Utrecht University

Characterization of the prodromal phase of FTD

Master Thesis

Master Neuropsychology, Utrecht University

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Date:	21 December 2024
Make publicly available:	yes
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Abstract

Frontotemporal dementia (FTD) is a heterogeneous young-onset type of dementia, with numerous biomarkers identified in its presymptomatic and prodromal stages. This study aims to characterize the prodromal stage of FTD to enhance early recognition of symptoms by longitudinally analyzing neuropsychological assessments and radiologists' MRI reports. The study included 20 prodromal FTD participants, 21 prodromal Alzheimer's disease (AD) participants, and 20 control participants. Linear mixed-effects models were used to investigate cognitive changes over time preceding diagnosis, while time-to-event analyses examined the onset of cognitive and MRI-reported deviations. Results reveal that cognitive changes in prodromal FTD were observed as early as 9 years before diagnosis, which is much earlier than previously reported. In contrast, MRI-reported deviations were detected approximately 3 years before diagnosis, occurring later than earlier findings suggested. Prodromal FTD showed a broad range of affected cognitive domains, with memory recall and social cognition impairment emerging later than other domains. On the other hand, prodromal AD was marked by more severe but slower-developing cognitive deterioration, predominantly characterized by memory deficits. These findings highlight the necessity of individualized patient evaluation to facilitate timely and accurate diagnosis.

Keywords: frontotemporal dementia, prodromal stage, cognitive decline, MRI biomarkers, longitudinal analysis

Characterization of the prodromal phase of FTD

Frontotemporal dementia (FTD) is a young-onset type of dementia, which means that it starts before the age of 65 years. FTD accounts for approximately 20% of neurodegenerative dementias among all young-onset dementia patients (Beber & Chaves, 2013). It is characterized by focal neuronal loss in the frontal and temporal lobes. Clinically, it presents with either behavioral symptoms (behavioral variant of FTD; bvFTD) or language disturbance (primary progressive aphasia; PPA) (Jiskoot et al., 2016; Rohrer et al., 2015). However, frontotemporal dementia is a very heterogeneous disease in terms of genetics, pathology, and clinical phenotypes (Benussi et al., 2021a; Russell & Rohrer, 2023).

In about a third of the patients, FTD is caused by an autosomal dominant genetic mutation, usually in one of the three genes: progranulin (*GRN*), microtubule-associated protein tau (*MAPT*), or chromosome 9 open reading frame 72 (*C9orf72*) (Rohrer et al., 2015). This allows for the identification and research of individuals in the presymptomatic stage,

before any symptoms appear. Multicohort studies showed that a variety of biomarkers already change many years before symptom onset, i.e., neuroimaging, fluid biomarkers and cognition (Benussi et al., 2019; Bocchetta et al., 2023; Jiskoot et al., 2018a, 2018b, 2018c; Lee et al., 2017; Le Blanc et al., 2020; Meeter et al., 2016; Planche et al., 2022; Poos et al., 2022a, 2022b; Rohrer et al., 2015; Tavares et al., 2019; van der Ende et al., 2019, 2020). However, these group effects are known to not always translate to the individual patient level (Barschke et al., 2020; Bocchetta et al., 2021; Feis et al., 2018; Heller et al., 2020; Jiskoot et al., 2018b, 2018c; Rohrer et al., 2015; Sudre et al., 2019; van der Ende et al., 2019, 2020). Therefore, it is hard to recognize these symptoms in the memory clinic. After the presymptomatic stage follows a stage of conversion, the prodromal phase. This entails the onset and progression of subtle clinical symptoms consisting of mild cognitive or behavioral impairment, with relatively preserved functional independence (Benussi et al., 2021a, 2021b), usually noticed by family or friends. The prodromal phase is however still poorly understood because these subtle changes cannot be objectified with a neuropsychological assessment or an MRI. Moreover, predictors on progression remain unclear (Benussi et al., 2021b). Therefore, this study aims to provide clarity on the characteristics of the prodromal phase of FTD.

Several studies have investigated the characteristics of the prodromal phase. However, a lot of studies did this by including participants who did not convert yet. Researchers then tried to predict their disease onset by using ‘expected years to onset’, instead of retrospectively investigating participants who already converted to FTD and thus using the actual years to onset (Benussi et al., 2024; Rohrer et al., 2015; Tavares et al., 2020). The cognitive prodromal phase usually starts with executive deficits (Barker et al., 2022; Benussi et al., 2021a) and naming impairments, whereas visuospatial skills and orientation in time and place remain intact (Barker et al., 2022). Aside from neuropsychological differences, behavioral changes also play a part, with mostly negative symptoms such as apathy and disinhibition (Barker et al., 2022; Benussi et al., 2021b). Concerning atrophy investigated in group studies using MRI, insular and temporal cortices are found to be affected initially, followed by the frontal cortex and subcortical areas, parietal, and cingulate cortices, and lastly, the occipital cortex and cerebellum (Jiskoot et al., 2018c; Rohrer et al., 2015). In sporadic FTD (not caused by a genetic mutation) patients, Planche et al (2022) found amygdalar and striatal atrophy to precede the fronto-temporo-insular atrophy described in the diagnostic criteria. It is important to see whether this information corresponds to individual patients as well.

Because there is no proper definition of the prodromal phase of FTD, diagnoses are delayed. This delay in diagnosis is associated with worse outcomes in cognitive and behavioral impairment, and causes inadequate treatment, institutionalization, and management difficulty for caregivers (Beber & Chaves, 2013; Benussi et al., 2021b). It also results in frequent misdiagnosis. Among other neurodegenerative disorders, FTD is commonly mistaken for Alzheimer's disease (AD) (Beber & Chaves, 2013). Alzheimer's is the most common early-onset type of dementia (Musa et al., 2020). Differentiating between AD and FTD poses a significant challenge, particularly in the beginning, due to several overlapping features (Heikkinen, 2024; Landin-Romero et al., 2017). AD patients can also exhibit severe impairment in executive functions and behavioral changes (Heikkinen, 2024; Musa et al., 2020), and bvFTD patients might have amnestic symptoms during the prodromal phase (Korhonen et al., 2020; Musa et al., 2020). Accordingly, clinicians tend to classify memory complaints or deficits as a symptom of typical Alzheimer's disease and find it difficult to recognize the main features of FTD (Beber & Chaves, 2013). As opposed to frontotemporal dementia, Alzheimer's has a criterium-based characterization of the prodromal phase of Alzheimer's, namely the Mild Cognitive Impairment (MCI) (Benussi et al., 2021a). The criteria of an MCI require the presence of a cognitive change reported by oneself or by an informant, along with objective cognitive decline (Petersen et al., 2014). A comprehensive characterization of the prodromal phase of FTD is essential, analogous to the established mild MCI stage in Alzheimer's disease, to address the diagnostic challenges inherent in FTD.

Therefore, this study aims to provide more insight into the prodromal phase of FTD by differentiating between the prodromal phase of FTD, the prodromal phase of Alzheimer's disease and healthy individuals over time. This will be done by investigating the years before diagnosis by looking at neuropsychological profiles and MRI-scans from FTD mutation carriers who converted to FTD, and from MCI-patients who converted to Alzheimer's disease. Identification of biomarkers that allow differentiation and accurate staging of the disease, will be important to identify individuals suitable for medical trials, to reduce heterogeneity and increase statistical power (Benussi et al., 2021a; Rohrer et al., 2015). The present research question is two-fold: the first question is, 'how early are the first clinical deviations detected in prodromal FTD and Alzheimer?', and the second question is, 'what are the differences in pre-diagnosis disease progression between patients with prodromal FTD and Alzheimer's disease, compared to healthy controls over time?' It is expected that prodromal FTD presents with executive dysfunctions and impairments in naming tests, becoming more prominent over time, combined with relative sparing of visuospatial skills and orientation, whereas these

latter functions are impaired in AD, together with memory impairments (Barker et al., 2022; Benussi et al., 2021a). Lastly, it is expected that atrophy in FTD patients will be seen in temporal, and frontal areas, followed by subcortical areas. By looking at these aspects, we hope to be able to distinguish FTD from AD in the prodromal stage of the disease, making early diagnosis possible, enabling timely patient care and accurate therapeutic trials.

Methods

Participants

A total of 64 participants are analyzed. 20 individuals with prodromal FTD, 21 with prodromal AD, and a control group of 20 non-mutation carriers matched by age, gender and education level were included. Individuals with prodromal FTD and controls were recruited via the FTD-RisC longitudinal study in Erasmus University Medical Center (EMC) in Rotterdam, and individuals with prodromal AD were included via the outpatient memory clinic of the Erasmus University Medical Center. Inclusion criteria for the prodromal FTD group were a pathogenic mutation in *MAPT, GRN* or *C9orf72* and conversion to symptomatic FTD (Rascovsky et al., 2011) during study follow-up. Inclusion criteria for the prodromal AD group were that individuals had an MCI-diagnosis (Albert et al., 2011) and ultimately converted to Alzheimer's disease (McKhann et al., 2011). Exclusion criteria for both groups were other neuropsychiatric or neurologic diseases. Participants in all groups had to be older than 18 years.

Table 1

Frequency of the number of participants at each follow-up

	NPA									
	1	2	3	4	5	6	7	8	9	10
FTD	20	19	9	8	5	4	2	2	1	0
AD	21	16	7	2	2	1	1	1	0	0
Control	20	20	20	19	19	17	15	12	7	1
	MRI									
	1	2	3	4						
FTD	10	5	4	2						
AD	19	6	0	0						
Control	19	16	12	4						

Note. Abbreviations: NPA = neuropsychological assessment, FTD = frontotemporal dementia, AD = Alzheimer's disease

Study design

Since 2010, Erasmus MC Rotterdam has an ongoing longitudinal cohort study of patients with FTD due to a pathogenic mutation (in either C9orf72, MAPT or GRN), and their healthy at-risk family members (either presymptomatic mutation carriers or non-carriers). Participants are followed yearly or two-yearly and underwent (among other things) a neuropsychological assessment, questionnaires, and an MRI-scan at every visit. In Table 1, the number of participants with each follow-up is made visible. The yearly neuropsychological assessment does differ in and between participants, because of changes in protocol during the study cohort. The informants that came along with the patients, were then interviewed about behavioral and cognitive changes in the patient. Written informed consent for use of their anonymized research data is obtained from all participants. The study has been approved by the Medical and Ethical Review Committee of the Erasmus MC.

Measurements

From the yearly neuropsychological assessment, a selection of these tests was made to cover the following domains (see Table 2): language (Boston Naming Test (Kaplan et al., 2001) and Animals fluency (Morris et al., 2006)), memory encoding (15-Words Test total score (Saan & Deelman, 1986), memory recall (15-Words recall score), executive function (Wisconsin Card Sorting Test (Berg, 1948), Letter fluency (Tombaugh et al., 1999), Trail Making Test Part B (Corrigan et al., 1987), Stroop part III, and Digit Span backwards (Morris et al., 2006)), attention and processing speed (Trail Making Test Part A (Corrigan et al., 1987), Stroop part I and II (Stroop, 1935), Digit Span forwards (Morris et al., 2006)) and social cognition (Ekman Faces Test (Ekman & Friesen, 1976), Happé Cartoons (Happé, 1994)). The selected tests were administered at least a few times to nearly all participants in each group. The Mini Mental State Examination (MMSE; Folstein et al., 1975), Frontal Assessment Battery (FAB; Dubois et al., 2000), Neuropsychiatric Inventory (NPI; Cummings et al., 1994) and Beck Depression Inventory (BDI; Beck et al., 1961) measured global cognitive functioning at baseline.

The yearly MRI scans were T1-weighted MRI scans. The reports of the radiologists were analyzed to see whether there were deviations in either the frontal, temporal, parietal, or occipital lobe, or in the hippocampi. Deviations were defined as atrophy scores higher than

zero in one of these areas, or descriptions of atrophy, such as '*The quantitative analysis shows a disproportionate atrophy of the temporal and frontal lobes over time, more pronounced on the left than on the right, both frontally and temporally.'*. Based on such a quote in an MRI report, deviations were assigned to the corresponding brain areas.

Table 2

Tests per cognitive domain

Language	Boston Naming Test, Animal Fluency
Memory encoding	15-Words Test total score
Memory recall	15-Words Test recall score
Executive functioning	Wisconsin Card Sorting Test, Letter fluency, Trail Making Test part B, Stroop part III, Digit Span backwards
Attention and processing speed	Trail Making Test part A, Stroop part I and II, Digit Span forwards
Social cognition	Ekman Faces Test, Happé Cartoons

Statistical analysis

Data-analyses were performed in R Studio version 4.4.1 (R Core Team, 2024) and SPSS statistics version 28.0.1.0 (142) (IBM Corp, 2024). The assumptions of normality and linearity were checked beforehand and verified with a Shapiro-Wilk test. Based on the assumption testing, it was found that the assumptions of linearity and normality of residuals were partially violated. Given the robustness of linear mixed-effects models to minor violations of these assumptions (Schielzeth & Forstmeier, 2009), it was decided to retain the model for further analysis. Age, sex, education level and global cognition (i.e., MMSE and FAB) at baseline were analyzed with a chi-square test for sex, and an ANOVA for age, education level and global cognition. The significance level was set at $p < 0.05$ (2-tailed) across all comparisons. As this is a prospective cohort study, not all pathogenic variant carriers had completed all study visits, which resulted in missing data. Linear mixed-effects models were used for each cognitive domain to examine whether differences existed between individuals with prodromal FTD, prodromal AD and healthy controls in cognitive decline since baseline. This type of model allows for the analysis of longitudinal data with unbalanced time points and missing data (Cnaan et al., 1997). Cognitive domains are the outcome measures and time in years, age, sex, and education level are the fixed effects. The unique

participant ID assigned to each participant was the random effect. All neuropsychological data were standardized to z-scores (i.e., raw score − mean score controls at baseline/SD controls at baseline). Z-scores for tests with reaction times 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. In the social cognition domain, the prodromal Alzheimer group was excluded due to limited observations.

Also, dummy variables were computed for the cognitive domains. A '1' on the dummy variable of a particular domain indicated that one had a z-score below -1.5, defined as a cognitive deviation in that domain. Vice versa, a '0' indicated that there were no deviations. A time to event analysis in R analyzed these scores to see when the first deviations in each cognitive domain occur in every group. For the MRI scans, the associated reports of the radiologists were analyzed, and scores of either 0 or 1 were given on dummy variables depending on whether there were deviations in certain brain regions. These scores were also analyzed by a time to event analysis. Kaplan-Meier curves are created, showing the cumulative proportion of participants who progressed from no deviations to a deviation in a certain cognitive domain/brain area within each group over time. The censoring date was the date of conversion. A log rank test was performed to compare the rate of progression between diagnostic groups.

Results

Demographical data

Demographical and neuropsychological data at baseline can be found in Table 3. People with prodromal AD were older than the other two groups ($F(2, 58) = 28.31$, $p < .001$). The AD group scored significantly lower on the MMSE than the other two groups ($F(2, 56) = 34.56$, $p < .001$), and significantly higher on the NPI ($F(2, 28) = 4.40$, $p = .022$).

At baseline, the prodromal AD group had significant lower scores in the language domain compared to control participants ($F(2, 57) = 8.24$, $p < .001$). For all other cognitive domains at baseline, people with prodromal AD had significant lower scores compared to control participants and people with prodromal FTD; memory encoding, ($F(2, 57) = 45.75$, $p < .001$), memory recall, ($F(2, 57) = 49.12$, $p < .001$), and executive functioning, ($F(2, 57) = 22.97$, $p < .001$). For attention, ($F(2, 56) = 25.56$, $p < .001$). In the social cognition domain, the prodromal FTD participants did not differ significantly from control participants at baseline.

Table 3

Demographics and neuropsychological data per group at baseline

	pFTD	pAD	Control	Sig.
Demographical data				
N	20	21	20	-
Age	50.25 (9.32)	68.19 (9.55)	47.85 (9.60)	AD > FTD, AD > Control, p = <.001
Education level	5.45 (1.23)	4.95 (1.07)	5.60 (0.94)	p = .144
Gender	M: 40%, F: 60%	M: 47,52%, F: 52,38%	M: 65%, F: 35%	p = .268
MMSE score	29.25 (0.91)	25.58 (2.43)	29.30 (1.03)	AD < FTD, AD < Control (p = <.001)
FAB score	16.25 (1.75)	13.92 (4.36)	16.45 (1.70)	p = .109
NPI score	3.55 (9.52)	11.00 (11.73)	0.07 (0.27)	AD > FTD, AD > Control, p = .022
BDI score	6.32 (8.79)	6.00 (-)	3.10 (2.27)	p = .292
Neuropsychological data	pFTD	pAD	Control	Sig.
Language	-0.61 (1.17)	-1.71 (1.15)	-0.36 (1.04)	AD < Control, p = <.001
Memory: encoding	-0.54 (1.15)	-3.06 (1.41)	-0.58 (0.77)	AD < FTD, AD < Control, p = <.001
Memory: recall	-0.57 (1.29)	-3.43 (0.83)	-0.57 (0.98)	AD < FTD, AD < Control, p = <.001
Executive functioning	-0.64 (0.93)	-2.53 (1.54)	-0.25 (0.78)	AD < FTD, AD < Control, p = < .001
Attention	-0.54 (0.88)	-2.04 (1.17)	0.005 (0.66)	AD < FTD, AD < Control, p = <.001
Social cognition	-0.19 (0.57)	-	-0.29 (0.65)	p = .138

Note. Abbreviations: pFTD = prodromal frontotemporal dementia, pAD = prodromal Alzheimer's Disease, MMSE = Mini Mental State Examination, FAB = Frontal Assessment Battery, NPI = Neuropsychiatric Inventory, BDI = Beck Depression Inventory. Education level: Dutch educational system categorized into levels from 1 = less than 6 years of primary education to 7 = academic schooling (Duits & Kessels, 2014).

The demographical numbers are based on 20 FTD, 21 AD and 20 control participants. The MMSE numbers are based on 20 FTD, 19 AD and 20 control participants. The FAB numbers are based on 8 FTD, 12 AD and 11 control participants. The NPI numbers are based on 11 FTD, 6 AD and 14 control participants. The BDI numbers are based on 19 FTD, 1 AD and 20 control participants. The scores on the cognitive domains are Z-scores, calculated by the raw score − mean score of controls at baseline/SD controls at baseline. The z-scores for each domain are represented by 20 participants of each group, except for 19 AD participants in the attention domain and 19 FTD participants in the social cognition domain.

Neuropsychological data – mixed linear effects model

The declines over time in each cognitive domain for each group are illustrated in Figure 1.

Language

A significant interaction effect between time and group was found ($F(2, 239.06) = 19.56$, $p < .001$). Post-hoc analysis revealed that the prodromal FTD group ($p < .001$) and the prodromal AD group ($p = .003$) had a significant steeper decline over time than the control group.

Memory encoding

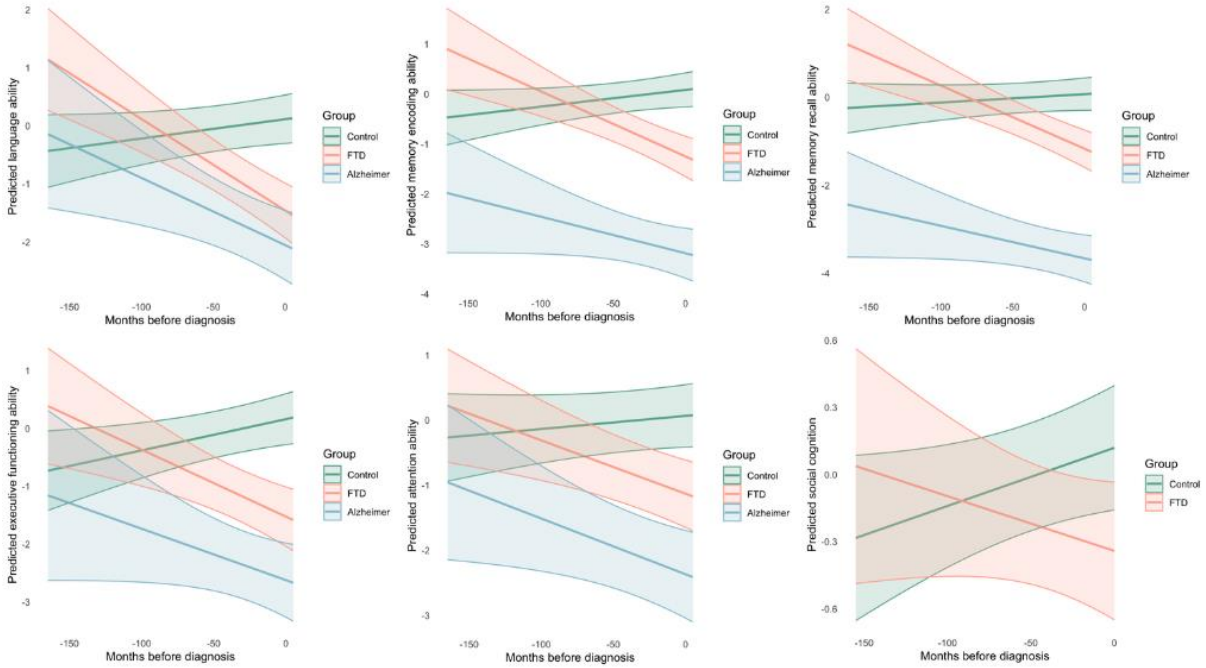
A significant interaction was found between time and diagnostic group ($F(2, 251.04) = 13.37$, $p < .001$). Post-hoc analysis revealed that the prodromal FTD group ($p < .001$) and the prodromal AD group ($p = .043$) had a significant steeper decline over time than the control group.

Memory recall

A significant interaction was found between time and diagnostic group ($F(2, 246.67) = 14.10$, $p < .001$). Post-hoc analysis revealed that the prodromal FTD group ($p < .001$) had a significant steeper decline over time than the control group.

Figure 1

Mixed linear effects models per cognitive domain and group



Note. Models displaying the changes in z-score in each cognitive domain in a prodromal FTD group (red), prodromal AD group (blue) and a control group (green). Cognitive domains from left to right, from top to bottom, are language, memory encoding, memory recall, executive functioning, attention/mental processing speed, social cognition.

Executive functioning

A significant interaction was found between time and diagnostic group ($F(2, 247.15) = 11.07$, $p < .001$). Post-hoc analysis revealed that the prodromal FTD group ($p < .001$) and the prodromal AD group ($p = .022$) had a significant steeper decline than the control group.

Attention

A significant interaction was found between time and diagnostic group ($F(2, 225.76) = 8.53$, $p < .001$). Post-hoc analysis revealed that the prodromal FTD group ($p < .001$) and the prodromal AD group ($p = .025$) both had a significant steeper decline than the control group.

Social cognition

The interaction between time and diagnostic group, in this case only between prodromal FTD participants and control participants, was significant ($F(1, 185.31) = 5.54$, $p = .020$).

Neuropsychological data – time to event analysis

The Kaplan-Meier curve for every cognitive domain can be found in Figure 2 and the probabilities for both prodromal groups are summarized in Table 4.

Table 4

Proportion of people with deviations in cognitive domains over time for both prodromal groups

Group	Time (months)	LA	ME	MR	EF	AT	SO
pFTD	-113/MR: -52	1.5%	1.5%	2%*	1.5%	1.5%	0%
	-41 till -37	7.8%	13.3%	6.7%	9.3%	17.3%	0%
	-23 till -20	22.5%	19.9%	12.9%	18.3%	26.5%	4.8%
	-12 till -11	37.2%	43.2%	33.7%	33.3%	40%	11.6%
	0	73%	75.7%	75.1%	82.8%	76.9%	36.8%
pAD	-164 till -152	2%	2%	2%	2%	2.04%	-
	-40 till -38	15.5%	28%	28%	20.98%	13.56%	-
	-27 till -23	23.2%	44%	48%	41.3%	31.36%	-
	-13 till -10	41.2%	62.32%	60.1%	55.76%	47.89%	-
	0	87.1%	97.78%	97.65%	94.39%	92.11%	-

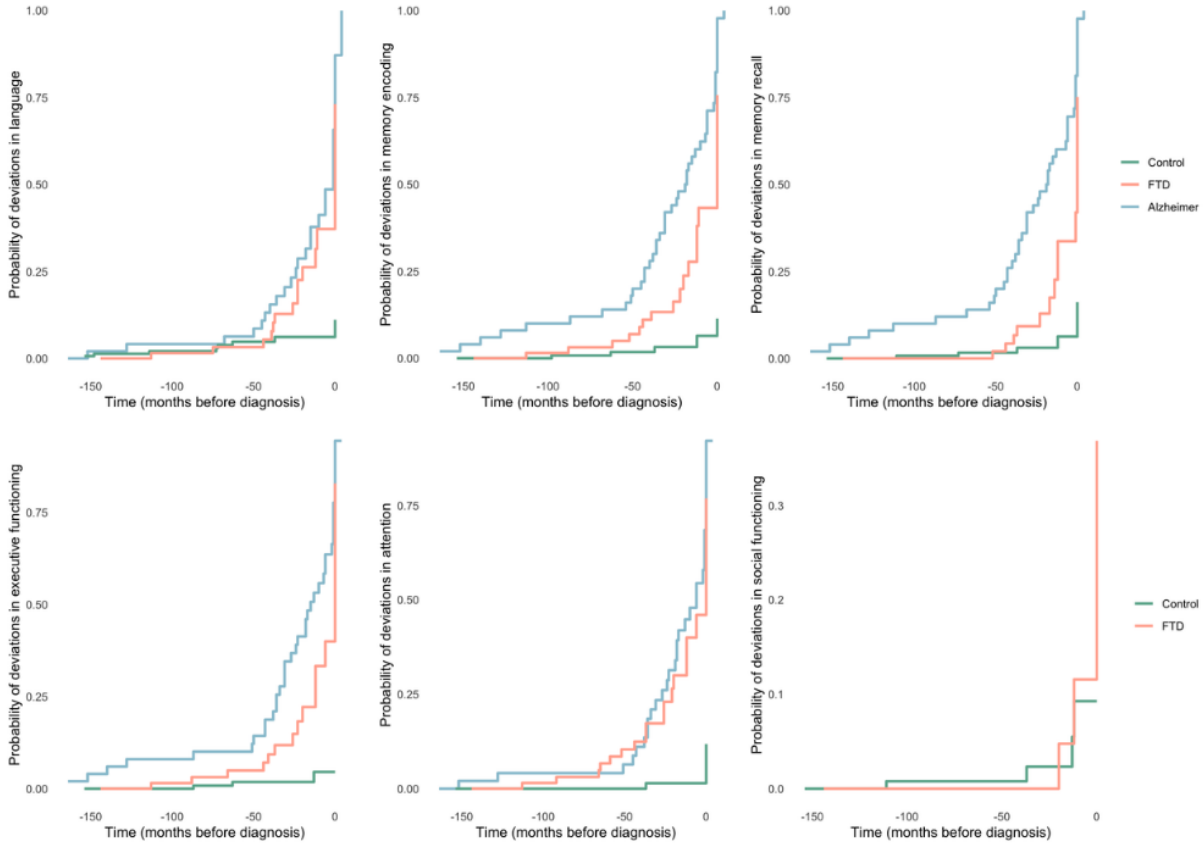
Note. First timepoint of MR is at -52, not at -113.
Time is measured in months before diagnosis. Abbreviations: pFTD = prodromal frontotemporal dementia, pAD = prodromal Alzheimer's Disease, LA = language, ME = memory encoding, MR = memory recall, EF = executive functioning, AT = attention, SO = social.

In the language domain, the first deviations started 113 months before diagnosis in the prodromal FTD group, and 152 months before diagnosis in the prodromal AD group.
In the memory encoding domain, the first deviations started at 113 months before diagnosis in the prodromal FTD group, and 164 months before diagnosis in the prodromal AD group.
Scores in the memory recall domain started deviating in 52 months before diagnosis in the prodromal FTD group, and 164 months before diagnosis in the prodromal AD group. For

executive functioning, the scores started deviating 113 months before diagnosis in the prodromal FTD group, and 164 months before diagnosis in the prodromal AD group. In the attention domain, scores in the prodromal FTD group started deviating 113 months before diagnosis, and 152 months before diagnosis in the prodromal AD group. Finally, social cognitive scores deviated first 20 months before diagnosis in the prodromal FTD group. So, for prodromal FTD, all domains except for memory recall and social cognition, deviated 113 months before diagnosis. For prodromal AD, scores in the memory encoding, memory recall and executive functioning started deviating first, i.e., 164 months before diagnosis.

Figure 2

Kaplan-Meier curves for every cognitive domain over time per group



Note. Kaplan-Meier curves displaying the proportion of people with a deviation in a certain cognitive domain in the months before the diagnosis. The prodromal FTD group is red, prodromal AD is blue, and the control group is green. Cognitive domains from left to right, top to bottom, are language, memory encoding, memory recall, executive functioning, attention and social cognition.

Deviations on MRI scans – time to event analysis

The Kaplan-Meier curve for every cognitive domain can be found in Figure 3 and the probabilities for both prodromal groups are summarized in Table 5. The control group did not have any deviations in one of the brain areas over the entire time course.

Frontal, temporal and occipital deviations first started to occur 37 months before diagnosis in the prodromal FTD group, and 50 months before diagnosis in the prodromal AD group. Parietal deviations also started to occur 37 months before diagnosis in the prodromal FTD group, and 52 months before diagnosis in the prodromal AD group. Hippocampal deviations only occurred at diagnosis in the prodromal FTD group, and in the prodromal AD group these started 50 months before diagnosis.

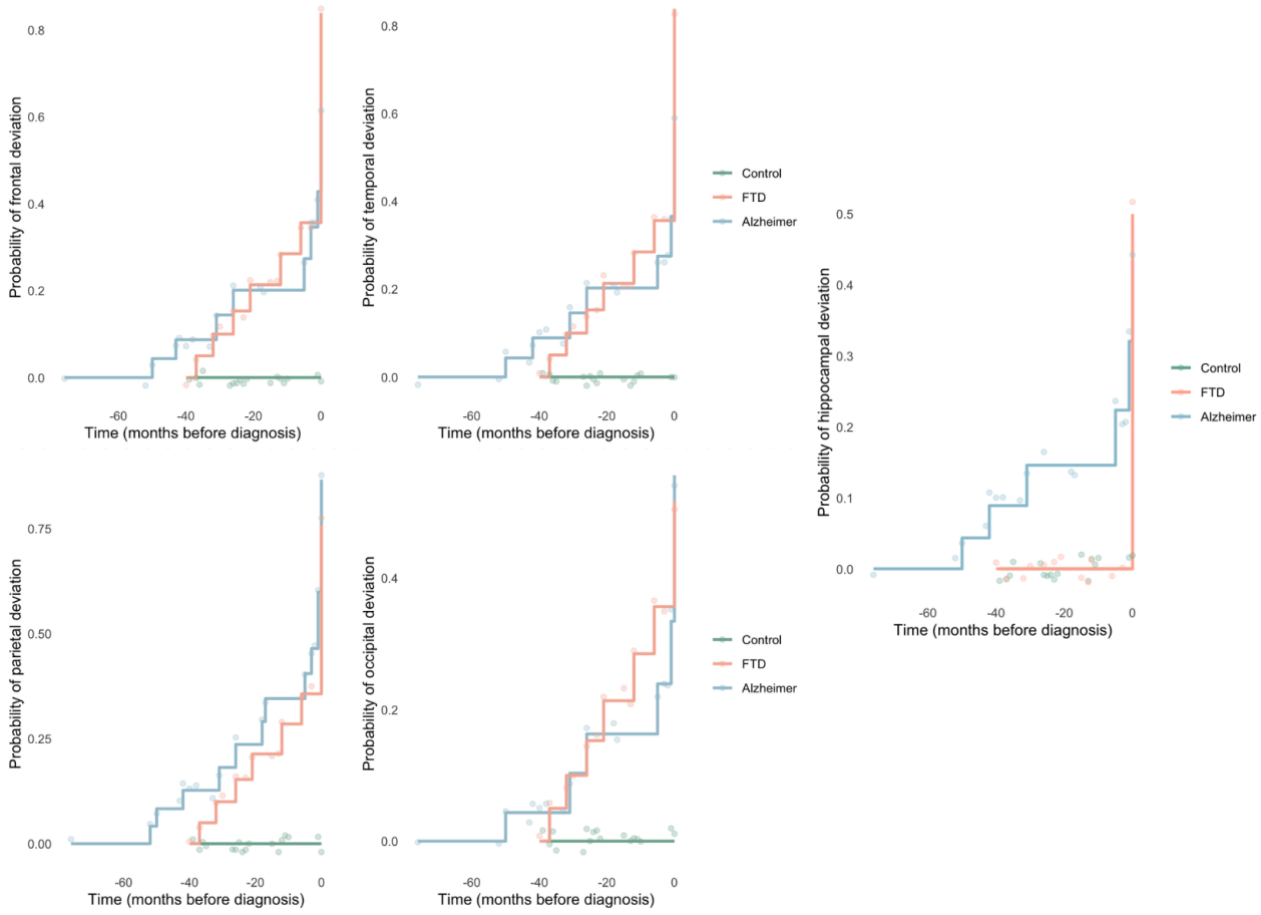
Table 5. % of people with deviations in brain areas over time for both prodromal groups.

Group	Time	Frontal	Temporal	Parietal	Occipital	Hippocampal
pFTD	-37	5%	5%	5%	5%	0%
	-26	15.3%	15.3%	15.3%	15.3%	0%
	-12	28.5%	28.5%	28.5%	28.5%	0%
	-6 till -5	35.6%	35.6%	35.6%	35.6%	0%
	0	83.9%	83.9%	75.9%	51.7%	50%
pAD	-52 till -50	4.3%	4.3%	4.2%	4.3%	4.3%
	-31 till -26	21.1%	21.3%	23.6%	16.3%	14.6%
	-6 till -5	27.4%	27.5%	40.5%	33.4%	22.4%
	0	61.9%	57.7%	86.6%	55.6%	43.4%

Note. Time is in months before diagnosis. Abbreviations: pFTD = prodromal frontotemporal dementia, pAD = prodromal Alzheimer's Disease.

Figure 3

Kaplan-Meier curves for deviations in each brain area over time per group



Note. Kaplan-Meier curves displaying the proportion of people with a deviation in a certain brain area in the months before the diagnosis. The prodromal FTD group is red, prodromal AD is blue, and the control group is green. Brain areas from left to right, top to bottom, are the frontal lobe, the temporal lobe, the hippocampi, the parietal lobe and the occipital lobe.

Discussion

This study aimed to characterize cognitive and brain changes in the prodromal stage of FTD and AD. Cognitive changes were observed as early as nine years before the diagnosis of FTD, significantly earlier than previously reported. In contrast, MRI scan abnormalities emerged later than anticipated, approximately three years before diagnosis. The study also revealed that while both type of dementias involve impairments in multiple cognitive domains, the patterns of brain atrophy and the progression of these neuropsychological changes differ between prodromal FTD and AD. These results can contribute to earlier

diagnoses and improve the differentiation between FTD and AD, which is often challenging in clinical practice.

In prodromal FTD, we found the earliest cognitive changes to appear consistently across nearly all cognitive domains, except for memory recall and social cognition, where deterioration manifests later in the disease. Although there are numerous studies showing early biomarkers in FTD in and before the presymptomatic stage (Benussi et al., 2019; Bocchetta et al., 2023; Jiskoot et al., 2018; Meeter et al., 2016; Planche et al., 2022; Poos et al., 2022a, 2022b; Rohrer et al., 2015; Tavares et al., 2019; van der Ende et al., 2019), the first neuropsychological changes in prodromal FTD have typically been documented closer to diagnosis (Jiskoot et al., 2018; Poos et al., 2022a; Rohrer et al., 2015; Tavares et al., 2020), compared to what we found. The cognitive domains that exhibited the most prominent early impairments included attention/mental processing speed, followed by memory encoding, language, and executive functions. This mirrors findings from previous research that highlights deficits in executive function as among the earliest manifestations of FTD (Barker et al., 2021, 2022; Benussi et al., 2021b; Geschwind et al., 2001; Janssen et al., 2005; Jiskoot et al., 2018b; Poos et al., 2021a; Staffaroni et al., 2020), just as deficits in the language domain (Barker et al., 2021; Jiskoot et al., 2018b; Olney et al., 2020; Rohrer et al., 2015), and attentional and mental processing speed impairments in prodromal FTD patients (Geschwind et al., 2001; Jiskoot et al., 2018). These cognitive functions do for a big part rely on frontal and temporal areas, the areas firstly affected in FTD (Piguet & Hodges, 2013; Rohrer et al., 2015). Memory recall and social cognition deviations occurred later than the rest, approximately around 4 and 2 years before diagnosis. There is considerable debate regarding the role of memory impairments in the early stages of FTD, since it is officially an exclusion criterion for FTD (Rascovsky et al., 2011). However, as highlighted in an increasing number of studies (Barker et al., 2021; Jiskoot et al., 2018; Olney et al., 2020; Poos et al., 2018, 2021b; Staffaroni et al., 2020), we found that memory encoding is already impaired in prodromal FTD. Memory encoding deficits arise early due to damage in the frontal lobes and anterior temporal regions, disrupting attention and organizational strategies necessary for encoding (Collette et al., 2010; Glosser et al., 2002; Karantzoulis & Galvin, 2014; Poos et al., 2018). On the other hand, memory recall remains relatively preserved in early stages as the hippocampus and medial temporal structures are less affected (Collette et al., 2010; Glosser et al., 2002; Poos et al., 2018). The late deviations in social cognition are not usual compared to previous studies, which state that social cognition is one of the first domains to be affected (Dopper et al., 2014; Jiskoot et al., 2018b; Rohrer et al., 2015). However, some studies also

failed to replicate the early changes observed in the social cognition domain (Bertrand et al., 2018; Papma et al., 2017). Therefore, more attention should be given researching the order and prominence of cognitive deterioration in genetic FTD.

In terms of MRI scan deviations for prodromal FTD, our analysis revealed MRI scan deviations to occur later than what has been previously reported. Changes in brain structures have been found to present themselves already 10 years before expected disease onset (Rohrer et al., 2015) and precede cognitive deficits (Benussi et al., 2019; Cash et al., 2018; Dopper et al., 2014; Papma et al., 2017; Poos et al., 2022a). In this study, for a few participants, deviations began appearing 37 months before diagnosis. However, in the months directly preceding diagnosis, there was a sharp increase in the proportion of participants with MRI scan deviations. This explosive start of symptoms has been reported before (Jiskoot et al., 2016, 2018; Poos et al., 2022a). In our study, three years before diagnosis, deviations in the frontal and temporal regions were most pronounced, followed by parietal regions, and lastly the occipital cortex. Hippocampal deviations, in contrast, did not become apparent until patients were diagnosed. This aligns with prior research highlighting temporal and frontal lobe reductions in FTD (Katisko et al., 2019; Olney et al., 2020; Rohrer et al., 2015). Additionally, Le Ber et al. (2008) suggest that early parietal dysfunction may be specific to GRN mutation carriers. Our findings suggest a delayed detection of atrophy compared to other studies, likely because our data relied on radiologists' reports rather than on direct imaging analyses. However, these are precisely the reports that clinicians use to base a potential diagnosis on. Based on these reports, we could not replicate these early brain changes demonstrated in group studies. This underlines the need to improve the knowledge on individual patient disease progression and supports the notion that group level statistics do not translate to the individual patients very well.

For prodromal AD, our study demonstrated that the earliest neuropsychological deviations are observed in memory recall, followed by impairments in memory encoding, executive functioning, attention, and language. These results align with the established model of AD as an amnestic syndrome primarily characterized by deficits in episodic memory, also shown in early stages of AD (Dubois, 2000; Dubois & Albert, 2004). Consistent with previous research, our findings suggest that impairments in executive functions and attention also appear early in the disease course, although they tend to emerge somewhat later than the memory deficits (Heikkinen et al., 2024; Musa et al., 2020). Additionally, the analysis of MRI scan deviations reveals that structural brain changes in prodromal AD tend to follow a unique progression. Subtle changes are first detected across distributed brain regions (Davatzikos et

al., 2008), before rapidly escalating closer to the time of diagnosis. Eventually, at diagnosis, parietal deviations are the most prominent. Studies demonstrate that atrophy begins in the medial temporal lobes (Fleisher et al., 2008), then extends to the parietal lobes and finally the frontal lobes (Bakkour et al., 2009; Blanc et al., 2016; Whitwell et al., 2007, 2008). We could not replicate this particular order. A notable aspect of our MRI data was that temporal and frontal lobe deviations were less prominent early in the disease than expected, with the parietal lobe showing more pronounced changes at earlier stages of the disease. These differences between other studies and this study, again argues for a better understanding of the individual view on the disease in early stages, instead of relying on group studies.

Comparing prodromal AD with prodromal FTD, this study found important differences in the nature and timing of cognitive and structural impairments. In prodromal FTD, cognitive impairments span a broader range of domains, including attention, language, memory encoding and executive functions, which are affected much earlier than memory recall and social cognition. In prodromal AD however, memory recall consistently emerges as the earliest and most prominent deficit. This is congruent with research by Shinagawa et al. (2006); they showed that attention disturbances were more frequently observed as initial symptoms in FTD patients than in AD patients. Lindall et al. (2000) did a similar study, in which they demonstrated that executive function symptoms are observed more often in FTD patients than in AD patients in the initial stage. The cognitive decline observed in prodromal FTD is more extensive across multiple domains, which suggests that FTD impacts multiple neural systems concurrently in its early stages. Interestingly, while prodromal AD participants showed lower scores overall, they experienced a slower decline than prodromal FTD participants. This applies to every cognitive domain, except for memory recall, where prodromal AD had more pronounced deficits. These differences between FTD and AD reflect the pattern of less evident memory problems in early-stage FTD (Barker et al., 2022; Cummings & Benson, 1986; Gregory et al., 1997; Kramer et al., 2003; Korhonen et al., 2020; Lindau et al., 2000; Shinagawa et al., 2006; Welsh et al., 1992), with problems in delayed recall being the most discriminative (Poos et al., 2018). Likewise, MRI scan deviations for prodromal FTD and AD followed a slightly different course. While prodromal FTD eventually showed more frontal and temporal deviations, these changes appeared later compared to prodromal AD. This atrophy is part of the diagnostic criteria of FTD (Rascovsky, 2011) and is associated with the behavioral and cognitive impairments typical of FTD (Lindau et al. 2000). The presence of parietal and hippocampal deviations was more pronounced in prodromal AD at the time of diagnosis, with hippocampal changes being absent in prodromal

FTD until symptom onset. This suggests that the patterns of MRI abnormalities in both conditions reflect the different neuropsychological trajectories. Overall, while both conditions exhibit subtle but detectable changes early on, the specific areas and temporal order of cognitive and structural decline diverge, which may serve as early diagnostic markers distinguishing between FTD and AD.

The present study has several important strengths. One key strength is the use of actual years to onset for both cognitive and MRI measures, which provided a more precise and realistic staging of the prodromal phase of FTD and AD compared to studies using expected years to onset data. Additionally, the study employed a thorough analysis of individual MRI reports written by radiologists, providing a nuanced understanding of structural changes that occur prior to diagnosis, instead of relying in imaging analyses. The use of a control group with neuropsychological and MRI assessments further strengthened the study by helping differentiate normal aging from the early signs of prodromal dementia. Also, the use of a longitudinal design instead of a cross-sectional design is beneficial for this study, as the course of biomarker development is different for each genetic FTD patient. However, there are notable limitations. The relatively small sample size of participants with prodromal AD and FTD may limit the generalizability of our findings. The study also included a younger control group compared to the prodromal AD group, which could have influenced certain comparisons, as this group then does not represent the normal aging signs for the AD group. Aside from that, some cognitive domains were represented by only 1 or 2 neuropsychological tests, which may not have fully captured these domains. Lastly, most of the radiologists' reports were written in the context of research, and therefore the reports are not as elaborate as clinical reports would be. Including clinical radiologist reports would have been better, as these are more informative about the participants disease status. In future studies, it would be beneficial to include larger, more age-matched samples to increase the statistical power and generalizability of the findings. Additionally, standardizing MRI protocols and including behavioral assessments would provide further insights into the changes occurring during the prodromal phase of both diseases. Future research could also explore the effects of different subtypes of FTD, such as primary progressive aphasia (PPA), and how these might relate to distinct patterns of cognitive and neuroanatomical changes. Furthermore, exploring genetic subtypes of FTD and their specific patterns of progression could deepen our understanding of the heterogeneity within FTD.

Conclusion

This study provides important insights into the early stages of both FTD and AD, highlighting differences in the timing and nature of cognitive and structural changes between the two conditions. Prodromal FTD can be distinguished from prodromal AD as it is characterized by deficits in several cognitive domains, especially in attention/mental processing speed, language and executive functions, and has an explosive start of symptoms. On the other hand, prodromal AD has evident memory recall deficits and a more gradual development of symptoms. Our findings also show that MRI changes derived from radiologists reports in both groups are subtly in the prodromal phase but become more pronounced as the diagnosis approaches. These deviations presented themselves much later than expected. This study underscores the notion that individual reports may not adequately reflect findings from group studies, making it challenging to recognize the underlying disease. Concluding, these findings contribute to a better understanding of the prodromal stage of frontotemporal dementia. The findings highlight the need to conduct research also individually and to not rely blindly on group statistics. The study offers potential diagnostic markers that could assist in earlier detection and intervention, which is crucial for providing tailored care for dementia patients and advancing medical trails aimed at preventing or curing dementia.

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