Longitudinal Brain Atrophy Rates in Presymptomatic Carriers of Genetic Frontotemporal Dementia

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Abstract
Background and Objectives: It is important to identify at what age brain atrophy rates in genetic frontotemporal dementia (FTD) start to accelerate and deviate from normal aging effects to find the optimal starting point for treatment. We investigated longitudinal brain atrophy rates in the presymptomatic stage of genetic FTD, using normative brain volumetry software.

Methods: Presymptomatic GRN, MAPT, and C9orf72 pathogenic variant carriers underwent longitudinal volumetric T1-weighted magnetic resonance imaging of the brain as part of a prospective cohort study. Images were automatically analyzed with Quantib® ND which consisted of volume measurements (CSF and sum of gray and white matter) of lobes, cerebellum, and hippocampus. All volumes were compared to reference centile curves based on a large population-derived sample of non-demented individuals (n=4951). Mixed-effects models were fitted to analyze atrophy rates of the different gene groups as a function of age.
Results: 34 GRN, eight MAPT, and 14 C9orf72 pathogenic variant carriers were included (mean age=52.1, standard deviation=7.2; 66% female). Mean follow-up duration of the study was 64±33 months (median=52; range 13-108). GRN pathogenic variant carriers showed faster decline than the reference centile curves for all brain areas, though relative volumes remained between 5th and 75th percentile between the ages of 45-70. In MAPT pathogenic variant carriers, frontal lobe volume was already at the 5th percentile at age 45, and showed further decline between the ages 50-60. Temporal lobe volume started in the 50th percentile at age 45, but showed fastest decline over time compared to other brain structures. Frontal, temporal, parietal and cerebellar volume already started below the 5th percentile compared to the reference centile curves at age 45 for C9orf72 pathogenic variant carriers, but there was minimal decline over time until the age of 60.

Discussion: We provide evidence for longitudinal brain atrophy in the presymptomatic stage of genetic FTD. The affected brain areas and the age after which atrophy rates start to accelerate and diverge from normal aging slopes differed between gene groups. These results highlight the value of normative volumetry software for disease-tracking and staging biomarkers in genetic FTD. These techniques could help in identifying the optimal time window for starting treatment and monitoring treatment response.

Introduction

Frontotemporal dementia (FTD) is the second most common form of young-onset dementia, typically demonstrating atrophy of the frontal and/or temporal lobes. It is characterized by a heterogeneous profile with deterioration of behavioral (behavioral variant FTD, bvFTD), language (primary progressive aphasia, PPA) or motor skills. FTD has an autosomal dominant inheritance pattern in up to 30% of cases, with pathogenic variants in the GRN, MAPT, and C9orf72 genes being the most common. Cohort studies investigating the presymptomatic stage of FTD have demonstrated early changes in neuroimaging, cognition, blood, and CSF. In particular, brain atrophy, measured by structural MRI, is of interest as biomarker of neurodegeneration and outcome measure in upcoming clinical trials.
GRN pathogenic variants often lead to an asymmetrical pattern of atrophy in the frontal, temporal and parietal lobes in later disease stages, and additional lower gray matter (GM) volume in the insula has been demonstrated in the presymptomatic stage. In symptomatic pathogenic variant carriers (PVC), this typically results in a clinical diagnosis of bvFTD or non-fluent variant PPA (nfvPPA) and is often accompanied by parkinsonism. Pathogenic variants in the MAPT gene typically lead to focal anterior temporal lobe degradation, including the hippocampus, with additional presymptomatic changes in the amygdala and insula. bvFTD is the main phenotype in the symptomatic stage, but can be accompanied by atypical parkinsonism such as corticobasal syndrome or progressive supranuclear palsy. Lastly, the atrophy associated with the C9orf72 repeat expansion is rather diffuse, with widespread GM volume loss, including the frontal and temporal cortices, but also subcortical and cerebellar regions. In presymptomatic C9orf72 PVCs, lower GM volume of the thalamus, cerebellum, and frontal, temporal, parietal and insular cortices has been found. In the symptomatic stage, this is usually accompanied by a clinical diagnosis of bvFTD, motor neuron disease, or a combination of both, but also notable psychiatric features.

Longitudinal studies in presymptomatic FTD provide a unique opportunity to determine the age at which atrophy rates start to deviate from normal. Identifying a potential change-point at which the atrophy rate accelerates compared to the normal aging process is essential for upcoming clinical trials, as it can provide the best time-window to start disease-modifying treatment. Yet, most studies investigating brain atrophy in presymptomatic FTD have been cross-sectional in nature and/or plotted using estimated years to onset as a proxy for actual symptom onset, which has been shown to be unreliable in C9orf72 and GRN as there is large variation between and within families. Only a few studies so far have investigated atrophy rates longitudinally. For example, Jiskoot et al. showed that the first changes occurred approximately two years before actual symptom onset in eight FTD converters. However, it remains unclear at what age atrophy starts to accelerate compared to normal aging effects.

Software packages that apply automated normative quantitative assessment of brain MRI data are now emerging for clinical use. They provide the user with quantification of brain atrophy by segmentation of brain tissues and structures and compare it to a group of age- and sex-matched cognitively healthy individuals. These approaches are interesting for presymptomatic cohorts, as there is evidence that they could lead to earlier identification of atrophy than visual rating scales and can improve the accuracy of dementia diagnosis. However, to date, no study has investigated the application of such normative volumetry software in analyzing longitudinal presymptomatic genetic FTD data.
The aim of this study was to investigate longitudinal atrophy rates in presymptomatic GRN, MAPT and C9orf72 PVCs, using the FDA-cleared normative volumetry software package Quantib® Neurodegenerative (ND), to estimate the change-points relative to age.

Methods

Participants

We included longitudinal data of 56 participants from the FTD Risk Cohort (FTD-RisC) of the Erasmus MC University Medical Center (Rotterdam, the Netherlands). FTD-RisC is an ongoing, longitudinal cohort study in which first-degree family members of C9orf72, GRN or MAPT PVCs are followed on a one- or two-year basis. Participants for this study were recruited between December 2009-October 2019. DNA genotyping at study entry assigned participants to either the PVC group or non-carrier group. Inclusion criteria of the current study were: 1) participants were C9orf72, GRN or MAPT PVCs, 2) at study entry all participants were presymptomatic (i.e. did not fulfill clinical diagnostic criteria for bvFTD, PPA and/or ALS), and had a Clinical Dementia Rating scale plus National Alzheimer’s Coordinating Center Frontotemporal Lobar Degeneration (CDR® plus NACC FTLD) of 0, and 3) had undergone at least one MRI scan. Exclusion criteria for the current study were: 1) other neurological conditions that can affect brain volumetry and/or primary psychiatric disorders, and 2) presymptomatic PVCs younger than 45 years old, as the reference population in Quantib® ND consists of cognitively healthy individuals between 45-95 years. This resulted in the inclusion of 34 GRN, eight MAPT and 14 C9orf72 PVCs at baseline, and 33 GRN, five MAPT and 11 C9orf72 PVCs underwent two or more MRI scans (Table 1). Six PVCs developed clinical symptoms during follow-up (C9orf72: one ALS and one FTD-ALS; GRN: one bvFTD and two nfPPA; MAPT: one bvFTD) and progressed on the CDR plus NACC FTLD global score (eFigure 1). Participants’ characteristics are summarized in Table 2.

Procedure

At every study visit, participants underwent a standardized clinical assessment consisting of a medical history, family history, neurological examination, neuropsychological assessment and brain MRI. Clinical status was based on these assessments and a structured clinical interview with the participant and a knowledgeable informant, including the CDR® plus NACC FTLD, modified Neuropsychiatric Inventory Questionnaire (NPI-Q), Cambridge Behavioural Inventory – Revised (CBI-R), and Frontotemporal dementia Rating Scale (FRS). The Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) were used as respectively global cognitive and frontal-executive screeners. Neuropsychological assessment consisted of tests assessing language (60-item version Boston Naming Test, categorical fluency), attention and mental processing speed (Trail Making Test A and B).
TMT – part A, Stroop Color-Word Interference Test (SCWIT) word and color naming card, Wechsler Adult Intelligence Scale (WAIS)-III, digit span forward), executive functioning (TMT – part B, SCWIT ink naming card, modified Wisconsin Card Sorting Test, letter fluency, WAIS-III digit span backwards), memory (Dutch Rey Auditory Verbal Learning Test, Visual Association Test), social cognition (Ekman Faces, Happé Cartoons) and visuoconstruction (clock drawing).

**Image acquisition**

Participants underwent volumetric T1-weighted MRI on a Philips 3T Achieva MRI scanner (Philips, Best, the Netherlands). We used an 8-channel SENSE head coil between December 2009-2016, and an 32-channel SENSE head coil from 2016 onwards. Due to ongoing recruitment, not all participants have the same number of scans made with either 8-channel or 32-channel head coil (for numbers per visit see eTable 1). A scanner software update was performed in May 2016. The following scan parameters were used: repetition time=9.7 ms, echo time=4.6 ms, field of view=224 x 177 x 168 mm, flip angle=8, slices=140, voxel size=0.88x0.88x1.20 mm, SENSE=none, total acquisition time=4.56 min. All scans underwent extensive visual quality check. Images were analyzed using Quantib® ND software.

**Normative volumetric image data processing**

Quantib® ND (https://www.quantib.com) is a post-processing image analysis tool for T1-weighted images, that quantifies the volume of brain tissues and various structures. The automatic analysis consists of segmentation and volume measurements of brain tissues (CSF and sum of GM and white matter (WM)), intracranial volume (ICV), total brain volume, brain lobes (frontal, temporal, parietal, and occipital), cerebellum and hippocampus. The algorithms for the segmentation are based on Vrooman et al. and Fortunati et al. The end outputs for each brain structure are total and lateralized volumes in mm$^3$. The lateralized volumes are expressed as a percentage of the total ICV (%ICV). Percentile scores are calculated by comparing %ICV scores to reference centile curves based on a large population of cognitively healthy individuals. The reference population consisted of 4951 people aged 45-95 years old from the Rotterdam Study, the largest Dutch prospective cohort study, whose scans were acquired on 1.5T MRI (GE Healthcare, US) between 2005-2015. The Rotterdam study is described elsewhere in more detail. See for an example output file from Quantib® ND eAppendix 1.

**Statistical analysis**

All statistical analyses were conducted using R v4.0.4. All raw neuropsychological test scores were standardized to z-scores, and composite cognitive domain scores were calculated by averaging the z-scores of the individual tests (as described in Procedure) per assessment. We compared the
continuous sociodemographic and clinical data at baseline between gene groups with one-way ANOVAs and chi-square tests for dichotomous variables. The significance level was set at p<0.05 (two-tailed). Clinical and cognitive data were longitudinally assessed with linear mixed-effects models including time since baseline, gene group, and for cognitive data also age at baseline and education level as fixed effects. We tested the best fitting model by comparing models with random intercepts and models with additional random slopes (eTable 2).

As this is an ongoing study, participants varied in the number of visits that were completed and seven individuals had only one available MRI scan (Table 1). All available data were included in the analyses to increase the sample size and match the age range of the control cohort within Quantib’s ND software. For five converters all MRI scans up until the clinical diagnosis were included, and for one converter one MRI scan one year after diagnosis was included. A mixed-effects model with natural cubic splines was fitted for each brain structure to analyze differences in brain atrophy between gene groups as a function of age. This type of model allows for the analysis of longitudinal data with unbalanced time points and missing data (including individuals with one MRI scan). In each model %ICV of the brain structure of interest was used as dependent variable and we specified the following fixed effects: age, gene group, age x gene group, sex, and scanner software update. Time interval between MRI scans was not included as a covariate, as age controls for the time between MRI scans.

Brain structures’ %ICV were calculated by dividing the volume of the structure by the total ICV at baseline and corrected for the change in head coil by estimating the beta coefficients of the change in head coil in non-PVCs from FTD-RisC (n=163), and subtracting the beta coefficient from the %ICV. We tested the best fitting model by comparing models with random intercepts and/or slopes with two or three splines. An overview of the best fitting models per brain structure can be found in eTable 2. All assumptions were checked and met. Abnormal brain volume was defined as a %ICV score ≤5th percentile. %ICV scores were plotted against the reference centile curves as outputted by Quantib’s ND.

**Standard Protocol Approvals, Registrations, and Patient Consents**

The study was approved by the Medical and Ethical Review Committee of the Erasmus Medical Center and participants’ written consent was obtained according to the Declaration of Helsinki.

**Data availability**

Anonymized data not published within this article will be made available upon reasonable request from any qualified investigator.
Results

Sociodemographic, cognitive and clinical data

There was a significant difference between gene groups in age ($F(2,53)=3.26$, $P=0.05$) at baseline (Table 2). At study entry, MAPT PVCs were younger than GRN PVCs ($P=0.04$). There were no differences between gene groups in sex ($X^2(2)=1.9$, $P=0.38$), education ($F(2,53)=1.33$, $P=0.27$), MMSE ($F(2,46)=0.69$, $P=0.51$), FAB ($F(2,22)=1.24$, $P=0.31$), NPI-Q ($F(2,30)=0.75$, $P=0.48$), CBI-R ($F(2,17)=0.63$, $P=0.54$), or FRS ($F(2,25)=2.11$, $P=0.14$) at baseline. A main effect of time was found on the MMSE ($F(1,120)=5.25$, $P=0.02$) and FRS ($F(1,56)=5.94$, $P=0.02$; Figure 1E), but there was no change over time on the FAB ($F(1,93)=3.5$, $P=0.07$; Figure 1B), NPI-Q ($F(1,85)=0.92$, $P=0.34$; Figure 1C), and CBI-R ($F(1,69)=0.06$, $P=0.81$; Figure 1D).

There were no differences between gene groups at baseline on any of the cognitive domains (all $P>0.05$; Table 1). There was no main effect of time on any of the cognitive domains (language: $F(1,133)=0.16$, $P=0.69$, Figure 2A; attention: $F(1,132)=2.16$, $P=0.14$, Figure 2B; executive function: $F(1,130)=1.19$, $P=0.28$, Figure 2C; memory: $F(1,131)=0.57$, $P=0.45$, Figure 2D; social cognition: $F(1,131)=2.01$, $P=0.16$, Figure 2E; visuoconstruction: $F(1,133)=1.32$, $P=0.25$. Figure 2F), but evidence indicated that C9orf72 ($\beta=-0.02$, SE=0.01, $P<0.01$) and MAPT ($\beta=-0.01$, SE=0.00, $P=0.05$) PVCs declined on language compared to GRN PVCs (Figure 2A).

Brain volume trajectories

There were significant interaction effects between age and gene group in the %ICV of the total brain ($LR=17.03$, $P=0.002$), frontal ($LR=25.00$, $P<0.001$), and temporal lobe ($LR=48.20$, $P<0.001$), indicating a different slope per gene group. Model output for lateralized and total brain structures are shown in eTable 3.

In GRN PVCs, a faster decline than the reference centile curves was visible in Figure 3A-3D for total brain, frontal, temporal and parietal lobe volume from age 45 onwards, though all brain structures’ percentile scores remained in the normal range between ages 45-70. For the occipital lobe, cerebellar and hippocampal volumes, a faster decline than the reference centile curves was visible from age 60 onwards. A steeper decline in brain volume was visible for the left than for the right temporal lobe (eTable 3).

The total brain volume in MAPT PVCs showed the fastest decline compared to the other gene groups, as it already crossed the 5\textsuperscript{th} percentile around age 50 (Figure 3A), while at age 45 it was still in the normal range. Frontal lobe volume was at the 5\textsuperscript{th} percentile at age 45, showing further decline between ages 50-60 (Figure 3B). The temporal lobe volume was still around the 50\textsuperscript{th} percentile at age
45, but subsequently showed the fastest decline compared to the other brain structures (Figure 3C). This decline was more pronounced in the left than right temporal lobe. Parietal lobe volume declined less steeply than the frontal and temporal structures, albeit still steeper than the reference centile curves, crossing the 5th percentile around age 60 (Figure 3D). Occipital lobe, cerebellar and hippocampal volume remained within the normal range across the entire age range.

C9orf72 PVCs had overall lower total brain volume than the other gene groups, already starting below the 5th percentile compared to reference/normative data at age 45, though with minimal decline over time until age 60 (Figure 3A). Frontal lobe volume was lowest, being already below the 5th percentile at age 45 (Figure 3B), and the temporal and parietal lobes and cerebellum largely followed the 5th reference centile curve between ages 45-70 (Figure 3C-3E). Occipital lobe and hippocampal volume remained in the average range.

Surprisingly, small increases in occipital lobe volume for C9orf72 and MAPT PVCs, and in hippocampus volume for MAPT PVCs were observed, though not statistically significant (eTable 3). Intra-individual trajectories revealed that this increase occurred between time points when the study switched from an 8-channel to a 32-channel head coil.

All analyses were rerun without the scans of the converters (n=6), and interpretation of the results remained similar. Atrophy rates for the six individual converters can be found in eFigures 1-2.

**Discussion**

The aim of this study was to investigate longitudinal atrophy rates in presymptomatic GRN, MAPT and C9orf72 PVCs older than 45 years, against a background of normal age-related brain changes. To this end, we used Quantib® ND which enabled comparison to a large normative population-derived reference dataset. We compared atrophy rates over time in lobar volumes, hippocampus and cerebellum between gene groups, and found gene-specific differences with respect to the age and brain areas at which atrophy rates start to diverge from normal. The results from this study confirm more progressive atrophy rates in cognitively healthy FTD PVCs than can be expected from normal aging, indicating the diagnostic value of normative brain volumetry software in genetic FTD. Furthermore, by identifying the pattern and timing of brain changes, as well as the speed of change over time, these results hold important potential for upcoming gene-specific clinical trials as they provide insight into the best time-window to start treatment in the different PVCs.

GRN PVCs showed brain structure volumes between the 5th-75th age- and sex-specific normative percentile over an age range of 45-70, but showed more progressive decline than the reference centile curves for frontal, temporal and parietal lobe volume from age 45 onwards, and for occipital
lobe, cerebellum and hippocampus from age 60, without evidence of cognitive decline. This means that although on group level presymptomatic \textit{GRN} PVCs were never in the absolute ‘abnormal’ range compared to the normative population, they declined faster over time than what would be expected in normal aging. This finding provides an explanation as to why previous cross-sectional studies did not find differences between presymptomatic \textit{GRN} PVCs and controls,\textsuperscript{8,10} and highlights the value of multi-time point data. A study on the temporal ordering of biomarker changes indeed showed that structural MRI biomarkers are relatively late to change in \textit{GRN}-related FTD, as compared to e.g. language functioning and neurofilament light chain\textsuperscript{32}. This coincides with other studies on cognitive and fluid biomarkers, that similarly showed no decline compared to controls in the presymptomatic stage, with rapid changes occurring in a short time frame before overt disease onset.\textsuperscript{6,9,10} A longitudinal imaging study demonstrated a time-window of approximately two years before symptom onset in which brain volume deteriorated rapidly in eight \textit{GRN} PVCs.\textsuperscript{5} The volume loss in three \textit{GRN} converters from this study similarly showed a steep decline over time from approximately the 80\textsuperscript{th} percentile to below the 5\textsuperscript{th} percentile in a five year time period. One hypothesis is that additional injury (“a second hit”) is required to start the neurodegenerative process, which is then followed by rapid brain volume loss and symptom onset.\textsuperscript{8,33,34} A second hypothesis is the asymmetry often seen in \textit{GRN}, which can variably affect the right or left hemisphere and thereby mediate effects found on group level.\textsuperscript{5,14,33} Nonetheless, in our study a more progressive decline was visible from the fourth decade of life compared to the reference centile curves in the absence of cognitive decline. Moreover, the brain areas that showed faster decline over time overlap with atrophy signatures found in symptomatic \textit{GRN} PVCs, including atrophy of dorsolateral and ventromedial prefrontal, superolateral temporal and lateral parietal lobe areas, anterior cingulate, insula, precuneus and striatum.\textsuperscript{8,15} This indicates the progression of a neurodegenerative process that is only accompanied by cognitive changes in later stages, most specifically in frontal-mediated executive functions and social cognition.\textsuperscript{14,15} A possible explanation for why our findings demonstrate a decline over time and previous studies did not, could be the longer follow-up time. It could be that although decline is not statistically detectable with follow-up of two or four years or on cognitive measures, marginal decline in brain volume is already set in motion. This underlines the importance of continuing current longitudinal cohort studies to further unravel disease processes.

Frontal lobe volume was already below the 5\textsuperscript{th} percentile at age 45 in \textit{MAPT} PVCs, with progressive decline over time in the frontal and parietal, but most notably temporal lobe, crossing the 5\textsuperscript{th} reference centile curve at age 55. This decline was more pronounced in the left than in the right temporal lobe, and was accompanied by a decline in language functioning. These findings are in line with previous studies investigating atrophy in symptomatic \textit{MAPT} PVCs, showing anteromedia
temporal lobe atrophy as the key neuroimaging feature and as a result semantic and/or episodic memory problems.\textsuperscript{8,14,35} Mild impairments have even been demonstrated as early as the presymptomatic stage.\textsuperscript{36,37} However, cross-sectional studies investigating presymptomatic MAPT PVCs have not been able to demonstrate differences that survived multiple testing correction compared to controls, while uncorrected results indicated similar temporal areas to be affected first.\textsuperscript{8,10,35} Rohrer \textit{et al.}\textsuperscript{7} found decline in the temporal lobe and hippocampus around 10-15 years before estimated symptom onset. Following this, a four-year follow-up study using actual age at symptom onset showed GM volume changes in the temporal lobe and WM changes in the uncinate fasciculus up to two years before symptom onset in MAPT converters.\textsuperscript{5} The progressive decline that is already seen from the age of 45 onwards in the current study is probably because the MAPT PVCs are closer to symptom onset due to the younger average age at symptom onset in this group.\textsuperscript{19} Most of the MAPT PVCs in our cohort come from families with a \textit{P301L} mutation, and previous studies have shown an average age at symptom onset of 51 years,\textsuperscript{38} explaining why our results indicate a fast decline in the frontal and temporal lobe in the first 10 year age bracket of our study (i.e. between ages 45-55).

\textit{C9orf72} PVC had lower volumes of the frontal lobe, temporal lobe and cerebellum at age 45 compared to the other two gene groups, and these were already below the 5\textsuperscript{th} percentile compared to the age-matched healthy controls. Notably, a decline in language functioning, but not any of the other cognitive domains, was observed compared to \textit{GRN} PVCs. Brain volume remained quite stable below the 5\textsuperscript{th} percentile between ages 45-70, showing minimal volume decline with increasing age. Previous cross-sectional studies investigating brain changes in presymptomatic \textit{C9orf72} PVCs have indeed shown differences in frontal, temporal and cerebellar structures compared to controls.\textsuperscript{7,8,10,18} A two-year follow-up study showed cross-sectional differences between presymptomatic \textit{C9orf72} PVCs and non-carriers in GM volume of the cerebellum, frontal and planum temporale, but without significant change over time.\textsuperscript{10} Lee \textit{et al.}\textsuperscript{39} showed focal GM, structural and functional connectivity deficits from the fourth decade of life, similar to what our current results showed. In addition, this is accompanied by early changes in other modalities, such as reduced WM integrity,\textsuperscript{5,39} and reduced cerebral blood flow.\textsuperscript{12} These deficits may represent the earliest signs of neurodegeneration that already starts before the fourth decade of life. Our data suggests that brain volume loss already occurs before the age of 45, but there is relatively minimal decline or cognitive deterioration over time. It could be that the neurodegenerative process associated with the \textit{C9orf72} repeat expansion can be very slowly progressive in nature. An alternative hypothesis suggests that early deficits in \textit{C9orf72} PVCs might be caused by abnormal brain development. The \textit{C9orf72} protein is believed to play an essential role in the development of the central nervous system, and loss of the protein as a
result of altered expression impacts brain development. Thus, it has been hypothesized that C9orf72 PVCs already have lower brain volume from birth, which is superimposed by an additional neurodegenerative process later in life. It has been suggested that presymptomatic C9orf72 PVCs exert a lifelong neuropsychiatric vulnerability that manifests as personality and behavioral changes early on in life. Recent studies investigating the neuroanatomical associations of psychiatric symptoms in C9orf72 PVCs have indeed shown a widespread pattern of cortical (i.e. frontal, temporal, parietal and occipital lobe, insula) and subcortical (i.e. basal ganglia, thalamus and cerebellum) GM volume loss similar to the widespread atrophy profile found in the current study.

Over the last decade, automated normative quantification of brain morphology, function, connectivity and pathology has improved considerably with machine and deep learning techniques. Different types of approaches have been investigated in the detection and classification of dementia and proven sensitive, but most often in Alzheimer’s dementia. Studies in FTD are more limited in number and focus on diagnostic accuracy and classification between different types of dementia. This is to our knowledge the first study that has investigated brain volume loss in presymptomatic genetic FTD with up to nine years of follow-up, using software for automated normative brain volumetry. Future work could combine this work with machine learning classification techniques, towards an artificial intelligence-based tracking tool for disease onset and progression predicting the change-point in atrophy and other biomarkers at an individual level.

Major strengths of this study are the inclusion of all three major genetic causes of FTD, the long follow-up time, the use of non-linear modelling and automated software for normative volumetry, allowing a direct comparison of the gene-specific model predictions to a very large reference population. Thus far, most studies in genetic FTD have compared to much smaller sample sizes of non-carrying family members with the same number of follow-ups, instead of comparing to normative data from a reference population. The relatively long follow-up time in this study also allowed the use of a mixed-effects model with natural cubic splines, so that a non-linear change of brain volume over time could be modelled without making assumptions about the shape of this change. Previous longitudinal neuroimaging studies in genetic FTD have typically used linear models, where a unit change in time is associated with a constant change in the outcome. As is reflected in the current results, this does not necessarily apply to the neurodegenerative process of genetic FTD. Non-linear models might be more suitable for the analysis of longitudinal atrophy rates, similar to what has been shown in presymptomatic atrophy in genetic Alzheimer’s Dementia. A limitation of our study is the relatively small sample size of the MAPT and C9orf72 groups, and should therefore be carefully interpreted. Replication in larger cohorts, such as GENFI, is therefore warranted. This is, in part, due to the age range 45-95 of the reference population used in Quantib®...
ND. As a result, we had to exclude presymptomatic PVCs younger than 45, resulting in smaller sample sizes. This is unfortunate, as our data suggests that for some gene groups the acceleration point lies before that time. Specifically, we cannot corroborate claims about a possible neurodevelopmental component in C9orf72-related FTD. Another drawback of this study is that Quantib ® ND only provides segmentation for the (lateralized) lobes, cerebellum and hippocampus, and no other substructures. Furthermore, six PVCs developed FTD during study follow-up and this could have affected the results. However, the analyses were also performed without the scans of the converters, and results remained largely similar, so that the influence is likely negligible. Lastly, a seemingly paradoxical increase in occipital lobe volume was visible for MAPT and C9orf72, and to a lesser extent in the hippocampus for MAPT PVCs, between ages 45-60. This appears to be caused by the change in head coil during study follow-up, which influenced the segmentation process, especially for the occipital lobe. This can be explained by a higher signal-to-noise ratio with the 32ch coil for specifically posterior cortical areas. Panman et al. compared the use of the 8ch and 32ch coil in FTD-RisC and found higher GM volume in the occipital lobe, cerebellum and subcortical areas using the 32ch coil, whereas frontal, temporal and parietal GM volume were smaller using the 32ch coil.

To conclude, we investigated longitudinal brain volume patterns in cognitively healthy GRN, MAPT and C9orf72 PVCs using automated software for normative volumetry. We provide evidence for accelerated brain volume loss in the presymptomatic stage of FTD, and in addition gene-specific atrophy patterns in the frontal and temporal lobe, in the absence of prominent cognitive decline. These results confirm the value of accelerated brain atrophy as a disease-tracking and staging biomarker in genetic FTD and could inform upcoming clinical trials in characterizing the optimal time-window for starting treatment and could help monitoring treatment response.

WNL-2022-201191_sup --- http://links.lww.com/WNL/C369

References


### Tables

**Table 1. Available longitudinal data.**

<table>
<thead>
<tr>
<th>Number of MRI scans</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9orf72</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>GRN</td>
<td>1</td>
<td>4</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>MAPT</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>7</td>
<td>9</td>
<td>16</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

Participants were followed on a one- or two-year basis. The mean interval between MRI scans was 22.5±5.3 months (median=22.5; range 11.7-40.5).
Table 2. Sociodemographic, cognitive and clinical data at baseline.

<table>
<thead>
<tr>
<th></th>
<th>C9orf72</th>
<th>GRN</th>
<th>MAPT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>34</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Sex, %female</td>
<td>79</td>
<td>65</td>
<td>50</td>
<td>0.38</td>
</tr>
<tr>
<td>Age</td>
<td>52.5 (8.5) [45.0-67.0]</td>
<td>53.2 (6.7) [45.0-67.0]</td>
<td>46.4 (3.5) [45.0-55.0]</td>
<td>0.05</td>
</tr>
<tr>
<td>Education level&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.7 (0.9) [4.0-7.0]</td>
<td>5.6 (0.9) [3.0-7.0]</td>
<td>5.0 (1.8) [1.0-7.0]</td>
<td>0.27</td>
</tr>
<tr>
<td>MMSE</td>
<td>29.4 (0.9) [27.0-30.0]</td>
<td>29.2 (1.3) [24.0-30.0]</td>
<td>29.0 (1.1) [27.0-30.0]</td>
<td>0.70</td>
</tr>
<tr>
<td>FAB</td>
<td>16.7 (1.2) [15.0-18.0]</td>
<td>17.3 (1.6) [13.0-18.0]</td>
<td>17.5 (0.8) [16.0-18.0]</td>
<td>0.40</td>
</tr>
<tr>
<td>NPI-Q</td>
<td>2.6 (4.1) [0.0-12.0]</td>
<td>1.2 (3.4) [0.0-13.0]</td>
<td>3.0 (3.0) [0.0-6.0]</td>
<td>0.48</td>
</tr>
<tr>
<td>CBI-R</td>
<td>6.0 (10.1) [0.0-30.0]</td>
<td>1.2 (2.2) [0.0-5.0]</td>
<td>4.3 (3.5) [0.0-8.0]</td>
<td>0.54</td>
</tr>
<tr>
<td>FRS</td>
<td>96.4 (4.8) [88.0-100.0]</td>
<td>99.1 (2.1) [93.0-100.0]</td>
<td>99.0 (2.0) [96.0-100.0]</td>
<td>0.14</td>
</tr>
<tr>
<td>Language</td>
<td>0.00 (0.86) [-1.29-1.35]</td>
<td>0.00 (0.81) [-1.78-1.56]</td>
<td>0.11 (0.86) [-1.22-1.28]</td>
<td>0.92</td>
</tr>
<tr>
<td>Attention</td>
<td>0.10 (0.62) [-1.02-3.5]</td>
<td>0.14 (0.72) [-1.37-1.77]</td>
<td>0.38 (0.66) [-1.02-1.35]</td>
<td>0.49</td>
</tr>
<tr>
<td>Executive function</td>
<td>0.07 (0.59) [-1.44-0.83]</td>
<td>-0.01 (0.65) [-1.35-1.41]</td>
<td>0.24 (0.61) [-0.64-1.08]</td>
<td>0.42</td>
</tr>
<tr>
<td>Memory</td>
<td>0.12 (0.43) [-0.55-0.83]</td>
<td>-0.22 (0.90) [-2.05-1.07]</td>
<td>0.04 (1.02) [-2.14-1.07]</td>
<td>0.24</td>
</tr>
<tr>
<td>Social cognition</td>
<td>-0.36 (0.67) [-1.71-0.70]</td>
<td>0.07 (0.76) [-1.62-1.25]</td>
<td>0.02 (0.91) [-1.37-1.57]</td>
<td>0.17</td>
</tr>
<tr>
<td>Visuoconstruction</td>
<td>-0.09 (0.65) [-1.71-0.41]</td>
<td>-0.08 (1.22) [-3.12-1.12]</td>
<td>0.06 (1.00) [-1.71-1.12]</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Values are presented as mean (SD) [range] unless otherwise specified. Abbreviations: MMSE = Mini-Mental State Examination; FAB = Frontal Assessment Battery; NPI-Q = modified Neuropsychiatric Inventory Questionnaire; CBI-R = Cambridge Behavioural Inventory – revised; FRS = Frontotemporal dementia Rating Scale. <sup>a</sup>Verhage Dutch educational system categorized into levels from 1 = less than 6
years of primary education to 7 = academic schooling. Clinical data availability: MMSE (14 C9orf72, 34 GRN, 8 MAPT), FAB (14 C9orf72, 10 GRN, 6 MAPT), NPI (11 C9orf72, 17 GRN, 5 MAPT), CBI (11 C9orf72, 5 GRN, 4 MAPT), FRS (8 C9orf72, 16 GRN, 5 MAPT), complete neuropsychological assessment (14 C9orf72, 33 GRN, 8 MAPT)

Figure legends

Figure 1. Longitudinal trajectories of the A) Mini-Mental State Examination, B) Frontal Assessment Battery, C) modified Neuropsychiatric Inventory, D) Cambridge Behavioral Inventory – Revised and E) Frontotemporal dementia Rating Scale.
Figure 2. Longitudinal trajectories of the A) language, B) attention and mental processing speed, C) executive function, D) memory, E) social cognition, and F) visuoconstruction domain.
Figure 3. Atrophy rates compared to reference centile curves for A) total brain, B) frontal lobe, C) temporal lobe, D) parietal lobe and E) cerebellum. Abbreviations: PCTL = percentile.
Longitudinal Brain Atrophy Rates in Presymptomatic Carriers of Genetic 
Frontotemporal Dementia
Jackie M. Poos, Leonie D.M. Grandpierre, Emma L. van der Ende, et al.
Neurology published online October 26, 2022
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