation), sex (Mann Whitney U test), and the language in which the test was administered (Kruskal-Wallis H test).

Mean differences on each FCSRT score between groups were analyzed with mixed models correcting for age, years of education, sex, language in which the test was administered, and family clustering with 95% bias-corrected bootstrapped confidence intervals with 1000s repetitions (due to non-normality).

Spearman rank correlations were used to investigate the association of each FCSRT test score with the Benson figure recall, BNT, category fluency, TMT-B and D-KEFS Color-Word tasks.

The relationship of performance on each FCSRT test score with GM density was explored in each mutation carrier (presymptomatic and symptomatic combined) group within the VBM analysis using multiple regression models. Age, sex, scanner and TIV were included as covariates. All comparisons were corrected for a Family-Wise Error rate of 0.05.

Results

Demographic data

Demographic data are shown in Table 1. There was a significant difference in sex between the groups, $X^2(6, N=707) = 16.8$, $p=0.010$, with more females in the presymptomatic and control group and more males in the symptomatic groups. Symptomatic groups were significantly older than controls and presymptomatic groups (all $p<0.001$). In addition, presymptomatic

MAPT mutation carriers were significantly younger than controls (p<0.001), presymptomatic *C9orf72* (p=0.009) and *GRN* mutation carriers (p=0.001). Symptomatic *C9orf72* and *GRN* mutation carriers had significantly lower years of education than controls and presymptomatic *C9orf72, GRN* and *MAPT* mutation carriers (all p<0.013). All symptomatic mutation carriers performed significantly lower on the MMSE and had higher CDR® plus NACC FTLD global scores than controls and presymptomatic *C9orf72, GRN* and *MAPT* mutation carriers (all p<0.005). In addition, symptomatic *GRN* mutation carriers had lower MMSE scores than symptomatic *C9orf72* and *MAPT* mutation carriers (both p<0.003) and symptomatic *C9orf72* mutation carriers had higher CDR® plus NACC FTLD global scores than symptomatic *MAPT* mutation carriers (p=0.028).

Table 1. Demographic information and FCSRT scores.

	C9orf72		***GRN***		***MAPT***		**Controls**
	PS	**S**	**PS**	**S**	**PS**	**S**	**-**
n	129	52	136	27	56	17	290
Age, y [range]	44.6±11.1 [20.1-69.34]	62.0±7.6 [39.4-74.5]	46.09±12.4 [20.2-75.5]	60.8±7.9 [49.2-78.5]	39.8±10.5 [20.6-74.1]	58.6±6.8 [44.0-78.9]	45.9±12.6 [19.5-82.3]
Sex ratio f:m	77:52	19:33	84:52	10:17	34:22	7:10	167:123
Education, y	14.4±3.0	12.8±3.3	14.7±3.5	12.0±3.5	14.5±3.0	14.5±3.9	14.6±3.4
MMSE	29.0±2.1	25.3±3.9	28.7±4.6	22.9±6.8	29.5±0.9	26.2±3.1	29.3±2.1
CDR® plus NACC FTLD global	0.1±0.3	1.9±1.0	0.1±0.3	1.8±0.9	0.1±0.3	1.6±0.9	0.1±0.2
FCSRT immediate free recall	28.8±7.1	13.9±8.4	31.2±6.2	13.8±12.5	31.6±7.0	12.8±10.2	31.5±6.8
FCSRT immediate total recall	44.4±5.4	34.2±13.1	45.8±2.5	26.4±17.5	45.3±4.6	29.7±13.1	45.7±3.5
FCSRT delayed free recall	11.0±2.9	4.7±3.5	11.9±2.8	5.2±4.7	12.0±3.1	4.5±4.7	12.0±3.1
FCSRT delayed total recall	15.3±1.4	11.5±4.7	15.5±0.9	10.0±6.3	15.3±1.8	10.3±4.9	15.5±1.2

All data is shown as mean ± standard deviation. Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; PS = presymptomatic; S = symptomatic; MMSE = Mini-Mental State Examination; CDR® plus NACC FTLD global = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration global score; FCSRT = Free and Cued Selective Reminding Test.

Normative data in the control population

Cumulative frequencies (Supplementary Table 1), percentile scores (Supplementary Table 2) and mean score stratified by age group and sex (Supplementary Table 3) for mutation negative controls can be found in the Appendix. 5th percentile cut-off scores were 19 (immediate free), 40 (immediate total), 7 (delayed free) and 13 (delayed total) for each of the FCSRT scores (Supplementary Table 2). There was a weak negative correlation with age (r between -0.14 and -0.36) and a weak positive correlation with years of education (r between 0.16 and 0.22) for each FCSRT score. Females performed better than males on all parts of the FCSRT:

immediate free recall (z=3.6, p<0.001), immediate total recall (z=2.6, p=0.010), delayed free recall (z=4.4, p<0.001), and delayed total recall (z=3.1, p=0.002). There was also a significant effect of language on FCSRT immediate free recall (H(7) =24.3, p=0.001), immediate total recall (H(7)=26.6, p<0.001), and delayed free recall (H(7)=25.9, p<0.001) but not delayed total recall (H(7)=11.3, p=0.127).

Group comparisons

All three symptomatic mutation carrier groups performed significantly worse than controls on FCSRT immediate free recall, immediate total recall, delayed free recall and delayed total recall (all p≤0.001) (Table 1 and 2). In addition, symptomatic *GRN* mutation carriers performed significantly worse on the FCSRT immediate total score than symptomatic *C9orf72* repeat expansion carriers (p=0.047). All symptomatic mutation carriers performed significantly worse than presymptomatic mutation carriers (all p≤0.004).

Presymptomatic *C9orf72* repeat expansion carriers performed significantly worse on FCSRT immediate free recall (p<0.001), immediate total recall (p=0.010) and delayed free recall (p<0.001) than controls, but not delayed total recall (p=0.066) (Table 1 and 2). Presymptomatic *MAPT* mutation carriers had significantly lower FCSRT immediate free recall (p=0.005), immediate total recall (p=0.002), delayed free recall (p=0.024) and delayed total recall (p=0.011) scores than controls. In addition, presymptomatic *C9orf72* and *MAPT* mutation carriers performed significantly worse than presymptomatic *GRN* mutation carriers on all four FCSRT test scores (all p<0.017).

Table 2. The adjusted mean differences between groups and 95% confidence intervals for all four FCSRT measures.

		FCSRT immediate free recall											
		C9orf72				***GRN***				***MAPT***			
		PS		S		PS		S		PS		S	
Controls		**-2.9**		**-12.5**		0.40		**-11.7**		**-2.4**		**-15.7**	
		-4.1	**-1.7**	**-14.8**	**-10.2**	-0.8	1.6	**-16.3**	**-7.1**	**-4.0**	**-0.7**	**-20.8**	**-10.6**
C9orf72	PS			**-9.6**		**3.3**		**-8.8**		0.5		**-12.8**	
				-12.0	**-7.2**	**1.8**	**4.8**	**-13.6**	**-4.0**	-1.3	2.3	**-18.0**	**-7.6**
	S					**12.9**		0.8		**10.1**		-3.2	
						10.5	**15.3**	-4.2	5.7	**7.3**	**12.9**	-8.76	2.3
GRN	PS							**-12.1**		**-2.8**		**-16.1**	
								-16.6	**-7.6**	**-4.6**	**-0.9**	**-21.3**	**-10.9**
	S									**9.3**		-4.0	
										4.7	**14.0**	-10.4	2.5
MAPT	PS											**-13.3**	
												-18.4	**-.8.3**

Table 2 continued

		FCSRT immediate total recall											
		C9orf72				***GRN***				***MAPT***			
		PS		S		PS		S		PS		S	
Controls		**-1.3**		**-8.7**		**0.7**		**-16.3**		**-2.1**		**-14.4**	
		-2.3	**-0.3**	**-12.0**	**-5.3**	**0.1**	**1.2**	**-22.8**	**-9.8**	**-3.3**	**-0.8**	**-21.2**	**-7.5**
C9orf72	PS			**-7.4**		**1.9**		**-15.0**		-0.8		**-13.1**	
				-10.8	**-4.0**	**0.8**	**3.1**	**-21.7**	**-8.4**	-2.2	0.7	**-20.0**	**-6.1**
	S					**9.3**		**-7.6**		**6.6**		-5.7	
						5.9	**12.7**	**-15.2**	**-0.1**	**3.0**	**10.2**	-13.6	2.2
GRN	PS							**-17.0**		**-2.7**		**-15.0**	
								-23.5	**-10.4**	**-4.1**	**-1.3**	**-21.9**	**-8.1**
	S									**14.2**		1.9	
										7.7	**20.8**	-7.1	11.0
MAPT	PS											**-12.3**	
												-19.2	**-5.4**
		FCSRT delayed free recall											
		C9orf72				***GRN***				***MAPT***			
		PS		S		PS		S		PS		S	
Controls		**-1.0**		**-5.3**		0.1		**-4.5**		**-0.9**		**-6.4**	
		-1.6	**-0.5**	**-6.3**	**-4.3**	-0.3	0.6	**-6.2**	**-2.8**	**-1.7**	**-0.1**	**-8.7**	**-4.0**
C9orf72	PS			**-4.3**		**1.1**		**-3.5**		0.1		**-5.4**	
				-5.4	**-3.2**	**0.5**	**1.8**	**-5.3**	**-1.7**	-0.8	1.0	**-7.8**	**-3.0**
	S					**5.5**		0.8		**4.4**		-1.0	
						4.4	**6.5**	-1.1	2.7	**3.2**	**5.7**	-3.5	1.5
GRN	PS							**-4.6**		**-1.0**		**-6.5**	
								-6.3	**-3.0**	**-1.9**	**-0.2**	**-8.9**	**-4.1**
	S									**3.6**		-1.9	
										1.8	**5.4**	-4.7	1.0
MAPT	PS											**-5.5**	
												-7.8	**-3.2**
		FCSRT delayed total recall											
		C9orf72				***GRN***				***MAPT***			
		PS		S		PS		S		PS		S	
Controls		-0.3		**-3.1**		0.1		**-4.3**		**-0.7**		**-4.5**	
		-0.6	0.0	**-4.4**	**-1.9**	-0.1	0.4	**-6.7**	**-1.9**	**-1.3**	**-0.2**	**-7.1**	**-1.9**
C9orf72	PS			**-2.8**		**0.4**		**-4.0**		-0.4		**-4.2**	
				-4.1	**-1.5**	**0.1**	**0.8**	**-6.4**	**-1.6**	-1.1	0.2	**-6.8**	**-1.6**
	S					**-3.3**		-1.2		**2.4**		-1.4	
						2.0	**4.5**	-3.9	1.6	**1.1**	**3.8**	-4.2	1.5
GRN	PS							**-4.5**		**-0.9**		**-4.6**	
								-6.8	**-2.1**	**-1.5**	**-0.3**	**-7.2**	**-2.1**
	S									**3.6**		-0.2	
										1.1	**6.1**	-3.6	3.3
MAPT	PS											**-3.8**	
												-6.3	**-1.2**

Values in bold are significant at p<0.05. Values are adjusted for age, years of education, sex and language in which the test was administered. Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; PS = presymptomatic; S = symptomatic; FCSRT = Free and Cued Selective Reminding Test

Association with other neuropsychological tests

Correlation coefficients for each FCSRT score with other neuropsychological tests by genetic group can be seen in Table 3. In the *C9orf72* mutation carriers, the strongest correlations were with the D-KEFS Color-Word task, particularly for the free recall scores, as well as category fluency, with additional significant correlations with the BNT and Benson figure recall, particularly in the symptomatic group. In the *GRN* mutation carriers, the strongest correlations were with TMT-B as well as with the Benson figure recall and BNT for the majority of scores, particularly for the symptomatic group. In the *MAPT* mutation carriers the strongest correlations were with the Benson figure recall (all significant except delayed free recall in the symptomatic group), followed by the BNT (for all scores), with no significant correlations with any of the executive function tasks or category fluency in the symptomatic group.

Table 3. Correlation coefficients between FCSRT scores and other neuropsychological tests in each genetic group.

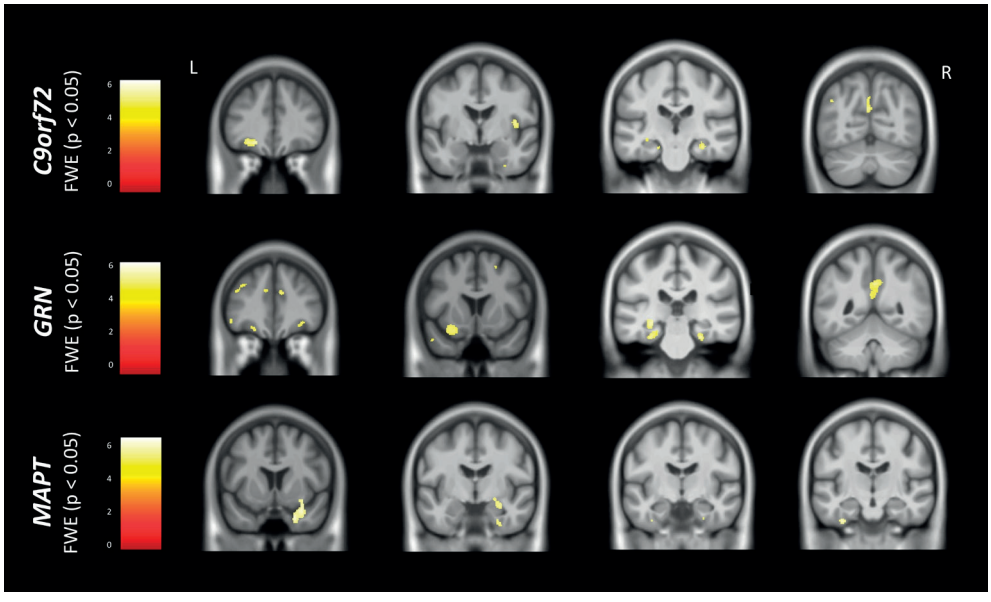
				Benson figure recall	BNT	Category fluency	TMT-B	D-KEFS Color-Word
C9orf72	PS	Immediate	Free	0.14	0.12	0.28**	-0.22*	-0.36***
			Total	0.21*	0.27**	0.30***	-0.22**	-0.30***
		Delayed	Free	0.20*	0.22**	0.28**	-0.26**	-0.41***
			Total	0.23**	0.23**	0.26**	-0.29***	-0.27**
	S	Immediate	Free	0.28	0.49***	0.46**	-0.21	-0.42**
			Total	0.29	0.55***	0.44**	-0.24	-0.28
		Delayed	Free	0.46**	0.47**	0.49***	-0.25	-0.54***
			Total	0.36*	0.56***	0.54***	-0.29	-0.44**
GRN	PS	Immediate	Free	0.27**	0.21*	0.36***	-0.31***	-0.29***
			Total	0.33***	0.26**	0.22**	-0.24**	-0.39***
		Delayed	Free	0.30***	0.26**	0.31***	-0.42***	-0.40***
			Total	0.34***	0.21*	0.24**	-0.21*	-0.19*
	S	Immediate	Free	0.52*	0.41	0.43	-0.50*	0.27
			Total	0.62**	0.53**	0.57*	-0.55*	0.25
		Delayed	Free	0.70**	0.59**	0.39	-0.58**	0.05
			Total	0.45	0.57*	0.56*	-0.51*	-0.03
MAPT	PS	Immediate	Free	0.40**	0.38**	0.38**	-0.49***	-0.52***
			Total	0.45***	0.37**	0.36**	-0.41**	-0.50***
		Delayed	Free	0.44***	0.38**	0.45***	-0.51***	-0.46***
			Total	0.45***	0.37**	0.25	-0.47***	-0.32*
	S	Immediate	Free	0.74***	0.59**	0.39	-0.30	-0.17
			Total	0.70**	0.62**	0.42	-0.31	-0.22
		Delayed	Free	0.48	0.60**	0.35	-0.34	-0.13
			Total	0.76***	0.53*	0.20	-0.31	0.07

Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; BNT = Boston Naming Test; TMT-B = Trail Making Test Part B; PS = presymptomatic; S = symptomatic. *p≤0.05, **p≤0.01, ***p≤0.001

Neuroanatomical correlates of performance on the FCSRT

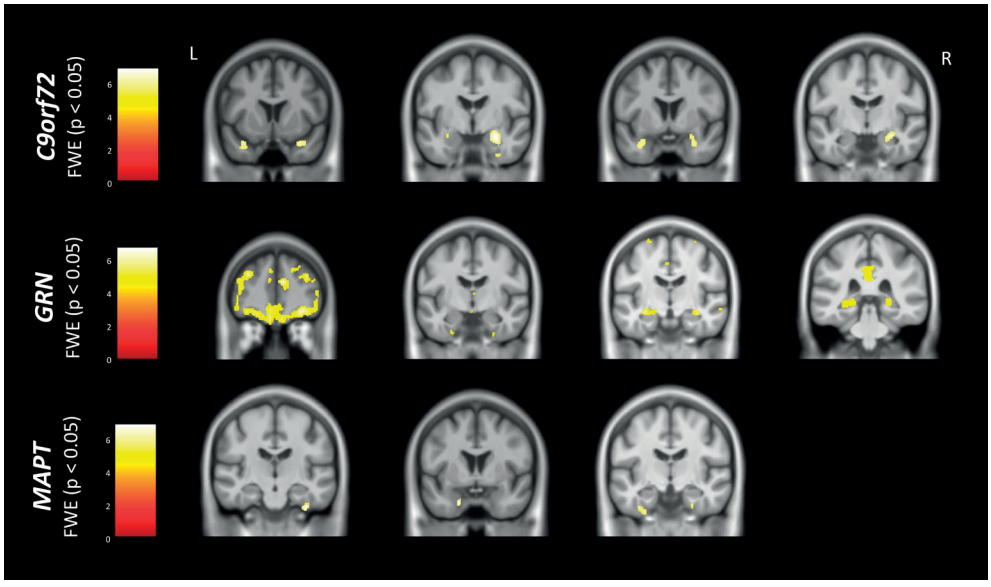
The VBM analyses revealed particular involvement of frontal (orbitofrontal and dorsolateral prefrontal cortices), insula, temporal (particularly medial cortical areas), and parietal (angular gyrus and precuneus) regions as well as the hippocampus in immediate free recall score in *GRN* and *C9orf72* mutation carriers carriers, with additional involvement of the thalamus and amygdala in the latter (Figure 1, Supplementary Table 4). For the immediate total recall score, a similar network was found in *GRN* mutation carriers as well as the thalamus, but in *C9orf72* mutation carriers exclusively areas in the medial temporal lobe including the hippocampus were found (Figure 2, Supplementary Table 4). In *MAPT* mutation carriers, both immediate free and total recall were correlated with atrophy of the medial temporal lobes bilaterally (Figures 1 and 2, Supplementary Table 4). The overlap and differences in statistical parametric maps between immediate free and total recall can be seen in Supplementary Figure 1. For *C9orf72* mutation carriers, similar findings were seen for delayed total recall (Supplementary Table 4), although only frontal areas were associated with delayed total recall for *GRN* mutation carriers. There were no associations in *GRN* and *MAPT* mutation carriers for delayed free recall or in *MAPT* mutation carriers for delayed total recall after FWE correction (Supplementary Table 4). All significant correlations were positive (i.e. lower grey matter volume associated with worse performance).

Figure 1. Neuroanatomical correlates of performance on the FCSRT immediate free recall. Results are shown on a study-specific T1-weighted magnetic resonance imaging template in Montreal Neurological Institute space and at P < 0.05 family-wise error corrected. Color bars represent T-values.



Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; FCSRT = Free and Cued Selective Reminding Test; FWE = family-wise error; *GRN* = progranulin; L = left; *MAPT* = microtubule-associated protein tau; R = right

Figure 2. Neuroanatomical correlates of performance on the FCSRT immediate total recall. Results are shown on a study-specific T1-weighted magnetic resonance imaging template in Montreal Neurological Institute space and at P < 0.05 family-wise error corrected. Color bars represent T-values.



Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; FCSRT = Free and Cued Selective Reminding Test; FWE = family-wise error; *GRN* = progranulin; L = left; *MAPT* = microtubule-associated protein tau; R = right

Discussion

This study demonstrates the presence of memory impairment in genetic FTD, including in the presymptomatic period of *MAPT* and *C9orf72* mutation carriers, and with differential underlying neural correlates in different genetic groups. Results showed that all symptomatic mutation carriers had lower performance than controls and presymptomatic mutation carriers. Presymptomatic *MAPT* mutation carriers performed lower on all four FCSRT scores compared to controls, and presymptomatic *C9orf72* mutation carriers performed lower than controls on all scores except delayed total recall. The strongest associations between the FCSRT and cognitive tasks were with measures of executive function as well as memory and language in *C9orf72* and *GRN* mutation carriers but mainly with memory and naming tests for *MAPT* mutation carriers. Neural correlates varied between genetic groups, with frontal and temporal as well as subcortical involvement in *C9orf72* and *GRN* mutation carriers, but almost exclusively temporal areas being implicated in the *MAPT* group. Interestingly, a difference in frontal versus temporal involvement was seen in respectively free versus total recall measures in *C9orf72* mutation carriers. Together these results indicate that the FCSRT is a sensitive test in the presymptomatic period of *C9orf72*- and *MAPT*-associated FTD, and provides important additional insight into the underlying basis of memory impairment in different forms of FTD.

All symptomatic mutation carriers had impaired memory as measured by the FCSRT compared to controls and presymptomatic mutation carriers, whereas only *MAPT*- and *C9orf72*-associated FTD were impaired presymptomatically. This is in line with previous studies investigating cognitive functioning in people with genetic FTD, demonstrating memory impairment in *C9orf72*-[18, 22, 33, 34], *GRN*-[19, 22, 35] and *MAPT*-[22] related FTD, earlier (and presymptomatically) in *C9orf72*[36] and *MAPT*[21, 37, 38] mutations, and only in the later symptomatic stages in *GRN*-related FTD[17, 22]. Some of these studies interpreted memory impairment as a distinctive characteristic of the specific gene mutation involved, but our results suggest that, although all (symptomatic) genetic groups were impaired, the underlying cause of memory impairment might differ between the genetic groups. This is illustrated by the finding of lower immediate free, total, and delayed free recall in presymptomatic *C9orf72* mutation carriers, while presymptomatic *MAPT* carriers performed worse on all four tests, including delayed total recall, compared to controls and presymptomatic *GRN* carriers. According to the classical view, the FCSRT total scores are assumed to represent a "true" form of memory consolidation due to the cued format and the free recall scores are believed to be more dependent on executive functioning as well[5]. In light of this theory, our results indicate that lower performance in *MAPT* mutation carriers might be the result of a pure memory impairment, that already starts in the presymptomatic stage, whereas memory performance in *C9orf72* mutation carriers is initially influenced by executive dysfunction resulting in an ineffective encoding and/or retrieval strategy. This theory is further corroborated by our finding that in the *C9orf72* group there were significant associations between the FCSRT and executive tests such as the D-KEFS Color-Word Interference Test in particular. In contrast, although there were moderate associations between the FCSRT and executive tests in the presymptomatic *MAPT* group as well, the FCSRT was exclusively associated with tests for visual and semantic memory in the symptomatic group, indicating a stronger underlying temporal component in this group. This is not surprising given that semantic impairment has been associated with anteromedial temporal lobe atrophy and is a common symptom in the later disease stages of people with a *MAPT* mutation[22, 39, 40]. As such, semantic impairment might also have influenced performance on the FCSRT. In *GRN* mutation carriers, memory processes appear to become affected at a later, symptomatic, stage of the disease possibly due to increasing cognitive impairment in executive function or language domains affecting memory performance as well[41]. *GRN* mutation carriers performed better than the other mutation carrier groups on the FCSRT in the presymptomatic stage, whereas they performed significantly worse than *C9orf72* mutation carriers in the symptomatic stage. This is in line with previous studies showing that there is minimal cognitive decline in presymptomatic *GRN* mutation carriers, with often rapidly progressive cognitive decline after symptom onset[21, 22, 35, 41], whereas in *C9orf72*-related FTD cognitive decline already starts at an early stage, and then may progress relatively slowly for several years after symptom onset[18, 22, 33, 34, 36].

Although the mean and standard deviation of FCSRT scores in the presymptomatic *MAPT* mutation carriers are similar to the entire control group (Table 1), this group is significantly younger than the overall control group, and the adjusted mean differences seen in Table 2, approximate to the difference between the mean of the presymptomatic *MAPT* mutation carriers and that of a younger control group (Supplementary Table 3), e.g. the mean for immediate free recall in this group was 31.6 with a mean age within this group of 39.8, whilst in the age 30-40 younger controls (Supplementary Table 3) the mean score was 34.0, 2.4 points higher than the presymptomatic *MAPT* mutation carriers.

The VBM analysis revealed that for *MAPT* mutation carriers both free and total recall were correlated almost exclusively with temporal lobe areas, including parts of the medial temporal lobe memory system (e.g. entorhinal and parahippocampal cortices)[42, 43]. Although this memory network, including the hippocampus, amygdala and fusiform gyrus, was implicated in *C9orf72* and *GRN* mutation carriers as well, there was additional involvement of the frontal cortices, thalamus and insula in these groups, areas that are involved with executive processes such as inhibitory control, initiative, planning of behaviour and attention[44-49]. Interestingly, this executive network was not implicated in the total recall measures in *C9orf72* mutation carriers reducing it to exclusively memory-related areas. This suggests that in *C9orf72*-related FTD, although frontal/executive processes influence free recall performance, temporal/memory processes affect performance on total recall measures. On the other hand, in *GRN*-related FTD frontal/executive processes appear to influence performance on both free and cued memory recall formats. These results are consistent with previous neuroimaging studies showing progressive deterioration of the brain areas that were correlated to FCSRT performance in each genetic group (e.g. [17-19, 23, 36, 50]). For example, a previous GENFI study revealed hippocampal loss followed by temporal lobe atrophy in presymptomatic *MAPT* mutation carriers from respectively 15 to 10 years before estimated symptom onset, whereas the insula and parietal areas were the earliest affected areas in *GRN* and the thalamus in *C9orf72*[23]. Overall, the neuroanatomical correlates were more extensive for the immediate than delayed recall scores. A possible explanation for this might be that there is a larger variance in the distribution of scores in immediate recall with a maximum score of 48, compared to delayed recall with a maximum score of 16, and therefore less sensitive to detect a change in grey matter volume.

A major strength of this study is the use of a large cohort of genetic FTD patients and presymptomatic mutation carriers, allowing not only gene-specific analyses, but also the use of a matched control group of mutation-negative family members. However, despite the large sample size, the *MAPT* mutation carrier group was still smaller than the other groups, which might have influenced particularly the power of VBM analyses, in which we did not find significant correlations with delayed recall test scores after FWE-correction. Another limitation of this study is that bulbar/motor symptoms of patients with FTD-ALS or severe

language difficulties in patients with PPA might have affected performance on the FCSRT or other cognitive tests, although these groups were in the minority compared with those with a primary diagnosis of bvFTD, and furthermore, instructions for test administration include example items for most cognitive tests to check if instructions are understood and if a patient is too severely affected the test is discontinued according to the judgment of an experienced neuropsychologist. Future research studies might investigate the loss of information over the delay between the immediate and delayed recall phases, however this data was not available in this study.

To summarize, we demonstrated significant episodic memory impairment in genetic FTD, already starting in the presymptomatic period of *MAPT* and *C9orf72*. Presymptomatic *C9orf72* mutation carriers were not impaired in delayed total recall (i.e. free + cued recall), and FCSRT free recall was more strongly associated with tests for executive functioning. This suggests that lower FCSRT free recall might initially be the result of an ineffective retrieval strategy, rather than a "true" memory impairment. On the other hand, presymptomatic *MAPT* mutation carriers performed, for their overall younger age, worse than controls on both immediate and delayed total recall, with strong associations with memory tests, suggesting that "true" memory processes affect performance on the FCSRT in this group. In contrast, FCSRT performance is only impaired at the symptomatic stage of *GRN* mutation carriers. These findings were corroborated by demonstrating an exclusive temporal/memory network association with FCSRT performance in *MAPT* mutation carriers, whereas areas important for executive functioning were also correlated with FCSRT performance in *GRN* and *C9orf72* mutation carriers. Only temporal memory-related areas were associated with total recall in *C9orf72*, suggesting that there is a pure memory component implicated in this group as well, possibly only at the symptomatic stage when the temporal lobes become affected. Together, these results demonstrate that memory deficits are an integral part of the clinical spectrum in *MAPT* and *C9orf72* mutation carriers. It suggests that comprehensive memory tasks that can delineate executive function and memory processes such as the FCSRT should be incorporated in the standard diagnostic work-up. In addition, they can potentially serve as a useful outcome measure in upcoming clinical trials that target specific pathologies.

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Supplementary file 1: Tables and Figures

Supplementary Table 1. Cumulative frequency in the controls.

FCSRT immediate free recall		
Score	**n**	**Cumulative frequency (%)**
6	1	0.3
7	0	0.3
8	0	0.3
9	0	0.3
10	0	0.3
11	0	0.3
12	0	0.3
13	2	1.0
14	0	1.0
15	3	2.1
16	0	2.1
17	2	2.8
18	5	4.5
19	2	5.2
20	4	6.6
21	3	7.6
22	5	9.3
23	6	11.4
24	9	14.5
25	9	17.6
26	10	21.0
27	14	25.9
28	13	30.3
29	15	35.5
30	19	42.1
31	24	50.3
32	20	57.2
33	9	60.3
34	14	65.2
35	17	71.0
36	11	74.8
37	9	77.9
38	17	83.8
39	12	87.9
40	12	92.1
41	7	94.5

Supplementary Table 1 continued

42	5	96.2
43	2	96.9
44	5	98.6
45	1	99
46	1	99.3
47	1	99.7
48	1	100
FCSRT immediate total recall		
Score	**N**	**Cumulative frequency (%)**
21	1	0.3
22	0	0.3
23	0	0.3
24	0	0.3
25	0	0.3
26	0	0.3
27	0	0.3
28	0	0.3
29	2	1.0
30	0	1.0
31	0	1.0
32	0	1.0
33	1	1.4
34	0	1.4
35	2	2.1
36	4	3.4
37	0	3.4
38	1	3.8
39	2	4.5
40	7	6.9
41	8	9.7
42	14	14.5
43	11	18.3
44	17	24.1
45	19	30.7
46	35	42.8
47	53	61.0
48	113	100

Supplementary Table 1 continued

FCSRT delayed free recall		
Score	**N**	**Cumulative frequency (%)**
3	2	0.7
4	2	1.4
5	2	2.1
6	4	3.4
7	9	6.6
8	10	10.0
9	15	15.2
10	28	24.8
11	40	38.6
12	45	54.1
13	39	67.6
14	44	82.8
15	35	94.8
16	15	100
FCSRT delayed total recall		
Score	**N**	**Cumulative frequency (%)**
8	1	0.3
9	2	1.0
10	1	1.4
11	4	2.8
12	1	3.1
13	7	5.5
14	14	10.3
15	44	25.5
16	216	100

FCSRT = Free and Cued Selective Reminding Test

Supplementary Table 2. Percentile FCSRT scores in the controls.

Percentile	**direct free**	**direct total**	**delayed free**	**delayed total**
5th	19	40	7	13
10th	23	42	8	14
20th	26	44	10	15
30th	28	45	11	16
40th	30	46	12	16
50th	31	47	12	16
60th	33	47	13	16
70th	35	48	14	16
80th	38	48	14	16
90th	40	48	15	16

Supplementary Table 3. Mean and standard deviation of the FCSRT test scores in controls stratified by age group and sex.

FCSRT immediate free recall									
	All			Females			Males		
Age group	N	Mean	SD	N	Mean	SD	N	Mean	SD
18.1-29.9	34	35.2	5.7	17	37.2	5.4	17	33.2	5.5
30.0-39.9	69	34.0	5.3	41	35.0	5.8	28	32.6	4.0
40.0-49.9	83	31.1	5.5	45	31.8	5.9	38	30.4	5.0
50.0-59.9	54	31.0	7.4	33	32.5	7.5	21	27.7	6.3
60.0-69.9	44	27.0	8.4	30	29.2	7.2	14	22.1	9.1
70.0-89.9	6	28.5	6.5	1	27.0	-	5	28.8	7.2
FCSRT immediate total recall									
	All			Females			Males		
Age group	N	Mean	SD	N	Mean	SD	N	Mean	SD
18.1-29.9	34	46.2	2.6	17	46.8	2.7	17	45.6	2.5
30.0-39.9	69	46.2	2.6	41	46.3	2.6	28	46.1	2.6
40.0-49.9	83	45.8	3.0	45	45.8	3.4	38	45.7	2.4
50.0-59.9	54	45.7	3.2	33	46.0	2.9	21	45.1	3.7
60.0-69.9	44	44.0	5.7	30	45.2	3.9	14	41.4	7.9
70.0-85.0	6	46.0	2.6	1	46.0	-	5	46.0	2.9
FCSRT delayed free recall									
	All			Females			Males		
Age group	N	Mean	SD	N	Mean	SD	N	Mean	SD
18.1-29.9	34	13.1	2.0	17	13.7	2.1	17	12.5	1.8
30.0-39.9	69	12.7	2.1	41	12.3	2.0	28	12.0	2.0
40.0-49.9	83	12.2	2.3	45	12.4	2.5	38	11.8	2.0
50.0-59.9	54	11.6	2.8	33	12.3	2.7	21	10.5	2.7
60.0-69.9	44	10.2	3.2	30	11.1	2.9	14	8.2	3.0
70.0-85.0	6	11.2	2.0	1	14.0	-	5	10.6	1.7
FCSRT delayed total recall									
	All			Females			Males		
Age group	N	Mean	SD	N	Mean	SD	N	Mean	SD
18.1-29.9	34	15.6	1.0	17	15.9	0.2	17	15.2	1.3
30.0-39.9	69	15.7	0.6	41	15.8	0.5	28	15.7	0.7
40.0-49.9	83	15.7	0.7	45	15.7	0.8	38	15.7	0.7
50.0-59.9	54	15.5	1.1	33	15.8	0.7	21	15.1	1.4
60.0-69.9	44	14.7	2.2	30	15.0	2.0	14	13.9	2.4
70.0-85.0	6	15.8	0.4	1	16.0	-	5	15.8	0.4

FCSRT = Free and Cued Selective Reminding Test

Supplementary Table 4. Positive neuroanatomical correlates of grey matter volume on all FCSRT test scores in each genetic group.

Genetic group	Region	Cluster	T	p(FWE-corr)	Co-ordinates (mm)		
					x	y	z
FCSRT direct free recall							
C9orf72	Left orbitofrontal cortex, left inferior frontal gyrus	273	6.29	<0.0001	-21	38	-14
	Left inferior temporal gyrus	220	6.16	<0.0001	-50	-54	-14
	Left superior and middle temporal gyrus	231	6.07	<0.0001	-50	-44	10
	Right temporal gyrus	86	5.69	0.002	60	-12	-12
	Left precuneus	364	5.68	0.002	-2	-57	21
	Left orbitofrontal cortex	182	5.59	0.002	-27	14	-10
	Right hippocampus	137	5.56	0.003	32	-24	-18
	Right insula	84	5.55	0.003	40	-4	8
	Right angular gyrus	32	5.52	0.003	52	-48	33
	Left angular gyrus	39	5.46	0.004	-44	-68	34
	Right hippocampus	32	5.36	0.006	30	-9	-16
	Right middle temporal gyrus	56	5.28	0.009	54	-32	-9
	Left thalamus	81	5.24	0.01	-18	-32	-2
	Right superior parietal lobule	18	4.94	0.014	34	-39	62
	Left middle frontal gyrus	18	5.16	0.015	-40	51	8
	Left middle frontal gyrus	34	4.92	0.015	-40	45	-3
	Left hippocampus	18	4.89	0.017	-20	-21	-21
	Left amygdala	20	5.05	0.022	-16	-9	-14
	Left hippocampus	68	5.02	0.024	-32	-22	-9
	Right putamen	17	4.76	0.03	24	14	-14
	Right fusiform gyrus	21	4.72	0.035	27	-6	-39
GRN	Left hippocampus, left fusiform gyrus	784	6.36	<0.0001	-18	-21	-20
	Right middle frontal gyrus	92	6.15	<0.0001	30	26	45
	Right middle frontal gyrus	154	6.01	<0.0001	38	51	18
	Right superior frontal gyrus	48	5.48	0.001	22	15	54
	Right superior frontal gyrus	105	5.80	0.001	8	42	21
	Right precuneus, left posterior cingulate gyrus	721	5.80	0.001	2	-54	26
	Left fusiform gyrus	42	5.76	0.001	-24	-9	-40
	Right parahippocampal gyrus	59	5.75	0.001	-24	-9	-40
	Left precuneus	55	5.70	0.002	-8	-56	6
	Left orbitofrontal cortex, left insula, left putamen	470	5.66	0.002	-20	6	-21
	Right entorhinal area	113	5.63	0.002	20	0	-42
	Left orbitofrontal cortex	82	5.52	0.003	-16	28	-20
	Left medial frontal cortex	114	5.36	0.006	-6	28	-20
	Left inferior frontal gyrus	27	5.36	0.006	-50	36	-9
	Left superior frontal gyrus	49	5.33	0.007	-10	56	15

Supplementary Table 4 continued

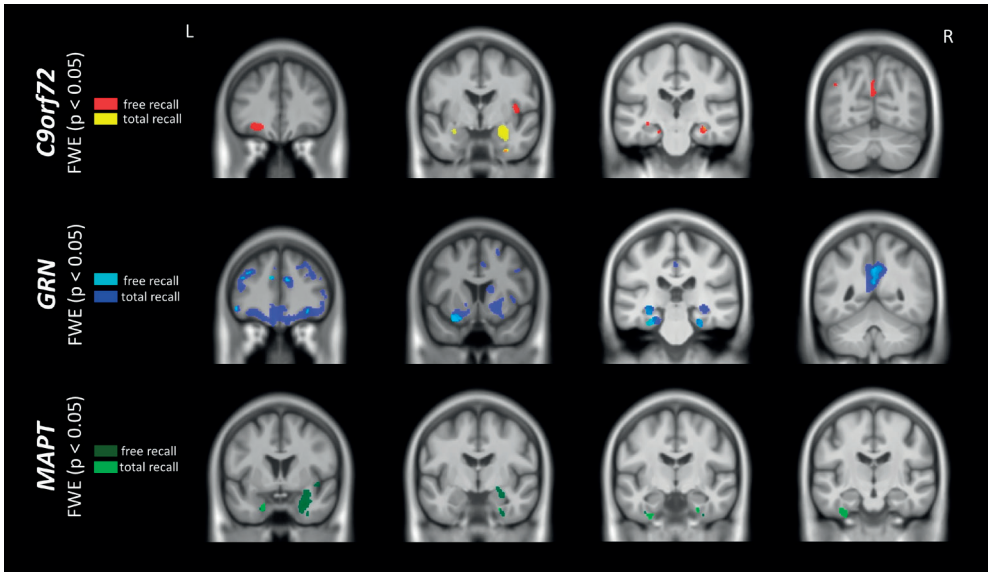
Genetic group	Region	Cluster	T	p(FWE-corr)	Co-ordinates (mm)		
					x	y	z
	Left orbitofrontal cortex	23	5.33	0.007	-38	42	-9
	Left middle frontal gyrus	44	5.33	0.007	-27	58	6
	Right orbitofrontal cortex	51	5.17	0.013	33	40	-10
	Left middle frontal gyrus	60	5.14	0.015	-44	39	26
	Right orbitofrontal cortex	51	5.17	0.013	33	40	-10
	Left middle frontal gyrus	60	5.14	0.015	-44	39	26
	Left superior frontal gyrus, left middle frontal gyrus	46	5.12	0.016	-22	22	46
	Left anterior insula	64	5.11	0.016	-27	27	-8
	Left superior frontal gyrus	20	5.09	0.018	-6	50	26
	Left superior frontal gyrus, left anterior cingulate gyrus	30	5.05	0.021	-4	44	21
	Left temporal pole	25	4.98	0.027	-50	10	-28
MAPT	Left entorhinal cortex	56	6.33	0.001	-20	4	-33
	Right entorhinal cortex, right temporal pole	1169	6.19	0.002	28	3	-30
	Left fusiform gyrus	53	5.84	0.006	-34	-15	-39
	Right insula	20	5.68	0.01	42	3	-6
	Right inferior temporal gyrus	19	5.51	0.018	32	2	-40
	FCSRT direct total recall						
C9orf72	Right hippocampus, right temporal pole	866	6.25	<0.0001	28	-6	-20
	Left temporal pole, left entorhinal area	325	5.84	0.001	-33	9	-26
	Right fusiform gyrus	22	5.02	0.024	30	-4	-40
GRN	Right middle frontal gyrus, right superior frontal gyrus	15972	7.47	<0.0001	38	32	45
	Left hippocampus	1175	7.18	<0.0001	-20	-21	-21
	Left and right precuneus	3945	6.59	<0.0001	-8	-57	8
	Right parahippocampal gyrus	191	6.28	<0.0001	27	-27	-26
	Right hippocampus	663	6.14	<0.0001	33	-12	-15
	Right superior frontal gyrus	170	6.03	<0.0001	22	15	54
	Right superior parietal lobule, right angular gyrus	128	6.02	<0.0001	32	-64	51
	Right superior frontal gyrus	127	6.00	<0.0001	21	60	20
	Right middle frontal gyrus	56	5.94	0.001	46	14	34
	Right lingual gyrus	73	5.63	0.002	3	-72	-3
	Right precuneus	56	5.54	0.003	12	-68	33
	Left precentral gyrus	74	5.44	0.005	-24	-16	72
	Left fusiform gyrus	30	5.34	0.007	-24	-9	-40
	Right middle occipital gyrus	34	5.34	0.007	48	-75	27
	Left cerebellum	208	5.31	0.008	-34	-63	-40
	Left middle cingulate gyrus	18	5.27	0.009	-3	-12	44
	Right thalamus	33	5.26	0.01	2	-2	4
	Right middle temporal gyrus	116	5.21	0.012	62	-15	-10

Supplementary Table 4 continued

Genetic group	Region	Cluster	T	p(FWE-corr)	Co-ordinates (mm)		
					x	y	z
	Left ventral diencephalon	32	5.16	0.014	0	-4	-15
	Right precentral gyrus	39	5.14	0.015	27	-18	70
	Right fusiform gyrus, right entorhinal area	38	5.09	0.018	20	0	-42
MAPT	Left entorhinal area	54	6.70	<0.0001	-20	4	-33
	Left fusiform gyrus	140	6.53	0.001	-34	-16	-39
	Right parahippocampal gyrus	20	5.57	0.015	24	-10	-34
FCSRT delayed free recall							
C9orf72	Left orbitofrontal cortex	436	6.40	<0.0001	-20	36	-14
	Left hippocampus, left putamen	1064	6.14	0.001	-28	34	-12
	Left inferior temporal gyrus	181	6.09	<0.0001	-48	-54	-16
	Left middle frontal gyrus	95	5.71	0.001	-42	45	-4
	Right hippocampus, right amygdala	126	5.71	0.001	30	-9	-15
	Right insula	66	5.60	0.002	44	-4	4
	Right angular gyrus	38	5.56	0.003	52	-50	34
	Right hippocampus	225	5.09	0.004	33	-39	58
	Left medial frontal cortex	94	5.44	0.005	-9	30	-18
	Left thalamus	174	5.43	0.005	-6	-21	15
	Left middle temporal gyrus	30	5.40	0.005	-58	-48	8
	Left caudate	265	5.22	0.011	-9	15	9
	Right superior parietal lobule	25	5.09	0.019	33	-39	58
	Right orbitofrontal cortex	47	5.06	0.019	9	34	-22
	Left middle frontal gyrus	17	5.02	0.024	-28	51	6
	Right putamen	23	5.02	0.025	24	9	-12
GRN	-	-	-	-	-	-	-
MAPT	-	-	-	-	-	-	-
FCSRT delayed total recall							
C9orf72	Right hippocampus, right amygdala, right temporal pole	1085	6.13	<0.0001	33	-22	-16
	Left thalamus, left hippocampus	292	5.83	0.001	-21	-32	-3
	Right fusiform gyrus	65	5.32	0.007	28	-6	-40
	Left temporal pole, left entorhinal area	157	5.28	0.009	-33	3	-32
GRN	Right frontal pole	26	5.57	0.003	26	64	3
	Right middle frontal gyrus	30	5.25	0.009	36	30	45
MAPT	-	-	-	-	-	-	-

Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; PS = presymptomatic; S = symptomatic; FCSRT = Free and Cued Selective Reminding Test.

Supplementary Figure 1. Differences in neuroanatomical correlates of performance on the FCSRT immediate free and total recall. Results are shown on a study-specific T1-weighted MRI template in MNI space and at $p<0.05$ Family Wise Error corrected. Colour bars represent T-values.



Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau. FWE = Family Wise Error; L = left; R = Right.

CHAPTER 4.3

Differences in discriminability and response bias on Rey Auditory Verbal Learning Test delayed recognition in behavioural variant frontotemporal dementia and Alzheimer's disease

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Abstract

Objective: Episodic memory is impaired in Alzheimer's disease dementia (AD), but thought to be relatively spared in behavioral variant frontotemporal dementia (bvFTD). This view is challenged by evidence of memory impairment in bvFTD. This study investigated differences in recognition memory performance between bvFTD and AD.

Method: We performed a retrospective analysis on the recognition trial of the Rey Auditory Verbal Learning Test in patients with bvFTD (n=85), AD (n=55) and control participants (n=59). Age- and education-adjusted between group analysis was performed on the total score and indices of discriminative ability and response bias . Correlations between recognition and measures of memory, language, executive functioning and construction were examined.

Results: Patients with AD had a significantly lower total Recognition score than patients with bvFTD (control 28.8±1.5; bvFTD 24.8±4.5; AD 23.4±3.6 , $p<0.01$). Both bvFTD and AD had worse discriminative ability than controls (A' control 0.96±0.03; bvFTD 0.87±0.03; AD 0.84±0.10, $p<0.01$), but there was no difference in response bias (B" control 0.9±0.2; bvFTD 1.6±1.47; AD 1.4±1.4, $p<0.01$). AD had worse discriminability than bvFTD ($p<0.05$). Discriminability was associated with memory for both patient groups (median correlation coefficient $r=0.34$) and additionally associated with language ($r=0.31$), but not executive functioning ($r=-0.03$) in bvFTD. Response bias was unrelated to other cognitive functions ($r=-0.02$).

Conclusions: Discriminability, but not response bias, differentiated patients with bvFTD from AD. The presence of an impaired discrimination index suggests a "pure" (recognition) memory deficit in bvFTD.

Introduction

Behavioral variant frontotemporal dementia (bvFTD) and Alzheimer's disease (AD) are the two most common early onset dementias[1]. In the clinical diagnostic phase neuropsychological assessment is used to detect impairments in cognitive functioning and to differentiate between these two types of dementia. The cognitive profile of bvFTD is characterized by impaired executive functioning, social cognition and language (related to atrophy in frontal and temporal brain areas[2]), with relatively spared memory and construction[3]. Theoretically, this cognitive profile is markedly different from the profile of Alzheimer's disease, which is most commonly characterized by memory deficits resulting from atrophy of the medial temporal lobe (MTL[4]). In the last decade this traditional view on the difference in cognitive profiles between bvFTD and AD has been challenged by multiple reports of (sometimes profound) memory impairments in patients with bvFTD, even in early disease stages[5-9]. Likewise, patients with AD may present with executive dysfunctioning and/or significant "frontal" behavioral symptoms[10], making the differentiation between bvFTD and AD in clinical practice particularly challenging.

Systematic investigations of episodic memory functioning in bvFTD are increasingly reported, but show inconsistent results (for review see Poos et al.[11]) that are only partly explained by differences in testing procedures (verbal versus visual memory tests; free versus cued recall) and variation in patient samples (e.g. inclusion of nonprogressive "phenocopy" bvFTD patients; disease duration; heterogeneous clinical presentation). Several studies report memory deficits in bvFTD (compared with controls) that are equal in nature and extent to those found in AD (e.g. [5, 7, 9, 12]). Others, however, demonstrate relative sparing of memory performance in bvFTD compared with AD (e.g. [13]). Free delayed recall measures appear to best discriminate AD from bvFTD, with patients with AD performing worse than bvFTD[7, 14], although this difference is not found invariably (Hornberger et al., 2010; Pennington et al., 2011).

Episodic memory impairment in bvFTD is commonly viewed as a consequence of executive dysfunctioning (i.e. poor organization, lack of efficient retrieval strategies[5, 6]) rather than "pure" or primary amnesia. In contrast, Glosser et al.[8] showed that recall performance in bvFTD is not enhanced by cueing (use of semantic clusters), indicating that memory impairments in bvFTD are associated with primary encoding deficits rather than suboptimal retrieval strategies. In addition, recent studies show impaired memory performance in patients with bvFTD even after controlling for executive load[15, 16]. These findings are not surprising as several brain structures important for memory performance, such as the medial temporal lobe (including the hippocampus and supporting structures) and brain regions that connect the MTL to prefrontal areas (such as the fornix)[17] are not only implicated in AD, but in bvFTD as well[18]. Indeed, deficits in delayed recall in both AD and FTD not only rely on the MTL, but on the integrity of prefrontal areas as well[19-21].

The majority of studies investigating episodic memory performance in bvFTD and AD focus on measures of immediate or delayed (free) recall, most commonly with verbal tests such as the Rey Auditory Verbal Learning test (RAVLT). Recognition memory is also routinely assessed as part of these memory tests (both in clinical practice and in scientific research) but has received much less attention. This is unfortunate as recognition memory paradigms may provide crucial information on memory and executive processes aiding the differentiation between AD and bvFTD. Recognition memory entails patients to indicate whether a certain stimulus was previously encountered ("old") or new. Patients with bvFTD tend to outperform AD patients in recognition memory[5] and sometimes even show no impairment compared to control participants[7, 22]. This finding may be attributed to the fact that cueing in recognition memory tasks enables patients with bvFTD to overcome retrieval problems (at least to some extent), but the recognition deficits in AD reflect true forgetting of the items. Under certain conditions patients with bvFTD may thus exhibit a greater ability to discriminate "old" from "new" items than patients with AD. Interestingly, differences in performance on recognition memory tasks between bvFTD and AD are not found invariably (see for example Pennington et al.[9]; Glosser et al.[8]), suggesting that certain characteristics of the recognition memory tasks (e.g. number of distractors, type of cueing) may elicit a trend or bias toward a more liberal (tendency to respond "yes" to any item that is presented) or conservative ("no" tendency) response. Theoretically, the ability to distinguish target words from distractor words ("discriminability") is indeed independent from the tendency to favor "yes" or "no" responses when there is uncertainty about the correct response ("response bias")[23]. A person can thus exhibit a liberal response bias when discriminative ability is either high or low[6]. Patients with AD generally have a more liberal response bias[24, 25], resulting in an increase in false positive responses ("yes" tendency) associated with both prefrontal and (para)hippocampal areas[24]. Response bias in bvFTD has only been scarcely examined. Recent work by Flanagan et al.[26] shows a higher rate of false positive responses in both AD and bvFTD that was most strongly correlated with measures of disinhibition in the latter. As of yet, it remains unclear whether discriminability and response bias as such are valuable measures in discriminating AD from bvFTD.

The aims of the present study were (1) to examine differences in recognition memory performance on a widely used verbal memory test (RAVLT) between patients with bvFTD and AD, (2) to specifically compare measures of discrimination and response bias between these groups, and (3) to investigate associations between recognition memory and other measures of memory, language and executive functioning within and between the groups, and disease severity.

Method

Participants

Retrospective data from 140 patients (85 bvFTD, 55 AD) and 59 control participants were included. Patients visited the memory clinic of the Erasmus MC University Medical Center between 2005 and 2018 for a standardized work up consisting of a neurological and neuropsychological assessment, laboratory testing (including lumbar puncture in subsample) and brain imaging. Clinical diagnoses were made in a multidisciplinary consensus meeting with an experienced neurologist, geriatrician, neuropsychologist and radiologist. All patients with bvFTD met core clinical diagnostic criteria for bvFTD with insidious onset, decline in social behavior and personal conduct, emotional blunting, and loss of insight reported by caregivers[3, 27]. Memory complaints and impaired episodic memory performance were allowed for if the other core diagnostic criteria were present. Non-progressive (i.e. phenocopy bvFTD) patients were excluded as these patients present with little or no memory dysfunction[9]. Thirty-four patients were part of an ongoing epidemiological study of Dutch pathologically confirmed genetic FTD families[28]; progranulin (*GRN*) n=12; microtubule-associated protein tau (*MAPT*) n=9; chromosome 9 open reading frame 72 (*C9ofr72*) n=13). Patients with AD met the NINCDS-ADRDA criteria for probable AD[4]. Control participants were included from two previous studies (n=28[29]; n=31[30]). These control participants reported no history of neurological (e.g. major stroke, brain tumor, epilepsy) or severe psychiatric disorder (e.g. major depression, substance abuse) negatively affecting cognition and a normal brain MRI. The study was approved by the local medical ethics committee. The research was completed in accordance with the Helsinki Declaration. All participants gave written informed consent.

Neuropsychological Assessment

Neuropsychological assessment was performed as part of the memory clinic work-up. Although the neuropsychological test battery was standardized, adaptations were made for individual patients according to type of symptoms and severity. Neuropsychological tests that were performed by <50% of participants were excluded from the analysis. Global cognitive functioning was screened by means of the Mini-Mental State Examination (MMSE[31]) and the Frontal Assessment Battery (FAB[32]).

Verbal learning and memory were assessed using the Dutch version of the Rey Auditory Verbal Learning Test (RAVLT[33]). The RAVLT is a supraspan verbal learning test consisting of five learning trials of 15 words, followed by a 20 to 30-minute delayed free recall and a 30-word delayed recognition trial including al 15 words from the learning trials and 15 unrelated words. For the purpose of the present analysis the following parameters were derived from the delayed recognition trial of the RAVLT:

1. Total score of delayed recognition (0 – 30)
2. Number of correctly recognized words in the recognition trial ("hits", 0 – 15)
3. Number of incorrectly recognized words in the recognition trial ("false positives", 0 – 15)

Level of performance on a yes-no recognition memory test is reflected in the number of correct hits and false positive errors. These data yield two measures of recognition memory (adapted from signal detection theory): recognition discriminability (the ability to distinguish target words from distractor words) and response bias (the tendency to favor "yes" or "no" responses when there is uncertainty about the correct response)[6]. Calculation of hits minus false positives is a widely used and easily obtained measure of discriminability and the ratio between "yes" and "no" answers entails a (crude) estimation of response bias. Snodgrass and Corwin provide a more elaborate distribution-free (nonparametric) model for calculating discriminability (A') and response bias (B") that is specifically suitable for a population of persons that may have poor discrimination performance (e.g. persons with dementia) and can be applied to not-normally distributed data[23]. Discrimination index A' and response bias B" are estimated by formulas (1) and (2):

(1) A' = 0.5 + ((hits-false alarm)(1 + hits – false alarms)) / ((4*hits(1-false alarms))

(2) B" = (hits(1-hits)-false alarms(1-false alarms)) / (hits*(1-hits) + false alarms(1-false alarms))

We chose to investigate both the simple and the more elaborate measures of discriminability and response bias:

4. Discrimination index "hits minus false positives"
5. Discrimination index A'
6. Response bias Yes/No ratio
7. Response bias index B"

Other neuropsychological tests that were included in the present analysis were the Story recall subtest of the Rivermead Behavioral Memory Test (RBMT; immediate recall score 0 – 42, delayed recall % retained[34]), the Visual Association Test (VAT; score 0-12[35]), the Boston Naming Test (BNT; score 0 – 60[36]), category fluency (animals, 1 minute), letter fluency (letters D-A-T which are the Dutch equivalent of F-A-S[37]), modified Wisconsin Card Sorting Test (WCST; concepts 0 – 6[38]), Trailmaking Test A and B (TMT; time for card A and B, B/A ratio score[39]), Stroop Color-Word Test (time for card I, II and III, card III/II interference ratio score[40]), and Clock drawing test (score 0 – 14[41]).

Statistical analysis

RAVLT recognition memory scores were compared between bvFTD, AD and control participants with analysis of variance for normally distributed data or Kruskal-Wallis tests for nonparametric data, adjusted for age, education and time since symptom onset. Post hoc pairwise comparisons (controls vs. patients groups, bvFTD vs. AD) were analyzed with Scheffe's tests and, in case of nonparametric data, with Mann-Whitney U tests. Within the bvFTD group differences in RAVLT recognition memory between sporadic versus genetic bvFTD and between patients with *GRN*, *MAPT* and *C9orf72* mutations were also explored. Bivariate correlation was used to assess the relation between RAVLT recognition memory scores and other cognitive functions (Pearson's r for normally distributed data or Spearman's r for non-parametric data; adjusted for age and level of education). Statistical analyses were performed using SPSS Statistics 21.0 (IBM Corp., Armonk, NY).

Results

Table 1 shows the characteristics of the 199 participants. Patients with bvFTD were significantly younger than patients with AD and controls ($F(2, 199) = 12.3$, $p<0.001$, $\eta^2 = 0.11$). Both patient groups had a lower level of education compared with the control participants ($H(2) = 6.7$, $p<0.05$). As expected patients with AD had the lowest MMSE score and the bvFTD group had an intermediate position between the AD and control group ($F(2,157) = 19.4$, $p<0.001$, $\eta^2 = 0.20$). The FAB was administered to 67/86 patients with bvFTD and 27/55 patients with AD, and showed no significant difference between groups ($F(1, 94) = 1.13$, $p=0.79$, $\eta^2 = 0.001$). Time since symptom onset (months) was shorter for bvFTD than AD ($t(136) = -2.69$, $p<0.01$). As expected, both patient groups showed significantly poorer performance than control participants on all cognitive tests (Table 1). Compared with bvFTD the patients with AD had lower scores on measures of memory (RAVLT, RBMT, Visual Association Test), executive functioning (WCST, TMT, Stroop) and construction (Clock drawing) (Table 1).

Group differences in RAVLT recognition memory

With regards to performance on the RAVLT, patients with AD had a significantly lower delayed recall and percentage savings score than the bvFTD group ($F (1, 140) = 7.16$, $p<0.01$, $\eta^2 = 0.05$), but there was no difference between the two patient groups in immediate recall ($F (1, 140) = 2.61$, $p =0.11$, $\eta^2 = 0.02$) (See Table 1 and Figure 1). Table 2 shows the differences in RAVLT recognition scores. Patients with bvFTD had a lower total recognition score and hit rate than the control participants and, in turn, the AD group performed significantly worse than the patients with bvFTD (total recognition score bvFTD vs. AD $U = 1826$, $p<0.05$; hits $U = 1705$, $p<0.01$). Both patient groups had significantly more false positives than controls, but there was no difference in number of false positives between patients with AD and bvFTD (bvFTD vs AD $U = 2746$, $p=0.08$). For the discrimination indices (Hits-FA and A') both patients with AD

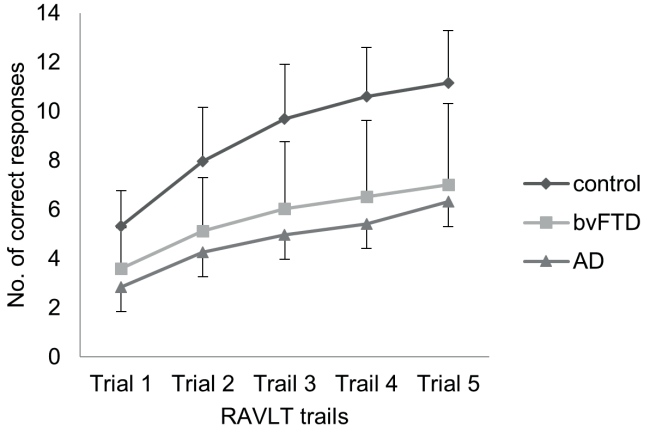
Table 1. Characteristics of the patients with bvFTD, AD and the control group.

	bvFTD	AD	Control	p value for difference[c]
n	85	55	59	
Age	62.0 ± 9.0	68.1 ± 7.2	67.0 ± 6.8	<0.01 (bvFTD<AD=con)
Male sex (%)	51 (60%)	32 (58%)	35 (59%)	ns
Education[a], median (IQR)	5 (4 to 6)	5 (4 to 6)	5 (5 to 6)	<0.01 (bvFTD=AD<con)
MMSE	25.0 ± 4.5	22.7 ± 4.6	28.8 ± 1.1	<0.01 (AD<bvFTD<con)
FAB[b]	12.3 ± 4.0	12.6 ± 4.1	-	ns
Months since symptom onset	30 ± 26	46 ± 42	-	0.02 (bvFTD<AD)
Cognitive tests				
RAVLT total trial 1-5 (0-75)	28.3 ± 11.5	23.8 ± 9.0	44.6 ± 8.7	<0.01 (AD=bvFTD<con)
RAVLT delayed recall (0-15)	4.8 ± 3.8	2.7 ± 2.7	9.3 ± 2.9	<0.01 (AD<bvFTD<con)
RAVLT % savings (0-100) [d]	59 ± 36	40 ± 39	82 ± 17	<0.01 (AD<bvFTD<con)
RBMT story immediate recall (0-42)	11.4 ± 10.3	7.5 ± 4.4	18.7 ± 5.6	<0.01 (bvFTD=AD<con)
RBMT story % recall	56.9 ± 29.5	46.6 ± 34.7	79.1 ± 18.3	<0.01 (bvFTD=AD<con)
Visual Association Test (0-12)	9.6 ± 3.3	5.6 ± 4.0	11.9 ± 0.3	<0.01 (AD<bvFTD<con)
Boston Naming Test (0-60)	40.3 ± 12.4	41.5 ± 10.0	55.6 ± 3.2	<0.01 (bvFTD=AD<con)
Category fluency	12.9 ± 5.1	12.2 ± 5.2	24.0 ± 5.1	<0.01 (bvFTD=AD<con)
Letter fluency	17.4 ± 10.3	19.7 ± 10.8	38.6 ± 13.0	<0.01 (bvFTD=AD<con)
mWCST concepts (0-6)	2.6 ± 1.8	1.7 ± 1.3	5.5 ± 1.1	<0.01 (AD<bvFTD<con)
Trailmaking A	63.4 ± 39.8	94.6 ± 55.8	38.5 ± 17.3	<0.01 (AD<bvFTD<con)
Trailmaking B	191.8 ± 92.4	269.4 ± 65.9	83.5 ± 34.6	<0.01 (AD<bvFTD<con)
Stroop Color-Word card III	172.6 ± 101.6	227.3 ± 124.4	104.0 ± 22.9	<0.01 (AD<bvFTD<con)
Clock drawing (0-14)	10.5 ± 2.2	8.8 ± 2.8	12.6 ± 1.1	<0.01 (AD<bvFTD<con)

[a] Level of education according to Verhage (1=less than primary school, 7=university degree)[42]; [b] Frontal Assessment Battery, available in 27 patients with AD; [c] between group differences adjusted for age and level of education; [d] Defined as (Delayed free recall/Trial 5) *100 ; bvFTD = behavioral variant frontotemporal dementia; AD = Alzheimer's disease; con = control participants; IQR = interquartile range; MMSE = Mini Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; RBMT = Rivermead Behavioural Memory Test; mWCST = modified Wisconsin Card Sorting Test.

and bvFTD had worse discriminative ability than controls (H =62.8, p < 0.01). Patients with AD had a lower A' than the bvFTD group, but there was no difference in "Hits minus false positives" (discrimination index A' U = 1789, p<0.05; Hits minus false positives U = 1846, p = 0.054; Figure 2). An effect size calculation for the comparison of A' between patients with bvFTD and AD showed a medium effect size of 0.3 to 0.4, which corresponds to a 72.6 to 78.7% overlap between the distributions[43]. With regard to the bias indices both dementia groups showed a higher Yes-No ratio and a lower B" than the controls (Yes-No ratio H = 6.37, p<0.05; B" H = 9.02, p<0.05) representing a (slightly more) liberal response bias for the patients. There was no difference in response bias between patients with bvFTD and AD (Yes-No ratio U = 2194, p=0.54, d = 0.12). For both AD and bvFTD the standardized total recognition score was lower than the standardized delayed recall score (z-scores standardized on the control group; AD delayed recall -2.3 ± 0.9, total recognition -3.5 ± 2.4, t(54) = 4.51, p<0.01;

Figure 1. Performance on the Rey Auditory Verbal Learning Test.



Abbreviations: bvFTD = behavioral variant frontotemporal dementia; AD = Alzheimer's disease.

bvFTD delayed recall -1.6 ± 1.3, total recognition -2.6 ± 3.0, t(84) = 4.34, p<0.01). There were no differences between patients with sporadic (n=51) versus genetic (n=34) bvFTD (see Supplementary Table 1). In the subgroup of patient with a known genetic mutation for bvFTD (n=34) no differences were observed in A' or B''(or any other measure of RAVLT) between *GRN* and *MAPT* mutation carriers and *C9orf72* repeat expansion carriers (see supplemental table in Appendix). Repeating the analysis in those patients with ≤24 months of time since symptom onset versus >24 months yielded highly similar results (data not shown).

Correlations with other cognitive functions and disease severity

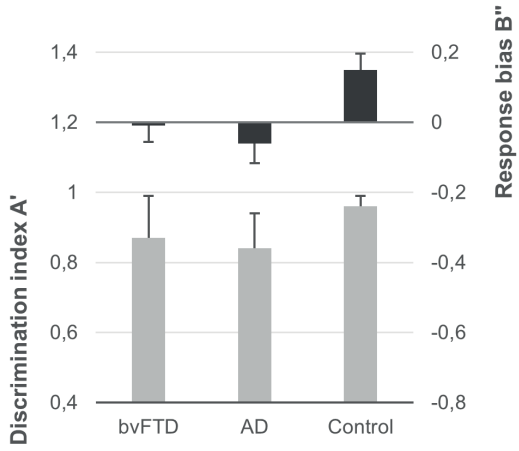
The results of the correlation analysis (Table 3) showed that the discrimination indices (Hits minus false positive and A') are associated with memory performance (RBMT, VAT) in the AD and bvFTD group. In the bvFTD group additional associations were found for measures of language (BNT, semantic and letter fluency). There were no significant associations between the discrimination indices and measures of executive functioning or construction in either

Table 2. Between-group differences in RAVLT recognition memory.

	bvFTD	AD	Control	Statistic[a]	Group differences
Delayed recognition (0-30)	24.8 ± 4.5	23.4 ± 3.6	28.8 ± 1.5	H = 62.9, p<0.01	AD<bvFTD<con
Total hits on recognition	13.2 ± 2.1	12.1 ± 2.6	14.1 ± 1.3	H = 28.8, p<0.01	AD<bvFTD<con
False positives on recognition	3.4 ± 4.3	3.6 ± 3.0	0.3 ± 0.6	H = 56.2, p<0.01	bvFTD=AD<con
Hits minus False positives	9.7 ± 4.5	8.4 ± 3.6	13.8 ± 1.5	H = 63.3, p<0.01	bvFTD=AD<con
Discrimination index A'	0.87 ± 0.12	0.84 ± 0.10	0.96 ± 0.03	H = 64.2, p<0.01	AD<bvFTD<con
Yes/No ratio	1.6 ± 1.7	1.4 ± 1.4	0.9 ± 0.2	H = 6.4, p<0.05	bvFTD=AD<con
Bias index B''	-0.01 ± 0.43	-0.06 ± 0.42	0.15 ± 0.35	H = 9.0, p<0.05	bvFTD=AD<con

[a]Analyses adjusted for age and level of education. RAVLT = Rey Auditory Verbal Learning Test; bvFTD = behavioral variant frontotemporal dementia; AD = Alzheimer's disease; con = control participants.

Figure 2. Discrimination and response bias indexes.



Abbreviations: bvFTD = behavioral variant frontotemporal dementia; AD = Alzheimer's disease.

Table 3. Association between recognition memory indices and other cognitive functions in patients with bvFTD and AD.

	bvFTD				AD			
	Hits-false positives	**A'**	**Yes/No ratio**	**B"**	**Hits-false positives**	**A'**	**Yes/No ratio**	**B"**
RBMT story immediate	0.34*	0.31*	-0.11	-0.05	0.40*	0.36^{+}	-0.28	0.24
RBMT story % recall	0.24	0.22	-0.19	-0.02	0.51**	0.51**	-0.09	-0.20
Visual Association Test	0.40**	0.40**	-0.22	0.15	0.55**	0.53**	-0.14	-0.15
Boston Naming Test	0.36**	0.38**	-0.14	0.13	0.29*	0.27^{+}	0.16	-0.12
Category Fluency	0.33**	0.36**	-0.07	0.11	0.07	0.08	-0.02	-0.08
Letter Fluency	0.25*	0.29**	-0.11	0.05	0.15	0.11	-0.03	-0.23
mWCST concepts	-0.07	-0.06	0.07	0.03	0.09	0.11	0.10	-0.19
Trailmaking B – A	-0.01	-0.05	-0.07	-0.07	-0.17	-0.17	0.11	-0.17
Stroop III – II	-0.03	-0.03	0.11	-0.20	-0.09^{+}	-0.25	0.08	0.29^{+}
Clock drawing	0.10	0.13	-0.05	0.14	0.16	0.10	-0.23^{+}	0.19

Data are Spearman correlation coefficients adjusted for age and level of education. *p<0.05, ** p<0.01, $^{+}$ p<0.1. bvFTD = behavioral variant frontotemporal dementia; AD = Alzheimer's disease; con = control participants. A', discriminability; B", response bias.

patient group. Similarly, there were no significant associations between indices of response bias (Yes/No ratio and B") and any of the other cognitive functions. Correlation analysis in the control group showed no clear patterns of associations, most likely resulting from ceiling effects on the RAVLT recognition trial. With regard to disease severity, the correlation analysis showed that 'Time since symptom onset' was significantly correlated with Delayed recognition (r=-0.23) and Total hits (r=-0.17), but not with A' (r=-0.16) or B" (0.06). Age was also not significantly associated with the recognition variables (range r -0.04 to -0.15).

Discussion

In the present study we investigated differences recognition memory between patients with bvFTD and AD. The main results showed that both patients with bvFTD and AD had a significantly lower discriminability on the recognition trial of the RAVLT than the control group. In turn, the AD group had a significantly lower discriminability than patients with bvFTD. Discriminative ability was mainly associated with memory for both patient groups and additionally associated with language, but not executive functioning in bvFTD. Although both patients with bvFTD and AD also had a slightly more liberal response bias ("yes" tendency) than control participants, there was no difference in response bias between the two patient groups. Response bias was also unrelated to other cognitive measures in our analysis.

These results corroborate the growing body of evidence showing considerable episodic memory impairment in bvFTD[5]. Multiple previous studies on delayed free recall and, to a lesser extent, immediate recall show that episodic memory can even be similarly impaired in bvFTD and AD (e.g. [5, 7, 9, 12]). Indeed, also in the present study delayed recall performance was impaired in both bvFTD and AD. Much less is known about differences in recognition memory in differentiating AD from bvFTD, which is surprising considering the high prevalence of recognition memory paradigms in functional neuroimaging studies in dementia[44, 45] and the fact that recognition memory is part of standard assessment of memory in clinical practice. Our results partly confirm findings from a recent study by Flanagan et al.[26] showing a significantly increased false positive rate for both patients with AD and bvFTD compared to controls and no difference in the simple discrimination index ("hits minus false alarms") for patients with bvFTD versus AD. In contrast, whereas Flanagan et al.[26] showed that discriminative ability was associated with executive functioning (disinhibition), our results indicate an association with memory, but not executive functioning (in both AD and bvFTD). This difference in involvement of executive functioning may be due to differences in the type of executive process that was measured (Interference on the Stroop test versus inhibition of a *semantically constrained* response in the Hayling test[46]). In the patients with bvFTD discriminability was associated with language performance, possibly resulting from the verbal nature of the RAVLT, it also reflects the (sometimes striking) language deficits that are present in bvFTD (i.e. naming, word comprehension, diminished propositional speech[47]).

Response bias B" was not previously examined in bvFTD, but Russo et al.[48] report a significantly lower discriminative ability and a liberal response bias in patients with AD, which is highly similar to our findings in the AD group. The lack of a difference in response bias between bvFTD and AD found in our study appears counter intuitive, but the (slightly) liberal response bias that was present in both patients groups (but not in controls) is in line with previous findings in patients with dementia[25]. Possibly, the cause of the liberal response bias is different between AD and bvFTD (overendorsement of a yes response in an uncertain situation versus

disinhibition/perseverative errors). In our view, the presence of an impaired discrimination index A' supports the presence of a "true" memory deficit in bvFTD, corroborating results from previous studies[18]. Whereas patients with bvFTD outperformed patients with AD in delayed recall, for both AD and bvFTD the recognition score was significantly lower than the free recall score (relative to the control group), indicating the additional value of the recognition memory paradigm. Post hoc analysis in the groups of bvFTD patients showed no differences in discriminability or response bias between *GRN* and *MAPT* mutation carriers and *C9orf72* repeat expansion carriers. This is surprising as increasing evidence indicates mutation-specific cognitive profiles in genetic bvFTD (e.g. [49]) and may have resulted from the modest sample size in this subgroup analysis.

Strengths of the present study include the large and well-defined patient samples, the use of the RAVLT as widely used memory test and involvement of both simple and elaborate measures of discriminative ability and response bias. Limitations include the lack of postmortem pathological confirmation in the patient groups, which is particularly problematic in bvFTD[50, 51]), albeit that 40% of the patients with bvFTD had a known genetic mutation for bvFTD. Also, although analyses were adjusted for time since symptom onset, the disease course is different between AD and bvFTD which makes it difficult to truly match the patient groups (as is reflected in our study in lower age in bvFTD patients and lower MMSE scores in AD patients). Moreover, in our sample time since symptom onset was shorter for bvFTD patients than for AD, which reflects our role as a expertise center for FTD and inclusion of a proportion of mutation carriers from known FTD families in the Netherlands. One can hypothesize that differences in memory performance in bvFTD and AD change with disease progression and accompanying atrophy of frontal and temporal brain areas. For example, it is hypothesized that frontal/dysexecutive impairment in AD increases as the disease progresses[48], which may result in a larger (liberal) response bias and a potential larger between-group difference. The mean age of the AD patients was relatively young (68.1 ± 7.2 years) with an MMSE score of 22.7 ± 4.6 indicating a substantial number of early-onset cases and a relatively mild disease severity. Generalization of our results to older patients and more severe disease stages should therefore be performed with caution. We used the recognition trial of the RAVLT as it is one of the most commonly used verbal episodic memory tests that is easily administered and readily available in clinical practice. Our analyses were thus constrained by the methodological limitations of such a clinical tool, thereby also limiting generalizability of our results. The paradigm of the California Verbal Learning Test (CVLT) may be even better suited to examine the relative contribution of memory and executive processes in these patient groups as it allows for examination of (proactive and retroactive) interference and cueing. It would also be valuable to vary the conditions of the recognition memory paradigm (number and type of distractor items) and see how this influences discriminative ability and response bias in patients with dementia. An important clinical implication that results from our study is that

although patients with AD show an overall worse recognition memory performance, the presence of a recognition memory deficits does not rule out bvFTD in individual patients.

In sum, our results show a difference in recognition memory performance between patients with bvFTD and AD, particularly in discriminative ability, but not in response bias. Discriminative ability was mainly associated with memory for both patient groups and was additionally associated with language, but not executive functioning in bvFTD. Response bias was unrelated to other cognitive functions.

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Supplementary file 1: Tables

Supplementary Table 1. Comparison of sporadic versus genetic bvFTD and 3 genetic mutations.

	Sporadic bvFTD	Genetic bvFTD	Statistics	MAPT	GRN	C9orf72	Statistics
n	51	34		9	12	13	
Age	63.3 ± 9.0	59.6 ± 8.7	ns	52.6 ± 6.4	58.3 ± 5.7	66.6 ± 7.0	c9orf72>MAPT=GRN
Male sex (%)	34 (67%)	17 (50%)	ns	7 (78%)	5 (42%)	5 (39%)	ns
Education[a], median (IQR)	5 (4-5)	5 (4-5)	ns	6 (5-6)	4 (4-6)	5 (4-5)	MAPT>GRN=c9orf
MMSE	25.1 ± 5.2	25.1 ± 5.2	ns	25.4 ± 2.5	21.6 ± 7.2	27.9 ± 1.4	MAPT=C9orf72>GRN
FAB[b]	12.4 ± 4.0	12.2 ± 4.1	ns	14.1 ± 3.6	8.9 ± 4.6	13.0 ± 2.7	MAPT=C9orf72>GRN
Months since symptom onset	37.8 ± 27.8	17.3 ± 16.4	spor>gen	12.8 ± 9.0	19.2 ± 25.9	27.2 ± 23.0	c9orf72>MAPT=GRN
Delayed recognition (0-30)	23.7 ± 4.5	26.6 ± 4.0	ns	26.0 ± 4.6	25.7 ± 4.8	27.7 ± 3.0	ns
Total hits on recognition	13.1 ± 2.0	13.5 ± 2.1	ns	13.2 ± 2.0	13.3 ± 1.7	13.5 ± 2.7	ns
False positives on recognition	4.4 ± 4.6	1.8 ± 3.3	ns	2.2 ± 3.7	2.7 ± 4.1	0.8 ± 1.5	ns
Hits minus False positives	8.7 ± 4.5	11.7 ± 4.1	gen>spor	11.0 ± 4.6	10.7 ± 4.8	12.7 ± 3.0	ns
Discrimination index A'	0.84 ± 0.13	0.91 ± 0.10	ns	0.90 ± 0.11	0.88 ± 0.13	0.94 ± 0.06	ns
Yes/No ratio	1.7 ± 1.8	1.4 ± 1.6	ns	1.4 ± 1.4	1.7 ± 2.3	1.0 ± 0.3	ns
Bias index B"	-0.08 ± 0.42	0.09 ± 0.42	ns	0.15 ± 0.44	0.08 ± 0.38	0.10 ± 0.45	ns

Data are mean and SD unless otherwise specified. Analyses are adjusted for age, level of education and time since symptom onset. ns, no significant difference between the groups; bvFTD = behavioral variant frontotemporal dementia; *MAPT* = microtubule-associated protein tau; *GRN* = progranulin; *C9orf72* = chromosome 9 open reading frame 72; IQR = interquartile range; MMSE = Mini-Mental State Examination; FAB = frontal assessment battery.

CHAPTER 5

Mindfulness-Based Stress Reduction in presymptomatic genetic frontotemporal dementia: a pilot study

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Abstract

Pre-symptomatic frontotemporal dementia (FTD) mutation carriers and first-degree family members that are 50% at-risk for FTD may experience symptoms of anxiety and depression as a result of the ambiguity of when or if symptoms of the disease will manifest. We conducted a pilot study to investigate the use of an online mindfulness-based stress reduction (MBSR) course to reduce symptoms of anxiety and depression in presymptomatic frontotemporal dementia (FTD) mutation carriers and individuals 50% at-risk. Seven known mutation carriers and six individuals 50% at-risk completed a standardized 8-week MBSR course, and filled out pre- and post and two-month follow-up questionnaires. The primary outcome measure was the Hospital Anxiety and Depression Scale (HADS). Measures of psychological distress (SCL-90-R), coping style (UCL), quality of life (SF-36) and mindfulness skills (FFMQ) were administered as secondary outcome. Group effects were analyzed with repeated measures ANOVA or Friedman's test, and the individual reliability change index (RCI) was calculated per participant for each outcome measure. Semi-quantitative data included an evaluation and process measure post-intervention. Significant decline was found on the HADS-A post-intervention and after 2 months ($p = 0.01$), with 54% and 62% of participants demonstrating a clinically significant RCI, respectively. On the HADS-D, significant decline was found 2 months post-intervention ($p = 0.04$), which was driven by 23% of participants whom had a clinically significant RCI. Additional changes were found between baseline and post-intervention on the seeking distraction and reassuring thoughts subscales of the UCL, the depression and interpersonal sensitivity subscales of the SCL, the observe subscale of the FFMQ, and on physical role limitations of the SF-36 (all $p < 0.05$). The process evaluation form indicated that the course was found beneficial by participants, and that they applied it in a wide range of everyday situations. This exploratory pilot study indicates the feasibility of MBSR in reducing anxiety and depression in presymptomatic FTD mutation carriers and 50% at-risk individuals. A randomized controlled trial is necessary to replicate these results.

Introduction

Frontotemporal dementia (FTD) is an early-onset neurodegenerative disorder, associated with behavioral, cognitive, and/or motor impairment[1-3]. It is a debilitating, fatal illness that has an autosomal dominant inheritance pattern in up to 30% of cases with high penetrance[4]. Each child of an affected person has a 50% chance of inheriting the genetic mutation and thus developing the disease in the future. Age of symptom onset and prognosis varies within families, and there are currently no disease-modifying therapies available[5]. Some individuals choose to undergo predictive testing to determine if they are carriers of a familial FTD mutation. However, knowledge of being a carrier represents unavoidable dementia onset and a dramatically shortened lifespan[5]. Knowing one will develop a life-limiting condition, with possibly first-hand experience of the effects of the disease from one or multiple family members, may influence plans and attitudes toward the future, such as life planning, financial care and insurances[6, 7]. It is therefore unsurprising that the ambiguity of being at risk for a neurodegenerative disorder with no cure may lead to a variety of adverse psychological reactions, such as anxiety and depression[8, 9].

Previous studies in other familial neurodegenerative disorders, such as familial Alzheimer's disease, Huntington's disease (HD) and Machado-Joseph disease, have indeed shown elevated depressive symptoms in presymptomatic mutation carriers aware of their genetic status, and individuals that are 50% at-risk of the disease[10-12]. Very few studies have investigated psychological distress in genetic FTD mutation carriers, and were from a biological perspective, presuming that biological factors are the main determinants of neuropsychiatric symptoms in the early stage of FTD[13, 14]. Yet, similar to what has been reported in premanifest HD individuals, reports from presymptomatic FTD mutation carriers often include emotional and social concerns such as anxiety about when symptoms will manifest, the impact of the disease on self and family, difficulties with acceptance of the disease, lack of support, perceived negative attitudes of others, and limited public awareness[15, 16]. In the absence of disease-modifying treatment, psychological interventions are necessary that can reduce psychological distress experienced by individuals at-risk of developing FTD.

To our knowledge, no psychological interventions have been investigated in presymptomatic FTD mutation carriers that experience psychological distress, nor are there tailored therapeutic programs offered to these individuals in the Dutch healthcare system. Although multiple psychotherapeutic interventions are available for treating anxiety and depression, such as cognitive behavioral therapy (CBT), these approaches are based on the idea that distortions in thinking are the cause of psychological problems, and that efforts to change these thinking patterns can relief symptoms of anxiety/depression[17]. Yet, the (often mild) psychological distress experienced by presymptomatic mutation carriers and 50% at-risk individuals is likely caused by the realistic scenario that one will or has a higher chance of

developing a debilitating and fatal illness, rather than (unrealistic) distortions in thinking. A mindfulness-based approach could prove more beneficial to these individuals due to its underlying principles and practices. Mindfulness involves paying attention purposefully, in the present moment and without judgment[18]. The focus is on cultivating conscious awareness on a moment-to-moment basis with an open and non-judgmental attitude by performing meditation-based exercises[18]. Accepting things as they are, without trying to change them is emphasized[18]. Hence, there has been an increasing interest in the application of mindfulness-based interventions, such as mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT), in populations with chronic diseases[19, 20]. Several studies have shown that such interventions are effective in cultivating acceptance of a long-term condition, and importantly that the social interaction with others that are in the same situation, in the form of group therapy rather than individual sessions, enhances the benefits of the intervention[21, 22]. In other neurological diseases, e.g., Parkinson's disease and multiple sclerosis, mindfulness-based interventions have proven effective in lowering symptoms of anxiety and depression, and/or improving quality of life[23-25]. Eccles et al.[6] have recently reported that MBCT was considered beneficial by premanifest HD individuals, but live sessions were not considered feasible due to recruitment issues as a result of the rarity of the disease. The authors suggested that online course delivery might be more feasible[6, 15]. No feasibility or pilot study has been published on psychological approaches in known mutation carriers or 50% at-risk individuals of a mutation causative of FTD.

The present pilot study aimed to explore the feasibility and efficacy of a MBSR course in lowering psychological distress in known mutation carriers or individuals with a 50% risk of developing FTD. The primary aim was to investigate the effect of MBSR on reducing symptoms of anxiety and depression, and secondary aims were to investigate whether MBSR can reduce symptoms of psychopathology and stress, whether it can lead to a more beneficial coping style and whether it can improve health-related quality of life.

Methods

Participants

Fourteen participants were recruited via the FTD risk cohort study (FTD-RisC), in which cognitively healthy first-degree family members of patients with genetic FTD are longitudinally tracked[26]. Participants had to be aged 18 or over. They had undergone predictive testing and were known mutation carriers of a *C9orf72*, *GRN*, *MAPT* or *TARDBP* mutation, or were 50% at-risk (i.e., did not undergo predictive testing). They had to report experience of (mild) emotional burden, reflected in a Hospital Anxiety Depression Scale (HADS) score of ≥1[27]. Participants had to be asymptomatic according to established diagnostic criteria for bvFTD[3], PPA[2], and ALS[1], and have a CDR® plus NACC FTLD global score ≤ 0.5[28]. Clinical status was

assessed as described previously[29]. The Mini-Mental State Examination (MMSE) measured global cognitive functioning[30]. Participant characteristics are given in Table 1. All participants' ethnicity was reported as Caucasian. Exclusion criteria included other neurological and/or psychiatric diagnoses, and participants had to attend at least six sessions of the MBSR training. Thirteen participants completed the MBSR training and one participant withdrew after session five. The latter missed three sessions early in the course due to personal circumstances and found it hard to immerse with the group and exercises after that. The study was approved by the Medical and Ethical Review Committee of the Erasmus MC University Medical Center (MEC-2019-0226).

Recruitment

All participants of the FTD-RisC study that fulfilled inclusion and exclusion criteria (n = 130) were invited for the training via an e-mail invitation that informed them about the MBSR training. Potential participants could then contact the research team to hear more about the study, after which the mindfulness teachers (LCJ and JMP) contacted the potential participant by telephone to discuss what participation involved. Twenty participants reached out to the research team and indicated to be interested in the study, of which five participants dropped out due to logistic reasons (i.e., dates and times did not suit them, training location too far away), and one participant was excluded due to a diagnosis of major depressive disorder according to the DSM-V[31]. We ran two separate groups with a maximum of eight individuals so that there would be time during the sessions for individuals to connect and share experiences and stories.

Table 1. Participants characteristics. Data are presented as mean (standard deviation) unless otherwise specified.

n	13
Mean age (SD) [Range]	52.3 (11.7) [29-67]
Sex, ratio f:m	8:5
Mean education level[a] (SD)	5.8 (0.8)
Known mutation carrier, yes:no	7:6
MMSE [Range]	29.1 (1.3) [26-30]
CDR® plus NACC FTLD global score 0, n 0.5, n	 9 4
Affected gene in family, n *C9orf72* *GRN* *MAPT* *TARDBP*	 5 5 2 1

Abbreviations: SD = standard deviation; f = female; m = male; MMSE = Mini-Mental State Examination; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration; *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; *TARDBP* = TAR DNA binding protein. [a]Level of education was recorded using seven categories in accordance with the Dutch educational system (1=less than 6 years of primary education to 7 = academic schooling).

Procedure

All participants gave written informed consent. Primary and secondary outcome measures, as described in Section Outcome measures, were administered pre- and post-intervention, as well as 2 months after ending the course (Supplementary Table 1). Directly post-intervention participants were asked to fill out an evaluation form that was designed specifically for the purpose of this study (Section Intervention). Participants completed the questionnaires from home via the online survey tool LimeSurvey[32]. The first three sessions of the first group were in person, but due to lockdown restrictions as the result of the COVID-19 pandemic, all other sessions of the first group were held online via Microsoft Teams. Due to positive reactions from the first group on the online course and in order to allow recruitment of people from a larger geographical area, all sessions of the second group were held online. Because of possible emotional reactions that may arise during the course, participants were invited to contact the MBSR teachers for any needs, questions, or practice support at any time outside the class setting.

Intervention

The MBSR training followed the standard 8-week MBSR program which included meditation, mindful movement and yoga exercises, and information on the physiological and psychological basis of stress[33]. An overview of the MBSR program per session is given in Supplementary Table 2. Each session lasted 120 min with a 15 min break. An all-day silent retreat as part of the standard program was not possible due to COVID-19 restrictions, and therefore we merged this aspect of the training with session 7 (Supplementary Table 2). Participants were asked to complete at least 45 min of daily home practice using provided audio fragments and worksheets that included stories, poetry and metaphors. This also included a personal log where participants were asked to fill out whether they performed the exercises. The course was taught by a certified MBSR trainer (LCJ) and an experienced MBSR practitioner (JMP), whom are both neuropsychologists with extensive experience in (presymptomatic) FTD.

Outcome measures

The primary outcome measure was the total, depression subscore (HADS-D) and anxiety subscore (HADS-A) of the HADS, developed to measure psychological distress in somatic patient populations[27, 34, 35].

In addition, five secondary outcome measures were included: the Symptom Checklist 90 Revised (SCL-90-R) for measuring psychological problems and symptoms of psychopathology[36], the Utrecht Coping List (UCL) for measuring coping styles[37], the 36-item Short Form Health Survey (SF-36) for measuring health-related quality of life[38], the Perceived Stress Scale (PSS) for measuring the perception of stress[39], and the 39-item Five Facet Mindfulness Questionnaire (FFMQ) for measuring mindfulness skills[40].

Further measurements included a visual analog scale (VAS) to measure the level of distress before and after each session, ranging from 0 (no distress) to 10 (very distressed)[41]. To evaluate participants' experiences of the training they were asked to fill out an evaluation form that consisted of the Applied Mindfulness Process Scale (AMPS)[42], a process measure for evaluating mindfulness-based interventions, and 10 additional questions that focused on (1) the satisfaction with the MBSR training; (2) whether it helped them cope better with the higher risk of FTD; and (3) in case of group 1, their opinions on the (change to) online course. In addition, an open-ended box was added where participants were asked to share their experiences with the course.

Statistical analysis

Statistical analyses were performed in R version 4.04. The significance level was set at $p < 0.05$ (2-tailed) across all comparisons. There was no missing data.

Group level

Parametric repeated measures analysis of variance (i.e., F-test statistic) or, in case of violated assumptions, non-parametric Friedman's tests (i.e., $\chi 2$ test statistic) were performed with the primary and secondary outcome measures (Section Outcome measures) as dependent variables and a within factor consisting of three time-points (i.e., baseline, post-intervention and 2 month follow-up). We performed pairwise comparisons between time points with parametric paired sample t-tests or non-parametric Wilcoxon signed-rank tests.

Individual level

To determine clinically significant change in individual participants, the individual reliable change index (RCI) was calculated according to the Jacobson-Truax (1991) formulae using the JTRCI package in R[43]. More specific, the RCI was calculated by dividing the absolute difference between the pre- and post-measurement by the standard deviation of the standard error of measurement for a difference score (Sdiff). The test-retest reliability coefficients were extracted from validation studies (35–37, 44–46). This study investigated mild symptoms of anxiety and depression in individuals that are a known mutation carrier or 50% at-risk of carrying a mutation causative of FTD; therefore we defined reliable change as ± 1 Sdiff.

Results

Quantitative data

Primary outcome measure

The means and standard deviations of the HADS per time point are reported in Table 2. There was a significant difference between time points on the depression [$F_{(2,24)} = 5.54$, $p = 0.01$, $\eta p^2 = 0.09$; Figure 1A], anxiety [$\chi 2(2) = 6.45$, $p = 0.04$, $W = 0.25$; Figure 1B] and total [$F_{(2,24)} =$

4.87, $p = 0.02$, $\eta p^2 = 0.07$; Figure 1C] score of the HADS. Significant differences between time-points are illustrated in Figure 1.

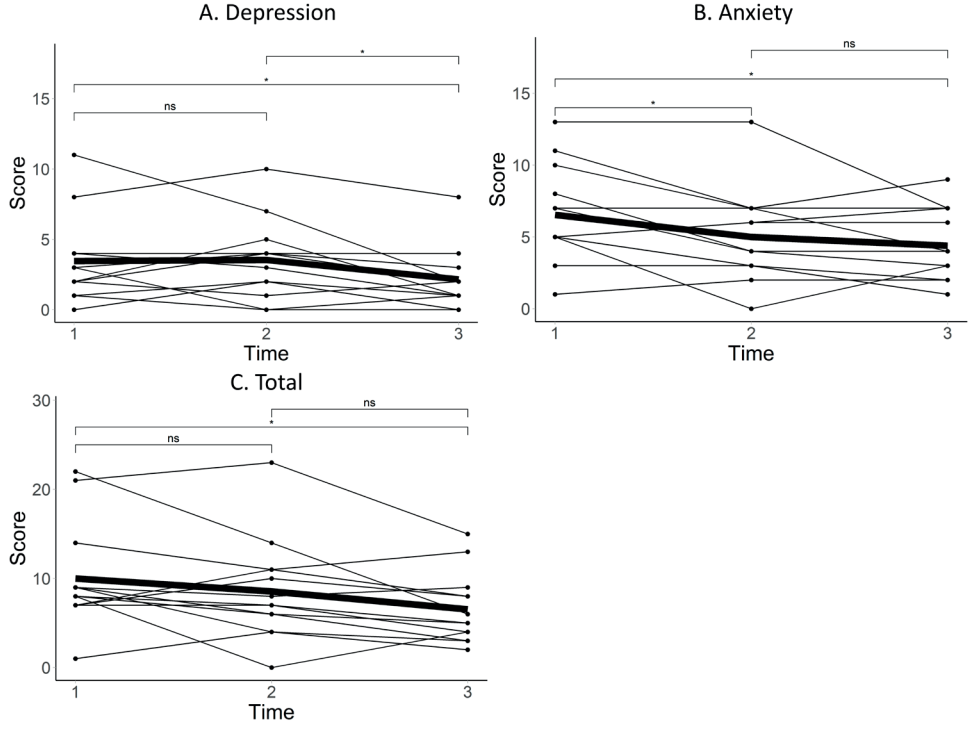
On the HADS-A, seven participants reported a clinically meaningful decline directly post-intervention, of whom 57% were known mutation carriers. Two months post-intervention eight participants reported a clinically meaningful decline, of whom 63% were known mutation carriers, whereas one participant, a known mutation carrier, reported an increase

Table 2. Mean, standard deviations per time point on the Hospital Anxiety and Depression Scale.

	Baseline			**Post-intervention**			**Two months follow-up**		
	Total	Known carriers	50% at-risk	Total	Known carriers	50% at-risk	Total	Known carriers	50% at-risk
Anxiety	6.54 (3.31)	6.71 (4.07)	6.33 (2.50)	5.00 (3.24)	5.00 (4.24)	5.00 (1.90)	4.38 (2.53)	4.14 (2.12)	4.67 (3.14)
Depression	3.46 (3.02)	4.14 (3.98)	2.67 (1.21)	3.54 (2.79)	4.14 (3.44)	2.83 (1.83)	2.15 (2.12)	2.00 (2.71)	2.33 (1.37)
Total	10.00 (5.80)	10.90 (7.73)	9.00 (2.61)	8.54 (5.67)	9.14 (7.63)	7.83 (2.48)	6.54 (3.95)	6.14 (4.38)	7.00 (3.74)

All data are presented as mean (standard deviation).

Figure 1. Self-reported (A) anxiety, (B) depression and (C) total scores on the Hospital Anxiety and Depression Scale at baseline, post-intervention and after 2 months.

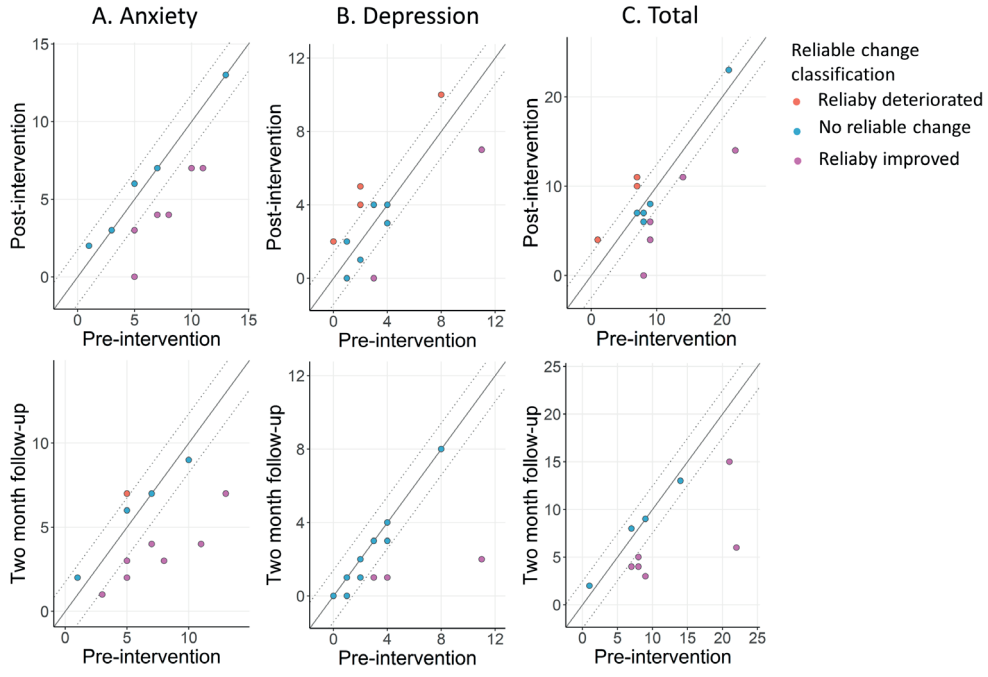


(Figure 2A). On the HADS-D, two participants reported a clinically meaningful decline directly post-intervention, whom were both known mutation carriers. Four participants reported an increase directly post-intervention, of whom 75% were known mutation carriers. After 2 months, three participants reported a decline, whom were all known mutation carriers (Figure 2B). Overall, five participants reported a clinically meaningful decline on the total score of the HADS, of whom 60% were known mutation carriers. Three participants reported an increase directly post-intervention, of whom 66% were known mutation carriers. After 2 months, eight participants reported a clinically meaningful decline, of whom 63% were known mutation carriers (Figure 2C).

Secondary outcome measures

The data on the secondary outcome measures are reported in Supplementary Table 3. Significant increases between time-points were found on the seeking distraction [$F_{(2,24)}$ = 3.48, p = 0.05, ηp^2 = 0.06] and reassuring thoughts [$F_{(2,24)}$ = 8.3, p < 0.01, ηp^2 = 0.12] subscales of the UCL, the observe [$F_{(1,15)}$ = 7.51, p = 0.01, ηp^2 = 0.15] and non-reactivity to inner experience [$F_{(1,15)}$ = 4.52, p = 0.04, ηp^2 = 0.14] subscales of the FFMQ, and physical [$\chi 2(13)$ = 6.09, p = 0.05, W = 0.23] and emotional role functioning [$\chi 2(13)$ = 6.74, p = 0.03, W = 0.26]

Figure 2. Reliable change indices on (A) anxiety, (B) depression and (C) total scores of the Hospital Anxiety and Depression Scale. The upper window represents the change between baseline and post-intervention and the lower window the change between baseline and after 2 months.



of the SF-36. A significant decline was found on the depression [$\chi2(13) = 8.92$, $p = 0.01$, W = 0.34], interpersonal sensitivity [$\chi2(13) = 13.7$, $p < 0.01$, W = 0.53] and total psychoneuroticism [$\chi2(13) = 7.41$, $p = 0.03$, W = 0.29] scores of the SCL-90-R and the general health perception [$F_{(2,24)} = 3.47$, $p = 0.05$, $\eta p^2 = 0.12$] subscale of the SF-36. *Post-hoc* pairwise comparisons between time-points revealed significant differences between baseline and post-intervention, except for non-reactivity to inner experience of the FFMQ, and emotional role functioning and general health perception of the SF-36, which were different between baseline and 2 months post-intervention. Calculation of the individual RCIs demonstrated that 2 months post-intervention more than 40% of participants increased on the seeking distraction (43% known mutation carrier) and reassuring thoughts (50% known mutation carrier) subscales of the UCL, the observe subscale of the FFMQ (67% known mutation carrier) and on the PSS (67% known mutation carrier) (Supplementary Table 3). Three participants reported an increase on the depression subscale of the SCL-90-R, of whom two were known mutation carriers. More than half of the participants reported a decline on general health perception of the SF-36 2 months post-intervention (71% known mutation carrier) (Supplementary Table 3).

Semi-quantitative data

Visual Analog Scale for Distress Level

Overall, participants reported a decline in distress level after each training session on the VAS with a mean delta of −1.94 and a standard deviation of 2.14. Only one participant experienced a strong increase in distress from 0.5 to 9 during session six. This was self-reported due to the mountain meditation at the end of that session, which reminded the participant of a recent personal stressful situation, but disappeared a few hours after the session.

Evaluation form

The frequencies that participants answered “mostly true” and “often” or higher on each item of, respectively, the evaluation form and the AMPS are reported in Table 3. All participants (*n* = 13) indicated that they looked back on the course feeling satisfied, that they wanted to continue applying the exercises and skills learned in the course, and that they would recommend the course to others. All but one participant indicated that the course met their expectations and that they underwent the course at the right moment in their lives. Most participants (*n* = 11) felt that the course fitted in well with their daily life activities and liked that the course was offered online. All participants from group 1 indicated that they were not affected by switching from physical to online sessions. Fewer participants reported that the course was relevant in dealing with fears and uncertainty with respect to FTD (*n* = 9) and that the support and experiences from other participants helped them (*n* = 8).

On the process measure scale, the two most reported daily-life situations where mindfulness skills were applied were to reduce tension when feeling stressed (*n* = 13) and to notice and appreciate pleasant situations (*n* = 12). This was followed in frequency by reports of having

used mindfulness to physically relax, enjoy little things more, calm down when feeling upset, view difficult situations from the positive side and realize that thoughts are not facts (*n* = 11). Ten participants reported to have used mindfulness practice to realize that their thoughts are not necessarily true, and nine participants used it to stop unhelpful reactions and learn that there are other ways to look at difficult situations. More than half of the participants reported that they used mindfulness practice to view their thoughts from a distance, not give into negative feelings right away, and notice pleasant things in difficult situations (*n* = 8). Only six participants indicated that they used it to realize that they can grow stronger from negative situations.

In addition, four themes were identified from the open-ended box at the end of the evaluation form:

(1) increased awareness e.g.,
"*Before the course a walk outside was nice. Now I experience my surroundings more intensely. I smell the air, feel my legs, enjoy the colours that I see."*
"*I have become more aware of everything around me. I am less often doing things on "autopilot"*.

(2) stress management e.g.,
"*The course has taught me tools to cope with stress. I have learned to put my situation into perspective. There are worse things that could happen. I am more observant of and accepting towards certain situations."*

(3) contact with others in the same situation e.g.,
"*Meeting others with similar experiences, and hearing their stories has helped me a lot. It strengthens me to know that I am not alone."*

(4) delivery mode e.g.,
"*The contact with fellow individuals at-risk for FTD was not completely successful for me due to the online aspect of the course, which was a disappointment."*
"*It is a shame that we were not able to come together in person. However, I liked that I did not have to travel."*

Discussion

The primary aim of this pilot study was to explore the feasibility and efficacy of a MBSR course in lowering symptoms of anxiety and depression in individuals that are 50% at-risk or known mutation carriers of autosomal dominant FTD. Quantitative analyses demonstrated

Table 3. Results from the evaluation form and AMPS post-intervention.

Evaluation form	
Statement	*% ≥ mostly true*
I look back on the mindfulness course with a satisfied feeling	100%
The mindfulness course met my expectations	92.4%
The mindfulness course fitted in well with my daily activities and obligations	84.6%
The mindfulness course was at the right time in my life for me	92.4%
The mindfulness course was relevant to me in dealing with my fear and uncertainty about FTD	69.3%
The support and experiences on FTD from my fellow students helped me a lot	61.5%
I want to continue to apply the exercises and skills I learned in the mindfulness course	100%
I would recommend the mindfulness course to others	100%
I liked that the course was partly offered online due to the COVID pandemic	84.6%
I have not been affected by the switch from physical to online meetings due to the COVID pandemic	77%
Applied Mindfulness Process Scale	
I have used mindfulness practice to…	*% ≥ often*
…view my thoughts from a distance	61.5%
…physically relax	84.6%
…realize that my thoughts do not have to be true	76.9%
…enjoy the little things more	84.6%
…calm myself down when I was feeling upset	84.6%
…not give into negative feelings right away	61.5%
…view a difficult situation from the positive side	84.6%
…reduce tension when I was feeling stressed	100%
…realize that I can grow stronger from negative situations	46.2%
…stop my unhelpful reactions to certain situations	69.2%
…notice and appreciate pleasant situations	92.4%
…put aside unpleasant thoughts or feelings	61.5%
…realize that my thoughts are not facts	84.6%
…notice the pleasant things in difficult situations	61.5%
…learn that there are other ways to look at certain situations	69.2%

Answer options on the evaluation form were: not true, mostly not true, neutral, mostly true and true. Answer options on the AMPS were: never, rarely, sometimes, often and almost always. Percentages reflect the relative number of individuals that answered mostly true and often or higher.

lower levels of anxiety on the HADS directly and 2 months post-intervention, and lower levels of depression 2 months post-intervention. Consistently, secondary analyses revealed a decline in depression and interpersonal sensitivity. Furthermore, participants reported to be more observant of their surroundings, to use the coping styles seeking distraction and reassuring thoughts more regularly, and to feel less restricted by role limitations due to physical health. An evaluation and process measure form indicated that participants were

overall satisfied with the MBSR course, and that they applied mindfulness skills in a wide range of daily activities. Taken together, the results of this exploratory pilot study indicate that an online MBSR course could be a feasible intervention for reducing symptoms of anxiety and depression in 50% at-risk individuals or known mutation carriers of autosomal dominant FTD.

Anxiety scores on the HADS declined at the first post-intervention measurement, and remained significantly lower 2 months after ending the MBSR program. Individual RCI calculations demonstrated that more than 60% of participants reported a clinically meaningful decline in anxiety level. These findings are consistent with the conceptual focus of the intervention: mindfulness principles focus on letting thoughts come and go easily, without attempting to alter, diminish or expand them[47]. Through MBSR participants learn to view their mental events (such as anxiety or stress) as transient, and not reality[47]. Eccles et al.[6] investigated the use of a mindfulness program in preclinical HD individuals, and suggested that mindfulness can help anchor individuals in the present rather than allowing fear to drive them into the future[6]. Qualitative results indicated that participants used mindfulness skills in everyday life, for example, to realize that thoughts are not necessarily true or factual, to not give in to negative feelings, to put aside unpleasant thoughts and feelings, to learn that there are other ways to look at certain situations and to put their situation (i.e., being at-risk for or a known mutation carrier of FTD) in a new perspective, which all potentially could have contributed to less anxious feelings and thoughts.

Depression scores on the HADS were not lower directly post-intervention, but they were lower after 2 months post-intervention. This significant group effect appeared to be driven by two to three participants that reported a clinically meaningful change directly post-intervention and after two months. Most participants remained unchanged and, surprisingly, four participants reported an increase post-intervention which was no longer present after 2 months. A possible explanation for this result is that, a floor effect was observed in ~50% of participants, as only two participants reported a HADS-D score higher than four at baseline. Due to the low variation in test scores, significant RCIs were observed in those participants that reported only small changes in test scores. Studies in other preclinical neurodegenerative populations have also been contradicting, with some reporting higher levels of depression in at-risk individuals, whereas other studies were unable to confirm this[8-12, 48-55]. One hypothesis is that the psychological distress experienced by known mutation carriers or 50% at-risk individuals for FTD mostly stems from stress-related and anxious feelings about an uncertain future rather than mood-related problems. Another hypothesis is that the complexity of feelings and emotional distress experienced by individuals that are at-risk of a life-limiting condition cannot be expressed in a quantitative measure such as the HADS. The HADS measures levels of anxiety and depression in the past 4 weeks, whereas the psychological distress that presymptomatic mutation carriers, and even individuals at 50% risk, experience is caused by a transient situation (i.e., they remain a mutation carrier or 50% at-risk for a

mutation). This raises the question whether mood-related problems that arise as a result of being at-risk can be captured with the HADS, or any quantitative measure. Interestingly, a significant decline from pre- to post-intervention and after 2 months was found on the depression subscale of the SCL-90-R, which appeared to be driven by three, partly different, participants that reported a clinically meaningful change. This suggests that the course was effective in lowering depressive symptoms for some individuals. Specifically known mutation carriers appeared to benefit from the intervention in lowering depressive symptoms as five out of six participants that reported a clinically meaningful decline on either the HADS-D or the SCL-90-R had undergone predictive testing and were found to carry a genetic mutation. This is possibly due to most of them having higher depression scores at baseline than individuals that are merely 50% at-risk. This heterogeneity in our sample might have influenced results on other outcome measures as well. Qualitative interviews with people at-risk for FTD might shed more light on the variety of adverse psychological reactions that they experience and can help identify a suitable outcome measure for a future randomized controlled trial (RCT).

A decrease in interpersonal sensitivity was observed on secondary outcome measures. This is in line with a previous study that showed that mindfulness traits are negatively correlated with interpersonal sensitivity[56]. Furthermore, an increase in reassuring thoughts and seeking distraction as coping styles was observed. It has been suggested that the central themes within a MBSR course, such as acceptance of thoughts and feelings and non-judgmental awareness to them, can show new ways to respond and cope with internal and external problems as well as help decrease habitual problematic patterns of thinking, feeling and behavior[47]. By shifting their thoughts' focus toward calming or tranquil thoughts, thereby reinforcing positivity, helps participants in realizing how unhelpful negative thoughts and feelings are. This was also reflected by the change in how limited they felt by physical role limitations on the SF-36, and by what was reported on the process measure scale (e.g., physically more relaxed, enjoy little things more, view difficult situations from the positive side, notice and appreciate pleasant situations). Surprisingly, only the observe subscale of the FFMQ significantly increased post-intervention, indicating that the other mindfulness facets did not change as a result of the course. Consistently, participants reported to have become more aware of their surroundings on the evaluation form. A possible explanation for why we did not find improvement on the other facets is that the group mean for non-judging to inner experience, acting with awareness and describing was at baseline already similar to that of experienced meditators, possibly causing a ceiling effect[57]. In contrast, the group mean for observing and non-reacting to inner experience were comparable to a non-meditating sample at baseline, allowing improvement over time[57]. Lastly, a change over time was observed on the emotional role restrictions and general health perception subscales of the SF-36. However, this effect was only visible 2 months post-intervention and it seems therefore more likely that these changes were caused by different health-related life events or the lower test retest reliability that has been reported previously on specifically these subscales[44].

All sessions led to a decrease in acute stress levels as measured by a visual analog scale. Furthermore, qualitative data indicated that the MBSR course was found beneficial by participants and that they wanted to continue applying what they had learned in their daily lives, which, according to what was reported on the process measure, included a wide range of activities. Most participants indicated that they liked the online aspect of the course, as it did not require them to travel far. Although some individuals indicated that it helped them to meet others with similar experiences, others indicated that they missed this specific aspect due to the online sessions and that they would have preferred to meet in person. Meeting online did allow us to recruit people from a larger geographical area.

To our knowledge this is the first pilot intervention study in individuals at-risk for and carriers of a gene mutation causative of FTD. There are a few limitations to this study that should be taken into account when interpreting the results. First, as this was an exploratory pilot study to determine the feasibility and efficacy of the intervention, no sample size calculations were performed and only a small sample of individuals were recruited. Furthermore, the high number of outcome measures may 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. For these reasons, quantitative analysis of questionnaires should be interpreted cautiously. Secondly, no control group was included as we did not have access to a large enough cohort of mutation carriers or at-risk individuals that experience psychological distress. It is therefore not possible to infer the specific effect of MBSR on lowering symptoms of anxiety and depression. A multi-center RCT that compares to an active control group as well as a larger sample size (e.g., within the Genetic FTD Initiative (GENFI)) is necessary to replicate the results from this pilot. Thirdly, most individuals from our sample of at-risk individuals and presymptomatic mutation carriers scored in the 'normal' range compared to a reference population on all outcome measures, likely resulting in floor and ceiling effects. A possible moderating factor could be estimated time to (potential) symptom onset, with older individuals experiencing different emotions and thoughts related to FTD than younger individuals. Inclusion criteria for a RCT should be carefully considered. Furthermore, future research should focus on developing and validating other outcome measures that cover the psychological distress experienced by individuals at-risk of a genetic form of dementia better. Lastly, due to the COVID-19 pandemic we had to switch from in-person to online meetings after session three of the first group. We cannot directly compare this online version of MBSR with the face-to-face version of the intervention, but it could be that the online structure of the MBSR course is less effective than a live one as it might have negatively impacted bonding and support between participants. A recent systematic review revealed medium positive effects of online MBSR/MBCT delivery on mental health outcomes compared with inactive controls, and little difference with active controls such as in-person delivery[58]. However, most included studies in the review had low methodological quality[58] and thus further studies to compare different delivery options in this field are necessary.

To conclude, this exploratory pilot study indicates the feasibility of online MBSR in individuals 50% at-risk and known carriers of a mutation causative of FTD in reducing symptoms of anxiety and depression. A randomized controlled trial in this population is necessary to confirm these results.

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Supplementary file 1: Tables

Supplementary Table 1. Outcome measures and assessments during MBSR programme.

Measure	Target	Baseline	Post-intervention	2 months follow-up
	Primary			
HADS	Psychological distress	x	x	x
	Secondary			
SF-36	(Health-related) Quality of life	x	x	x
UCL	Coping	x	x	x
SCL-90-R	Psychological problems and symptoms of psychopathology	x	x	x
PSS	Stress	x	x	x
FFMQ	Mindfulness skills	x	x	x
	Other			
VAS Distress thermometer	Psychological distress	Before and after each training session		
Calendar	Mindfulness adherence	Monthly during study period		
Evaluation form	Evaluation of the training aspects process measure for evaluating mindfulness-based interventions	Only post-intervention		

Supplementary Table 2. Overview of MBSR program per session.

Week	Theme of session	Exercises	Didactic teaching	Homework
1	Automatic pilot (living in the present, not the insecure future)	Body scan	Intention of participating Introduction mindfulness Raisin exercise	Body scan Eating one meal mindfully Attention for routine activity
2	Dealing with obstacles	Body scan Sitting meditation	Awareness of pleasant and unpleasant events Imaginary exercise to demonstrate relationship between thoughts and feelings The seven essential attitudes of mindfulness	Body scan Attention for breathing Awareness of pleasant events Attention for routine activity
3	Observing your limits, recognizing signs from your body	Yoga while lying down 3 minute breathing space	Breathing as an anchor for attention	Body scan or yoga Sitting meditation Awareness of unpleasant events 3 minute breathing space
4	Opening up to distress	Meditation on hearing Yoga while standing Sitting meditation	Interrelatedness of feelings, thoughts, and bodily sensations Psychoeducation about stress	Sitting meditation or yoga Awareness of stressfull events 3 minute breathing space
5	Responding to stress	Sitting meditation Walking meditation 3 minute breathing space	Psychoeducation about stress Reacting vs. responding Introducing silent session	Sitting meditation and walking meditation (interchangeably) Awareness of reaction in difficult situation 3 minute breathing space
6	Thoughts are no facts	Mountain meditation	Exercise focus on something difficult Exercise automatic negative thoughts	Sitting meditation or yoga Awareness of automatic negative thoughts 3 minute breathing space during stress
7	Here and now (silent session)	Sitting meditation Yoga while lying down walking meditation		Own programme Daypart in silence
8	Taking care of yourself	3 minute breathing space Body scan Short sitting meditation	Exercise energy givers vs. energy takers Letter to your future self Evaluation How to keep mindfulness in your life	Further sources of information

Supplementary Table 3. Mean, standard deviations and percentage of participants that had a reliable in- or decrease per time point on the secondary outcome measures.

	Pre-intervention		Post-intervention				Two months follow-up			
	M	SD	M	SD	+	-	M	SD	+	-
Utrechtse Coping List										
Active coping	11.80	3.10	12.20	3.47	15	8	13.40	3.15	31	8
Seeking distraction	8.54	2.70	10.10	3.52	39	8	10.20	2.58	54	8
Avoidance	9.23	2.52	9.62	1.94	0	0	10.10	2.81	31	8
Seeking social support	8.54	3.43	8.85	3.21	15	8	9.77	3.03	23	8
Passive coping	3.46	2.54	3.85	3.26	31	15	3.15	1.62	8	23
Expressing emotions	1.92	1.12	2.00	0.82	8	0	1.69	1.11	0	8
Reassuring thoughts	8.00	2.77	9.38	3.25	23	0	10.50	2.90	77	0
Symptom Checklist 90 Revised										
Anxiety	4.62	5.42	3.62	3.28	23	0	2.62	2.40	15	0
Agoraphobia	2.46	4.41	1.46	2.50	23	8	1.15	2.27	23	0
Depression	10.40	10.10	6.62	6.36	23	0	4.69	3.75	23	0
Somatization	5.46	4.45	4.38	3.43	31	31	4.23	4.07	23	15
Insufficiency	6.69	5.45	4.77	2.77	23	0	4.23	2.46	31	0
Sensitivity	8.23	8.20	6.08	11.3	15	8	5.54	6.44	15	0
Hostility	1.38	1.71	1.00	1.78	23	8	0.62	1.19	31	0
Sleeplessness	2.85	2.88	2.23	2.80	8	8	2.08	2.56	15	0
Total psychoneuroticism	44.80	36.50	32.40	30.60	23	0	27.20	19.20	15	0
Five Facet Mindfulness Questionnaire										
Observe	26.10	4.79	29.10	4.07	39	8	29.90	3.55	46	0
Describe	29.00	6.44	28.10	6.64	8	31	28.80	6.25	15	23
Acting with awareness	28.60	5.68	27.50	3.69	8	8	29.20	5.29	15	8
Non-judging of inner experience	29.50	5.44	30.20	5.86	8	8	30.80	4.42	15	8
Non-reacting to inner experience	22.50	5.36	24.50	2.22	23	0	25.90	2.87	39	0
36-item Short Form Health Survey										
Physical functioning	29.20	0.90	28.30	2.50	8	39	28.90	1.26	8	23
Social functioning	9.08	1.19	9.54	0.88	8	0	9.69	0.48	23	0
Physical role functioning	7.00	1.47	7.23	1.48	15	8	8.00	0.00	31	0
Emotional role functioning	5.46	0.88	5.62	0.77	31	8	6.00	0.00	39	0
Mental health	22.40	4.74	23.90	3.73	39	8	24.30	2.93	23	0
Vitality	16.80	4.00	18.10	1.80	31	15	18.20	2.80	39	8
Pain	51.60	7.88	50.70	10.20	15	23	54.10	5.63	31	8
General health perception	18.60	2.84	18.20	3.29	15	23	16.40	1.76	15	54
Perceived Stress Scale										
Total	28.70	3.40	28.50	2.60	23	15	27.40	1.85	46	31

+ indicates a reliable increase,–indicates a reliable decrease.

CHAPTER 6

General discussion

General discussion

Frontotemporal dementia (FTD) is the second most common cause of early-onset dementia and is associated with a highly heterogeneous clinical presentation of behavioral, language and/or motor impairments as a result of different underlying pathologies and genetic causes[1-3]. Currently, early detection is hampered by the subtlety of cognitive symptoms in the early stages and the overlap in symptoms between clinical syndromes and other neurodegenerative/psychiatric disorders. Clinical trials testing disease-modifying agents are now underway, but a major challenge facing these trials is the lack of sensitive clinical endpoints to measure potential treatment effects. In up to thirty percent of cases FTD is caused by autosomal dominant genetic mutations, most commonly a chromosome 9 open reading frame 72 repeat expansion (*C9orf72*), microtubule associated protein tau (*MAPT*) or progranulin (*GRN*) mutation[4]. This provides a unique framework to identify and study (bio)marker changes as well as other psychological challenges before symptom onset and during the conversion from the presymptomatic to the symptomatic disease stage, in order to improve patient management and treatment planning across disease stages[5].

To this end, the aims of this thesis included the identification of sensitive clinical and cognitive instruments for early detection and monitoring disease progression across the FTD spectrum, and the evaluation of a mindfulness-based stress reduction program for reducing anxiety and depression in the presymptomatic stage. We have analyzed data from the Frontotemporal Dementia Risk Cohort (FTD-RisC), the Genetic FTD Initiative (GENFI) and the outpatient memory clinic of the Erasmus Medical Center.

Disease trajectories in genetic ftd

The studies performed within this thesis demonstrate overt gene-specific patterns of cognitive decline in *C9orf72*, *GRN* and *MAPT* mutation carriers, which already start in the presymptomatic and prodromal disease stages. Different neural correlates appear to underlie these gene-specific cognitive patterns. The following paragraphs describe our most interesting findings per genetic group in more detail.

C9orf72

Our studies on presymptomatic and symptomatic *C9orf72* repeat expansion carriers demonstrate global cognitive impairment and relatively minimal decline over time, with the first changes in attention/mental processing speed, executive function, verbal fluency, memory and social cognition already being detected in the presymptomatic stage (Chapters 2.1; 2.2; 3.3; 4.2). In Chapter 3.2 we developed gene-specific cognitive composite scores, and this study confirmed that a combination of tests from all cognitive domains was most

sensitive to differentiate *C9orf72* repeat expansion carriers from controls, underlining once more the global nature of cognitive impairment in this specific group. These results are in line with other studies demonstrating widespread cognitive impairment in symptomatic *C9orf72* repeat expansion carriers [6, 7, 8]. Fewer studies investigated cognition in presymptomatic *C9orf72* repeat expansion carriers, but several recent studies have indicated an early deficit in social cognition, language and attention/mental processing speed [9, 10-14]. These early deficits in cognition are unsurprising, as our longitudinal normative brain volumetry study in presymptomatic *C9orf72* repeat expansion carriers demonstrated abnormal frontal, temporal and cerebellar volume from age 45 onwards compared to a large reference population, but without evident decline with increasing age (Chapter 2.3). Previous neuroimaging studies have indeed demonstrated cross-sectional differences between presymptomatic *C9orf72* repeat expansion carriers and controls in grey matter volume, but also reduced white matter integrity and reduced cerebral blood flow, without decline over time[15-18]. Similar to our results, Lee et al. demonstrated focal grey matter, structural and functional connectivity deficits from the fourth decade of life onwards[19]. It could be that these early changes represent the earliest signs of neurodegeneration that is very slowly progressive in nature[8, 14, 19]. Our results indicate that the time point at which brain atrophy starts to accelerate compared to normal aging lies before the age 45, but unfortunately we were unable to investigate before that time as the age range of 45-90 in the reference population did not allow for such an analysis. On the other hand, the lack of decline over time do not fit with a progressive underlying process and raises the intriguing possibility whether these early deficits are the result of a neurodevelopmental disorder in *C9orf72* repeat expansion carriers, superimposed by an additional neurodegenerative process at a later age[14, 19].

Taken together, the results from our different studies confirm the value of neuropsychological assessment and accelerated brain atrophy as staging biomarkers in *C9orf72*-associated FTD, but the slowly progressive nature complicates the identification and/or development of sensitive measures for disease onset and progression. The use of a combination of tests from all cognitive domains is recommended, and thus a composite score might be particularly promising in upcoming clinical trials for *C9orf72*. However, the continuation of current longitudinal cohort studies is crucial to investigate changes during the conversion phase more in-depth, in order to identify sensitive (bio)markers for tracking disease onset and progression in *C9orf72* repeat expansion carriers.

GRN

Our genetic FTD studies indicated that the disease trajectory of *GRN* mutation carriers is characterized by the absence of cognitive deficits or changes during the presymptomatic stage (Chapters 2.2; 3.3; 4.2), mild deficits in executive function and social cognition and a decline in verbal fluency and visuoconstruction in the prodromal stage (Chapter 2.2), and rapid cognitive changes occurring in all cognitive domains after symptom onset compared

to other genetic groups (Chapters 2.1; 2.2; 4.2). Specifically tests for executive function, attention/mental processing speed and social cognition appeared sensitive cognitive markers for this specific group (Chapters 2.1; 2.2; 3.2). Overall, these results are in line with previous studies demonstrating no or minimal cognitive deficits in presymptomatic *GRN* mutation carriers, with a steep decline occurring only in proximity of symptom onset [20-23]. Studies investigating several other biomarker changes in *GRN* mutation carriers have also shown minimal changes in e.g. grey matter volume, white matter integrity and neurofilament light chain during the presymptomatic stage, with rapid changes occurring in a relatively short time frame before overt clinical disease onset [5, 15, 16, 20, 24]. One hypothesis is that additional injury, referred to as a "second hit", is required to start the neurodegenerative process, reflected by rapid brain volume loss, cognitive decline, and symptom onset [15, 25, 26]. However, our normative brain volumetry study demonstrated that, although presymptomatic *GRN* mutation carriers remained in the "normal range"(i.e. between the 5th and 95th age- and sex- specific normative reference curve) between the age range 45-70, they showed more progressive decline than the reference centile curves for the frontal, temporal and parietal lobe from age 45 onwards (Chapter 2.3). They declined faster over time than expected in normal aging, indicating that a neurodegenerative process has been set into motion. The fact that brain volume in presymptomatic *GRN* mutation carriers was never in the abnormal range may also explain why cognitive changes have not been previously detected with standard pencil-and-paper tasks, as these might not be sensitive enough to reflect the marginal decline in brain volume.

In summary, our results confirm the value of neuropsychological assessment and accelerated brain atrophy as disease tracking and staging biomarkers. Due to the "explosive" nature of changes in proximity of symptom onset they are particularly sensitive to detect disease onset in *GRN* mutation carriers. Overall, tests for executive function (e.g. verbal fluency, concept shifting) currently appear to provide the most promising candidate cognitive markers to be used as endpoints in upcoming clinical trials in prodromal and mildly symptomatic *GRN*-associated FTD. However, as disease-modifying treatments are believed to be most effective at an earlier stage, development and/or identification of sensitive (bio)markers for tracking progression during the presymptomatic stage of *GRN*-FTD is necessary.

MAPT

Overall, our different studies indicate that the cognitive profile associated with a *MAPT* mutation is initially strongly focused on semantic and episodic memory, with executive function and social cognition disorders developing at a later, more progressed, stage of the disease (Chapter 2.1; 2.2; 3.2; 4.2). The composite score differentiating *MAPT* mutation carriers from controls was also strongly focused on semantic and episodic memory tests, in addition to a test for attention/mental processing speed and social cognition (Chapter 3.2). These results are corroborated by other studies in *MAPT* mutation carriers, demonstrating impairment on episodic memory and semantic memory in the presymptomatic stage, with

in addition executive function and social cognition impairment in the prodromal stage [10, 20, 27]. Both tests for episodic and semantic memory have been linked to anteromedial temporal lobe, which is considered the key neuroimaging feature in *MAPT* [7, 28]. Indeed, our voxel-based morphometry study on memory impairment in genetic FTD demonstrated that, although frontal areas were involved in the other two genetic groups, almost exclusively temporal areas were associated with memory performance in *MAPT* mutation carriers (Chapter 4.2). Furthermore, our normative brain volumetry study showed that presymptomatic *MAPT* mutation carriers showed the most progressive brain volume loss in the temporal lobe, crossing the 5th reference centile curve at age 55. Other neuroimaging studies have indeed shown that the earliest changes occur in temporal lobe, hippocampus, amygdala and insula [5, 15, 16]. Interestingly, our findings demonstrated the most pronounced decline in the left temporal lobe. Given that language processes are strongly left-lateralized, this result possibly explains the strong focus on semantic deficits in the early stages of *MAPT*-associated FTD[29].

In sum, results from our different studies confirm that neuropsychological assessment and accelerated brain atrophy are valuable biomarkers for both disease tracking and staging in *MAPT* mutation carriers. A clear gene-specific profile was found across studies (more so than in the other genetic groups), that focuses on temporal-associated cognitive functions. Both neuropsychological tests for episodic and semantic memory appear promising endpoints for upcoming *MAPT* trials, including those for presymptomatic cases.

Implications

In conclusion, the results from our genetic FTD studies indicate different cognitive and atrophy trajectories between *C9orf72*, *GRN* and *MAPT* mutation carriers. Importantly, although we identified gene-specific profiles of cognitive deterioration on group level, there is still a large amount of overlap between and within genetic groups and it remains challenging to identify or predict gene-specific cognitive profiles at an individual level. Our findings should be viewed as guidance for selecting sensitive endpoints in future clinical trials rather than recommendations on the 'best' neuropsychological test per genetic group to be used. Furthermore, our results can inform upcoming clinical trials in characterizing the optimal time window for starting treatment in all three genetic groups.

New cognitive instruments

The work described in the previous section evaluated the use of well-validated cognitive tests that have long been included in the diagnostic work-up in memory clinics, e.g. Trail Making Test, Stroop, Boston Naming Test and Rey Auditory Verbal Learning Test [30-33]. Although our findings indicate that some tests hold potential in tracking clinical onset and progression in genetic subtypes of FTD, multiple studies have demonstrated the non-specificity of such

tests in differentiating FTD subtypes from one another and from other types of dementia, e.g. AD dementia [34-38]. Performance on language and social cognition tests is considered an important aspect of the diagnostic process of FTD[7]. Yet, available cognitive tests often result in ceiling effects due to the subtlety of symptoms in the beginning of the disease. In light of upcoming clinical trials, a composite score combining the results of multiple sensitive assessments into a single measure is preferred to using a wide range of cognitive tests as individual endpoints. In the following paragraphs we will discuss findings from three studies evaluating new cognitive instruments in the FTD spectrum: a test for abstract semantic associations, a cognitive composite score (GENFI-Cog), and an emotion recognition test[39, 40].

Abstract semantic associations

The Test Relaties Abstracte Concepten (TRACE) is a semantic memory test measuring a person's understanding of abstract words[41]. Most semantic memory tests that are included in standard neuropsychological assessment focus on concrete words[42]. However, patients in the early stages of FTD often perform relatively well on such tasks due to the subtlety of symptoms. Our findings showed that the TRACE, however, has high sensitivity and specificity in differentiating patients with bvFTD, lvPPA and svPPA, but not nfvPPA, from healthy controls, and patients with svPPA from other subtypes (Chapter 3.1). The pattern of performance across subtypes suggests that a test for the degradation of abstract word knowledge was sensitive to detect mild semantic deficits in patients with bvFTD and lvPPA, whereas a test for concrete semantic knowledge was more specific to identify svPPA. Patients with nfvPPA are spared on both type of tests. This is in line with previous studies demonstrating worse performance on abstract semantic tasks compared to concrete tasks in bvFTD, but partly contradicts studies demonstrating superior performance on abstract semantic tasks compared to concrete tasks in svPPA[43, 44]. Very few studies have investigated semantic memory in lvPPA and nfvPPA, but those that have indeed corroborate that patients with lvPPA can present with mild semantic impairments[45, 46]. Taken together, our results suggest that the TRACE is sensitive to detect subtle semantic deficits, differentiate FTD subtypes and provides new relevant information that can aid the differential diagnosis between FTD subtypes. However, the pattern of performance on both type of tests (i.e. abstract and concrete word knowledge) appeared to discriminate best between subtypes. Thus, incorporating a combination of tests for abstract and concrete word knowledge in the standard diagnostic work-up for FTD is recommended.

GENFI-Cog composite

Composite scores are often used in clinical trials to reduce the number of variables used as outcome measures. Such composites have been developed in for example AD dementia, Parkinson's disease and HD, but were at the start of this thesis, lacking in (genetic) FTD[47-50]. Therefore, we empirically developed gene-specific cognitive composite scores for *C9orf72*, *GRN* and *MAPT* mutation carriers in the prodromal and symptomatic stage based on the most

sensitive combination of tests to differentiate each genetic variant from healthy controls (Chapter 3.2). Overall, the composition of each GENFI-Cog score was largely in line with what we and other studies have demonstrated regarding cognitive decline in genetic subtypes of FTD (Chapter 2; 4.2)[6, 11, 18]. In addition, we demonstrated that the use of GENFI-Cog would require substantial lower sample sizes for clinical trials to evaluate the effect of treatment on clinical progression from the prodromal to the symptomatic stage than using individual cognitive tests (Chapter 3.2). This indicates that GENFI-Cog has the potential to be a primary cognitive outcome measure in upcoming clinical trials for *C9orf72*, *GRN* and *MAPT*-associated FTD. Currently, the CDR plus NACC FTLD is often used as clinical endpoint in FTD trials[51]. A previous study has demonstrated sensitivity of the CDR plus NACC FTLD to change with disease progression[52], but our results demonstrate that approximately 50% of mutation carriers with a CDR plus NACC FTLD global score of 0.5 progressed to a score of 1 or higher in a three year period (Chapter 3.2). This indicates that for trials with a duration of three years only half of the patients with a CDR plus NACC FTLD of 0.5 on entry to trial would be expected to progress to CDR plus NACC FTLD of 1 in the absence of disease modifying treatment. This means that if drug treatment is, for example, expected to have a 20% effect, the sample size estimations need to be calculated for a 10% assumed effect in order to demonstrate a treatment effect, as only ~50% of mutation carriers would be expected to progress from CDR plus NACC FTLD 0.5 to 1 without treatment (i.e. the effect size need to be divided by 2). These results have important implications for recruitment and trial duration in upcoming clinical trials.

Emotion Recognition Test

Deficits in recognizing others emotions are believed to lie at the core of misinterpreting social cues causing difficulties with social conduct in patients with bvFTD[34, 53]. Currently available tests for measuring emotion recognition abilities often present static images of actors that mimic full-blown emotions, e.g. the Ekman 60 Faces Test[54]. However, such tests are not always sensitive to detect subtle emotion recognition deficits in the early stages of the disease, or to differentiate between patients with FTD from AD dementia[53]. The use of static photographs of actors mimicking full-blown emotions does not resemble the complexity of processing and responding to facial expressions in daily life[55]. The ERT was developed to overcome these shortcomings and presents dynamically morphed facial expressions of the six basic emotions across different levels of intensity[55]. Our findings demonstrate that the ERT differentiates patients with bvFTD from controls and patients with AD dementia, but classification accuracy between patients with bvFTD and AD dementia was low (Chapter 3.3). Interestingly, subtle deficits were found in presymptomatic *C9orf72* repeat expansion carriers as well. Overall, our findings are in line with a large number of studies that showed impaired emotion recognition across all emotions in patients with bvFTD and AD dementia, with some studies reporting superior performance in the latter[53, 56-62]. Emotional processing is known to be associated with the anterior temporal, orbitofrontal and insular cortex as well as subcortical areas, brain areas

that are known to deteriorate early in the disease process of bvFTD, but also tend be affected in AD[61, 63-66]. In contrast to previous studies using static images of facial expressions, no ceiling effects were observed in our study[53]. This suggests that the use of dynamically morphed facial expressions across different levels of intensities improves sensitivity to detect impairment. Our findings highlight the importance of incorporating dynamic paradigms for facial emotion recognition into the standard diagnostic work-up in differential dementia diagnostics and suggest that they could serve as potential outcome measure in upcoming clinical trials. However, the low classification accuracy between dementia syndromes illustrates that it remains challenging to accurately distinguish AD from bvFTD on the basis of facial emotion recognition tests alone, underlining the complexity of differential dementia diagnosis in early-onset populations. A combination of tests measuring different levels of social cognition, including e.g. theory of mind, moral reasoning and the understanding and interpretation of social information, might be more sensitive to detect differences in social cognitive profiles between bvFTD and AD dementia[34].

Memory in ftd

Memory is according to current diagnostic criteria relatively spared in patients with bvFTD[67]. This criterion has, in the past, been considered one of the clinical gold standards to differentiate patients with bvFTD from AD dementia, as episodic memory impairment is considered the key feature in AD dementia[34]. However, over the past decade that notion has been challenged by several studies showing that patients with bvFTD can present with severe amnesia, similar to patients with AD dementia[68]. In this thesis, we set out to further characterize memory dysfunctions in the FTD spectrum.

Our studies on memory in the FTD spectrum all demonstrated impaired performance in patients with FTD, already starting in the presymptomatic stage (Chapter 4.2), but with a relative sparing compared to patients with AD dementia (Chapters 4.1; 4.3). The literature on memory deficits in patients with FTD have been inconsistent, with some studies revealing equal impairment in patients with FTD and AD dementia, whereas others report worse performance in the latter[69-74]. One hypothesis is that patients with bvFTD are impaired on free recall memory formats due to executive functions disorders, i.e. poor organization and a lack of efficient learning/retrieval strategies, and that they would benefit more from cued or recognition memory formats[75-77]. Another hypothesis is that patients with bvFTD can present with "true" consolidation problems[78-80]. Taken together, the findings from our studies suggest that both hypotheses may be confirmed, and that it depends on the underlying genetic mutation, pathology and disease stage. The pattern of performance and associations with other cognitive tests and neural correlates in Chapter 4.2 indicates that *MAPT* mutation carriers can present with true amnesia at an early stage, whereas *GRN* mutation carriers

become impaired on memory tests at a later stage due to frontal/executive dysfunctioning. Furthermore, it appears that the two hypotheses are not necessarily mutually exclusive. In *C9orf72* repeat expansion carriers, free recall deficits were already present at an early stage and were associated with frontal areas and executive processes, whereas total recall deficits developed at a later stage and were associated with temporal areas and memory processes. This suggests that there is a pure memory component implicated in this group as well, possibly only in a later stage when the temporal lobe becomes affected. Taken together these findings confirm that memory deficits are an integral part of the clinical FTD spectrum, contradicting the current diagnostic criteria[67]. This conclusion has important scientific and clinical implications, as it suggests that, on an individual level, memory tests cannot always accurately discriminate patients with bvFTD and AD dementia, thereby complicating the differential diagnosis further. Indeed, a considerable amount of overlap (37-62%) on all memory scores was found in our meta-analysis comparing bvFTD and AD dementia. As such, memory impairments should be cautiously interpreted as they do not necessarily rule out an FTD diagnosis. It is important that expert centers distribute these findings to general memory clinics. Tests that can disentangle the underlying cause of memory impairment could be a valuable addition to the neuropsychological test protocol, as they can help the neuropsychologist in providing psycho-education to patients with FTD and their caregivers in how to cope with memory deficits in daily life[81].

A psychological perspective on the presymptomatic stage

In previous paragraphs I described disease trajectories of genetic FTD mutation carriers from a clinical perspective. From a psychological perspective, however, these individuals are faced with a wide range of other challenges as well, that may express long before the first (bio) marker start to change. Some studies in other familial neurodegenerative disorders, such as familial AD and HD, have shown elevated depressive symptoms in presymptomatic mutation carriers that were aware of their genetic status, as well as individuals that are 50% at-risk[82-84]. No study has investigated psychological distress experienced by presymptomatic mutation carriers or individuals that are 50% at-risk of FTD. It is not surprising that being at-risk or knowing your carrier status may lead to a variety of adverse psychological reactions[85, 86]. We aimed to determine the feasibility and efficacy of a Mindfulness-Based stress reduction (MBSR) course in lowering symptoms of anxiety and depression in presymptomatic mutation carriers and 50% at-risk individuals (Chapter 5). On a group level, our pilot study demonstrated lower levels of anxiety and depression. These results are similar to previous studies investigating Mindfulness-Based approaches in other neurological diseases, e.g. Parkinson's disease and multiple sclerosis[87-89]. Several of these studies have shown that mindfulness interventions are effective in cultivating acceptance of a long-term condition, and sharing experiences with individuals that are in the same situation enhances the benefits

of the intervention[90, 91]. For example, Eccles et al. recently reported that Mindfulness-Based cognitive therapy was considered beneficial by premanifest HD individuals[92]. However, on an individual level some participants did not report a significant decrease on anxiety and/or depression, possibly due to floor effects prior to the intervention. Findings from other studies on depression in presymptomatic populations have been contradicting, and not all studies report higher levels of depression[82-84, 93-100]. Yet, qualitatively, participants from our study indicated to have significantly benefited from the MBSR course in dealing with stress related to FTD by being able to put their situations in perspective. One hypothesis is that the complexity of feelings and emotional distress experienced by at-risk individuals cannot be expressed in the quantitative measures we used in our study[101]. A qualitative analysis of the psychological distress experienced by these individuals, or the use of questionnaires that are specifically designed for presymptomatic and/or at-risk individuals might be more appropriate[101]. In conclusion, the results from this pilot study indicated that MBSR can be an effective intervention for lowering symptoms of anxiety and depression in presymptomatic mutation carriers and 50% at-risk individuals, but a randomized controlled trial is necessary to confirm these results. Inclusion criteria and/or suitable outcome measures for such a trial should be carefully considered. Furthermore, different delivery options (e.g. online and/or apps, virtual reality or a hybrid model) should be explored as recruitment was hampered by the relative rarity of the disease. It may be possible to run groups with individuals with conditions that are similar in terms of psychological distress as a result of an autosomal dominant genetic neurodegenerative disorder that runs in the family, although this requires further research.

Considerations and future directions

Early life studies in *C9orf72* repeat expansion

Mutations causative of a neurodegenerative disorder are present from conception, but typically cause clinical symptoms only later in life[19]. Recently, the hypothesis has been raised that early deficits in *C9orf72* repeat expansion carriers are the result of abnormal brain development rather than preclinical signs of neurodegeneration[14, 19]. This is an important alternative hypothesis to further investigate, as a neurodevelopmental component would have major implications for the conceptualization, monitoring and treatment of the disease[19]. Although there have been reports of *C9orf72* repeat expansion carriers with childhood intellectual or developmental disorders, it is not a common feature[19, 102, 103]. The identified brain abnormalities in previous studies thus appear to represent a compensated lesion, but mild cognitive differences compared to controls have been identified (Chapter 2; 4.2)[9-14, 19]. Furthermore, recent literature has revealed that family members of patients with *C9orf72*-associated FTD have a higher probability of developing psychiatric disorders[104, 105]. A recent paper by Gossink et al. suggested that it is possible that *C9orf72* repeat expansion carriers

exert a lifelong neuropsychiatric vulnerability that manifests as personality and behavioural changes early on in life[104]. Future studies focusing on ascertaining early-life radiological and clinical assessments to test the hypothesis that a neurodevelopmental deficit underlies early deficits in *C9orf72* repeat expansion carriers are currently being set up within GENFI.

Towards prediction at the individual level

The last decade has seen major advances in the identification of biomarkers for tracking clinical onset and disease progression on group level[106]. However, studies have shown that these biomarkers have insufficient predictive value at an individual level[5, 18, 20, 24, 107-112]. Yet, classification and prediction of clinical onset on single-subject level is crucial for improving clinical diagnosis and early treatment planning. Classification algorithms for classifying patients with FTD from healthy controls or other subtypes of dementia with MRI data have been developed, but multimodal prediction tools combining information from multiple biomarkers are the next step[113-117]. Furthermore, MRI classification algorithms are based on data from symptomatic cases, thereby limiting generalizability to presymptomatic cases[116-120]. Future work could combine our work with machine learning classification techniques, towards an artificial intelligence based multimodal prediction tool for disease onset and progression at an individual level.

Ethical considerations in the early identification of disease mechanisms

Much research is currently devoted to developing biomarkers that can aid early detection, as this can improve early diagnosis, treatment planning and identifying the best time window to start treatment[5]. As clinical trials testing disease-modifying treatment are emerging, this is an important endeavor. However, this trends brings forth important ethical considerations as well. In the absence of an available cure, early detection is not automatically considered beneficial by all[121-123]. Genetic testing allows family members of affected individuals to determine if they are a carrier of the mutation causative of the disease or not (i.e predictive testing)[124]. Not surprisingly this may lead to a variety of adverse psychological reactions, as knowledge of a positive test result (i.e. carrying the mutation) represents unavoidable dementia onset and a dramatically shortened lifespan[85, 86]. The literature on the psychological consequences of predictive testing in neurodegenerative diseases has been contradicting, with some reporting higher levels of depression and anxiety post-testing, and others finding no such results[93, 95, 98, 125]. Future research should further characterize the psychological distress experienced by individuals at-risk or presymptomatic mutation carriers, in order to help identify or develop suitable psychological outcome measures (e.g. questionnaires or semi-quantitative interviews). Importantly, the development of predictive (bio)markers adds another layer of complexity, as these do not only help in identifying *who* will develop symptoms, but also *when* symptoms will manifest. Gaining insight into the impact and psychological consequences of biomarker-based predictions from end-users (i.e. individuals with a genetic risk of dementia and clinicians) is vital in order to effectively develop ethical

and counselling guidelines that can facilitate client decisions about testing and adaptation to results, but also in developing adequate psychosocial support interventions[121, 122, 126].

Improving differential early-onset dementia diagnosis in memory clinics

The findings from this thesis underline once more the complexity of early differential diagnosis in early-onset dementia populations, such as FTD and AD dementia, despite the availability of refined diagnostic criteria[3, 67, 127]. For example, criteria from Rascovsky et al. state executive function disorders and a relative sparing of memory as inclusion critera for bvFTD diagnosis[67]. Yet, our findings clearly demonstrate patients with bvFTD can present with impaired memory, even as the most prominent symptom in some subtypes (Chapter 4). Similarly, impaired emotion recognition deficits are not specific to patients with FTD (Chapter 3.3). Thus, early differential diagnosis requires a thorough review of all available clinical and cognitive data. A standardized and focused neuropsychological assessment is crucial for early differential diagnosis, including tests for memory and social cognition[34]. An important future aim of our FTD expertise center will be to distribute and implement these findings and ideas in general (Dutch) memory clinics. Furthermore, a major challenge in the coming years will be to develop standardized reliable cognitive instruments that are more sensitive and better fit the clinical practice in memory clinics. Importantly, once identified, research should be devoted to cross-validation in terms of language and culture and the psychometric qualities of such instruments[34].

Technological innovations in neuropsychological assessment

Promising avenues to overcome shortcomings of standard pencil and paper tasks include the use of technological solutions such as eye-tracking, automated speech quantification, app-based neuropsychological assessments, and the development of immersive technologies such as virtual reality (VR) based assessments[128-138] . Such technological solutions offer several advantages as they improve measurement accuracy by controlling what stimuli are presented, as well as its properties and location, but also can induce more reality-like emotional and behavioral responses[138-140]. App-based neuropsychological assessments have been developed for patients with other types of brain injury, but are currently also underway in GENFI[141-143]. Multiple studies have demonstrated the sensitivity of e.g. eye-tracking and automated speech quantification in FTD and other types of dementia[131, 144-147]. Research in the presymptomatic and prodromal stages has been limited thus far, but the first eye-tracking studies in presymptomatic mutation carriers are emerging[144, 148]. VR solutions have been developed in research settings, e.g. for spatial navigation abilities, but its' application for measuring socio-affective processes has been limited thus far[138, 149, 150]. Yet, VR-based assessments might specifically prove beneficial for measuring social cognitive processes, as the measurement of higher level processes, such as reasoning and regulation, remains challenging with pencil and paper tasks[140].

Conclusion

In this thesis I have characterized disease stages in the FTD spectrum from a neuropsychological perspective, thereby identifying the most sensitive instruments to track clinical onset and disease progression, and to differentiate between clinical syndromes as well as from other types of dementia. In addition, we gained insight into how to reduce psychological distress experienced by presymptomatic mutation carriers and individuals 50% at-risk of inheriting FTD. These results add to the understanding of (bio)marker and psychological changes before and during the conversion from presymptomatic to symptomatic FTD, thereby facilitating their use in clinical practice and clinical trials. This ultimately contributes to better patient management and treatment planning across disease stages, and improves the lives of people living with FTD.

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6

CHAPTER 7

English and Dutch summary

English summary

In this dissertation I identified cognitive and brain volume changes during different disease stages of genetic subtypes of frontotemporal dementia (FTD), presented new cognitive instruments that can improve early FTD diagnosis, and evaluated a psychosocial intervention to address psychological challenges during the presymptomatic stage. Based on my results I provided recommendations on which cognitive measures can aid the standard diagnostic work-up and serve as potential endpoints in upcoming clinical trials testing disease-modifying treatments for FTD.

Chapter 1 provides a general introduction of the FTD spectrum and introduces the aims of this thesis.

The results from the studies in **chapter 2** confirmed the value of neuropsychological assessment and accelerated brain atrophy as disease tracking and staging biomarkers in genetic FTD. In **chapter 2.1** I cross-sectionally compared cognitive profiles between symptomatic *C9orf72*, *GRN* and *MAPT* mutation carriers with bvFTD, while in **chapter 2.2** I longitudinally investigated cognitive decline in the presymptomatic, prodromal and symptomatic disease stage. Longitudinal brain atrophy in presymptomatic mutation carriers was compared to a large reference population in **chapter 2.3**. These studies demonstrated overt gene-specific patterns of cognitive and brain volume decline in *C9orf72*, *GRN* and *MAPT* mutation carriers, with the earliest changes already occurring in the presymptomatic and prodromal disease stages. The *C9orf72* repeat expansion is characterized by a profile of widespread cognitive impairment. Cognitive deficits and abnormal brain volume were already present in the presymptomatic stage in this group, but there was relatively minimal decline over time. Impaired episodic and semantic memory were key features of *MAPT*-associated FTD. The first deficits emerged in the presymptomatic and prodromal stages, and were accompanied by a strong decline in temporal lobe volume. Executive function tests appeared sensitive measures in *GRN*, but the disease trajectory was characterized by minimal cognitive changes during the presymptomatic stage with progressive decline in multiple domains in proximity of symptom onset. Brain volume remained in the normal range in this group but with a steeper decline over time compared to a reference population.

In **chapter 3** I investigated the differential ability of three new cognitive instruments in the FTD spectrum: the Test Relaties Abstracte Concepten (TRACE), a cognitive composite score for genetic FTD (GENFI-Cog), and the Emotion Recognition Test (ERT). In **Chapter 3.1**, I evaluated a test for abstract semantic associations in the FTD spectrum. My results suggest that the TRACE is sensitive to detect subtle semantic deficits and differentiate behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA) subtypes. However, the pattern of performance on respectively tests with abstract and concrete stimuli differentiated best

between subtypes. It is therefore recommended that neuropsychologists include both type of tests in their clinical assessment for early FTD diagnosis. In **Chapter 3.2**, I created gene-specific cognitive composite scores for *C9orf72, GRN* and *MAPT* mutation carriers, which resulted in substantially lower estimated sample sizes to detect a treatment effect than using individual cognitive tests. This indicates that GENFI-Cog composites have the potential to be used as primary cognitive endpoints in upcoming clinical trials. The results presented in **Chapter 3.3** demonstrated emotion recognition deficits in both bvFTD and AD, and subtle emotion recognition changes in presymptomatic *C9orf72*-FTD. These findings highlight the importance of incorporating dynamic paradigms for facial emotion recognition into the standard neuropsychological assessment for differential dementia diagnostics.

In the past, a relative sparing of memory was considered the gold clinical standard to differentiate patients with bvFTD and AD. In **Chapter 4**, I investigated whether this assumption (i.e. a spared memory in FTD) is justified. In **Chapter 4.1**, I reported a meta-analysis on episodic memory performance in patients with bvFTD compared to healthy controls and patients with AD. This study points to memory disorders in patients with bvFTD, with performance at an intermediate level between controls and patients with AD. **Chapter 4.2** reports on a study assessing free and cued memory recall in presymptomatic and symptomatic *C9orf72*, *GRN* and *MAPT* mutation carriers, using voxel-based morphometry to investigate underlying neural correlates. Impaired memory performance was found in all symptomatic, and presymptomatic *C9orf72* and *MAPT* mutation carriers, but with different underlying neural correlates. Lastly, in **chapter 4.3** I assessed differences in recognition memory between patients with bvFTD and AD. Similar to what was found in the meta-analysis, patients with bvFTD were impaired on recognition memory, although less severely than patients with AD. Taken together, these findings confirm that memory deficits are an integral part of the clinical FTD spectrum, and should not be considered an exclusion criterion for FTD diagnosis.

In **Chapter 5** I assessed the efficacy and feasibility of a mindfulness-based stress reduction program on lowering anxiety and depression in presymptomatic mutation carriers and individuals that are 50% at-risk of having a genetic mutation causative of FTD. Quantitative and qualitative results demonstrated positive effects of the program on lowering symptoms of anxiety and depression, but a larger randomized-controlled trial is necessary to confirm these results.

In **Chapter 6**, I summarized and interpreted the findings of this thesis, discussed how they relate to other findings in the field, and provided suggestions for future research.

Nederlandse samenvatting

In dit proefschrift heb ik veranderingen in cognitie en hersenvolume gedurende het ziektebeloop van verschillende erfelijke vormen van frontotemporale dementie (FTD) in kaart gebracht, heb ik nieuwe cognitieve instrumenten die FTD diagnostiek kunnen verbeteren onderzocht, en heb ik een psychosociale interventiestudie voor het verlagen van angst en depressieve gevoelens in de presymptomatische fase van FTD geëvalueerd. Op basis van mijn resultaten heb ik aanbevelingen gedaan over welke cognitieve maten sensitief zijn ten behoeve van het verbeteren van de diagnostiek, en welke potentie hebben om gebruikt te worden als uitkomstmaat in opkomende klinische trials.

Hoofdstuk 1 geeft een algemene introductie op het FTD spectrum, en introduceert de doelstellingen van dit proefschrift.

De resultaten behaald binnen **hoofdstuk 2** bevestigen de waarde van neuropsychologisch onderzoek en normatieve hersenvolumetrie als gevoelige (bio)markers voor het volgen van het ziektebeloop in genetische FTD. In **hoofdstuk 2.1** heb ik cognitieve profielen cross-sectioneel vergeleken tussen symptomatische *C9orf72, GRN* en *MAPT* mutatiedragers met gedragsvariant FTD, en in **hoofdstuk 2.2** heb ik cognitieve achteruitgang longitudinaal gemeten in de presymptomatische, prodromale en symptomatische fase. Longitudinale hersenatrofie in de presymptomatische fase in vergelijking met een grote referentiepopulatie wordt beschreven in **hoofdstuk 2.3**. Deze studies laten duidelijke gen-specifieke patronen van cognitieve achteruitgang en atrofie zien in *C9orf72*, *GRN* en *MAPT* mutatiedragers, waarbij de eerste veranderingen al gemeten worden in de presymptomatische en prodromale fase. Het profiel van *C9orf72* mutatiedragers wordt gekarakteriseerd door globale cognitieve stoornissen. Cognitieve tekorten en afwijkend hersenvolume zijn al aanwezig in de presymptomatische fase, maar er is minimale achteruitgang over de tijd. Stoornissen in het episodisch en semantisch geheugen zijn kenmerkend voor een *MAPT* mutatie. De eerste tekorten ontstaan al in de presymptomatische en prodromale fase, en gaan gepaard met een sterke achteruitgang in temporaalkwab volume. Executieve functie tests lijken sensitief voor *GRN* mutaties, echter er zijn minimale cognitieve veranderingen in de presymptomatische fase, met progressieve achteruitgang in meerdere domeinen rond het ontstaan van klachten. Het hersenvolume van *GRN* mutatiedragers blijft in het normale bereik, maar gaat wel sneller achteruit over de tijd in vergelijking met een referentiepopulatie.

In **hoofdstuk 3** heb ik drie nieuwe cognitieve instrumenten in het FTD spectrum onderzocht, namelijk: de Test Relaties Abstracte Concepten (TRACE), een cognitieve samengestelde (composite) score (GENFI-Cog), en een dynamische emotieherkenningstaak (Emotion Recognition Test; ERT). In **hoofdstuk 3.1** heb ik een test voor het meten van abstracte semantische associaties in het FTD spectrum onderzocht. Resultaten lieten zien dat de TRACE

sensitief is in het vaststellen van subtiele semantische tekorten, en onderscheid kan maken tussen gedragsvariant FTD en verschillende vormen van primair progressieve afasie (PPA). Echter, het patroon van prestaties op zowel een taak voor concrete als abstracte stimuli leek de meest aanvullende informatie te leveren om onderscheid te maken tussen subtypes. Daarom raad ik neuropsychologen aan om zowel een test voor concrete als abstracte woordkennis af te nemen bij een verdenking op een FTD diagnose. In **hoofdstuk 3.2**, heb ik gen-specifieke cognitieve samengestelde (composite) scores voor *C9orf72*, *GRN* en *MAPT* mutatiedragers ontwikkeld. De steekproefgroottes voor een hypothetische klinische trial waren aanzienlijk lager bij het gebruik van GENFI-Cog als uitkomstmaat dan de individuele neuropsychologische testen. Dit betekent dat GENFI-Cog potentie heeft om als primaire cognitieve uitkomstmaat gebruikt te worden in opkomende klinische trials. De resultaten uit **hoofdstuk 3.3** laten stoornissen in emotieherkenning in zowel patiënten met gedragsvariant FTD als de ziekte van Alzheimer (AD) zien, en daarnaast ook subtiele tekorten in presymptomatische *C9orf72* mutatiedragers. Deze bevindingen benadrukken de waarde van het gebruik van dynamische paradigma's voor het herkennen van emoties in de diagnostiek bij jonge dementie.

In het verleden werd een relatief gespaard geheugen gezien als de gouden standaard om patiënten met FTD te onderscheiden van AD. In **hoofdstuk 4** onderzoek ik of deze assumptie (een gespaard geheugen in FTD) gegrond is. In hoofdstuk 4.1 rapporteer ik een meta-analyse over episodisch geheugen in patiënten met gedragsvariant FTD in vergelijking met gezonde controles en patiënten met AD. De resultaten laten geheugenstoornissen in gedragsvariant FTD zien, alhoewel deze minder ernstig zijn dan bij AD. **Hoofdstuk 4.2** beschrijft een studie waarin geheugen in presymptomatische en symptomatische *C9orf72*, *GRN* en *MAPT* mutatiedragers alsook de onderliggende neurale mechanismen onderzocht zijn. Een geheugenstoornis werd in alle symptomatische, maar ook presymptomatische *C9orf72* en *MAPT* mutatiedragers geobjectiveerd, met verschillende onderliggen neurale mechanismen. Tot slot, heb ik in **hoofdstuk 4.3** herkenningsgeheugen vergeleken tussen patiënten met gedragsvariant FTD en AD. Vergelijkbaar met de resultaten uit de meta-analyse, vond ik een stoornis in patiënten met gedragsvariant FTD, echter minder ernstig dan in AD. Tezamen genomen laten deze resultaten zien dat geheugenproblemen een integraal onderdeel zijn van het klinische FTD spectrum, en niet als exclusiecriterium gezien moeten worden voor een FTD diagnose.

In **hoofdstuk 5** heb ik de effectiviteit en uitvoerbaarheid van een mindfulness stress reductie programma onderzocht op het verlagen van angst en depressie in presymptomatische mutatiedragers en individuen die 50% kans hebben op een genetische mutatie die FTD veroorzaakt. Zowel kwantitatief als kwalitatief verzamelde data laten zien dat de cursus positieve effecten heeft op het verlagen van angst en depressieve symptomen, echter gerandomiseerde trial is nodig om deze resultaten te bevestigen.

In **hoofdstuk 6**, bied ik een samenvatting van en interpreteer ik de resultaten behaald binnen mijn proefschrift, beschrijf ik hoe deze relateren aan andere bevindingen binnen het veld, en geef ik suggesties voor vervolgonderzoek.

Curriculum vitae

Jackie Martine Poos was born on May 31st, 1993 in Capelle aan den IJssel, the Netherlands. She graduated secondary school in 2011 at the Emmauscollege in Rotterdam, and subsequently started studying Psychology at Utrecht University. Here she obtained two master degrees in Neuropsychology and Neuroscience & Cognition. Her interest in dementia research was triggered during a research internship at the Alzheimercenter Amsterdam, and further nurtured during a clinical internship at the department of Neurology of the Erasmus MC University Medical Center. Following her graduation in 2017, she briefly worked as a research assistant and clinical trial rater before starting her PhD research at the Alzheimercenter Erasmus MC under supervision of Prof. dr. van Swieten, dr. van den Berg and dr. Papma. Jackie currently lives in Nieuwerkerk aan Den IJssel with her partner Vincent, and will continue in dementia research as a postdoctoral researcher at the Alzheimercenter Erasmus MC after obtaining her PhD.

List of publications

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Phd portfolio

PhD training	Year	ECTS
Courses		
Good Clinical Practice (BROK)	2018	1.5
Biostatistical Methods I: Basic Principles (NIHES)	2018	5.7
Repeated Measurements (NIHES)	2019	1.7
Biomedical English Writing and Communication (MolMed)	2021	1.7
Scientific Integrity (MolMed)	2021	0.3
FSL course (Oxford University)	2018	1.5
Using R for Statistics in Medical Research (NIHES)	2019	1.7
Personal Leadership, Management & Communication (MolMed)	2019	1
Mindfulness (Mindfulness Rotterdam)	2019	1.8
Introduction to Linux (Leiden University Medical Center)	2018	0.3
Introduction to Endnote (Erasmus MC)	2018	0.2
Conferences and seminars		
11th International Conference on Frontotemporal Dementias, Sydney, Australia – poster presentation	2018	1
7th Meeting of the Federation of the European Society of Neuropsychology, Milan, Italy – two oral presentations	2019	2
12th International Conference on Frontotemporal Dementias, virtual – attendance	2021	1
Alzheimer's Association International Conference, virtual – oral presentation	2021	2
Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment , Frontotemporal Dementia Personal Interest Area, virtual – oral presentation	2021	2
GENFI Investigator meetings – oral presentations	2018-2021	2
Mix & Match meetings, Alzheimer Nederland – attendance	2018 – 2021	0.6
Nederlandse Vereniging voor Neuropsychologen conferences – attendance	2018 – 2021	1.0
Other		
GENFI site coordinator	2021	3.0
FTD-RisC study coordinator and rater	2017 – 2019	25
Clinical trials rater (Emerge, Alector)	2017 – 2021	5.0
Alzheimer center weekly research meetings	2017 – 2021	4.0
Speaker and attendant FTD Lotgenoten	2017 – 2019	1.0
Teaching		
Supervision of Masther's theses 12 students	2017 – 2021	18.0
Vaardigheidsonderwijs, opleiding Geneeskunde, Erasmus Medical Center	2021	1.0
Psychiatry course, Neuroscience master, Erasmus Medical Center	2020	1.0
Total		**87**

List of abbreviations

AAT	Aachen Aphasia Test
AD	Alzheimer's disease
AI	artificial intelligence
ALS	amyotrophic lateral sclerosis
AMPS	Applied Mindfulness Process Scale
AUC	area under the curve
BNT	Boston Naming Test
bvFTD	behavioral variant frontotemporal dementia
C9orf72	chromosome 9 open reading frame 72
CBS	corticobasal syndrome
CDR plus NACC FTLD	Clinical Dementia Rating scale plus National Alzheimer's Coordinating
Center	Frontotemporal Lobar Degeneration
CHMP2B	Charged Multivesicular Body Protein 2B
CI	confidence interval
CSF	cerebrospinal fluid
CVLT	California Verbal Learning Test
DINAD	Australian Dominantly Inherited Non-Alzheimer Dementias
D-KEFS	Design Fluency Test
DNA	deoxyribonucleic acid
ERT	Emotion Recognition Test
FAB	Frontal Assessment Battery
FCSRT	Free and Cued Selective Reminding Test
FFMQ	Five Facet Mindfulness Questionnaire
FPI	Frontotemporal dementia Prevention Initiative
FTD	frontotemporal dementia
FTD-ALS	frontotemporal dementia with amytrophic lateral sclerosis
FTLD	frontotemporal lobar degeneration
FTD-RisC	Frontotemporal dementia Risk Cohort
GENFI	Genetic Frontotemporal dementia Iniatitive
GM	grey matter
GRN	progranulin
HADS	Hospital Anxiety and Depression Scale
HD	Huntington's disease
ICV	intracranial volume
LEFFTDS	Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects
LR	likelihood ratio
lvPPA	logopenic variant primary progressive aphasia
MAPT	microtubule-associated protein tau

MBCT	Mindfulness-Based Cognitive Therapy
MBSR	Mindfulness-Based Stress Reduction
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
MND	motor neuron disease
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
mWCST	modified Wisconsin Card Sorting Test
nfvPPA	nonfluent variant primary progressive aphasia
OL	overlap
PALPA	Psycholinguistic Assessments of Language Processing in Aphasia
PPA	primary progressive aphasia
PSP	progressive supranuclear palsy
PSS	Perceived Stress Scale
RAVLT	Rey Auditory Verbal Learning Test
RBMT	Rivermead Behavioral Memory Test
RCI	Reliability Change Index
RCT	Randomized controlled trial
ROC	Receiver operating characteristic
SAT	Semantic Association Test
SCL-90-R	Symptom Checklist 90–Revised
SCWT	Stroop Color Word Test
SD	standard deviation
SF-36	36-item Short Form Health Survey
svPPA	semantic variant primary progressive aphasia
TARDP	TAR DNA-binding protein 43
TBK1	TANK-binding kinase 1
TIV	Total intracranial volume
TMT	Trail Making Test
TRACE	Test Relaties Abstracte Concepten
UCL	Utrechtse Coping Lijst
VAS	Visual Analogue Scale
VAT	Visual Association Test
VBM	Voxel-Based Morphometry
VCP	Valosin Containing Protein
VR	Virtual Reality
WAIS-III	Wechsler Adult Intelligence Scale III
WAIS-R	Wechsler Adult Intelligence Scale – Revised
WM	white matter
WMS-R	Wechsler Memory Scale–Revised