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 with reference centile curves based on a large population-derived sample of nondemented individuals (n = 4,951). Mixed-effects models were fitted to analyze atrophy rates of the different gene groups as a function of age.

Results
Thirty-four *GRN*, 8 *MAPT*, and 14 *C9orf72* pathogenic variant carriers were included (mean age = 52.1, standard deviation = 7.2; 66% female). The mean follow-up duration of the study was 64 ± 33 months (median = 52; range 13–108). *GRN* pathogenic variant carriers showed a faster decline than the reference centile curves for all brain areas, though relative volumes remained between the 5th and 75th percentiles between the ages of 45 and 70 years. In *MAPT* pathogenic variant carriers, frontal lobe volume was already at the 5th percentile at age 45 years and showed a further decline between the ages 50 and 60 years. Temporal lobe volume started in the 50th percentile at age 45 years but showed fastest decline over time compared with other brain structures. Frontal, temporal, parietal, and cerebellar volume already started below the 5th percentile compared with the reference centile curves at age 45 years for *C9orf72* pathogenic variant carriers, but there was minimal decline over time until the age of 60 years.

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.

Glossary

FAB = frontal assessment Battery; **FTD** = frontotemporal dementia; **GM** = gray matter; **ICV** = intracranial volume; **MMSE** = Mini-Mental State Examination; **NPI-Q** = Neuropsychiatric Inventory Questionnaire; **PVCs** = pathogenic variant carriers; **TMT** = Trail Making Test; **WM** = white matter.

Frontotemporal dementia (FTD) is the second most common form of young-onset dementia, typically demonstrating atrophy of the frontal and/or temporal lobes.[1] It is characterized by a heterogeneous profile with deterioration of behavioral (behavioral variant FTD, bvFTD), language (primary progressive aphasia, PPA), or motor skills.[1-3] 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.[4] Cohort studies investigating the presymptomatic stage of FTD have demonstrated early changes in neuroimaging, cognition, blood, and CSF.[5-13] In particular, brain atrophy, measured by structural MRI, is of interest as a biomarker of neurodegeneration and outcome measure in upcoming clinical trials.[5,7,8,10,13]

GRN pathogenic variants often lead to an asymmetrical pattern of atrophy in the frontal, temporal, and parietal lobes in later disease stages,[14,15] and additional lower gray matter (GM) volume in the insula has been demonstrated in the presymptomatic stage.[8,14] In symptomatic pathogenic variant carriers (PVCs), this typically results in a clinical diagnosis of bvFTD or nonfluent variant PPA (nfvPPA) and is often accompanied by parkinsonism.[15] Pathogenic variants in the *MAPT* gene typically lead to focal anterior temporal lobe degradation, including the hippocampus,[14] with additional presymptomatic changes in the amygdala and insula.[7,8,10] bvFTD is the main phenotype in the symptomatic stage but can be accompanied by atypical parkinsonism such as corticobasal syndrome or progressive supranuclear palsy.[14] Last, the atrophy associated with the *C9orf72* repeat expansion is rather diffuse, with widespread GM volume loss, including not only the frontal and temporal cortices but also subcortical and cerebellar regions.[16] In presymptomatic *C9orf72* PVCs, lower GM volume of the thalamus, cerebellum, and frontal, temporal, parietal, and insular cortices has been found.[7,8,10] In the symptomatic stage, this is usually accompanied not only by a clinical diagnosis of bvFTD, motor neuron disease, or a combination of both, but also notable psychiatric features.[16]

Longitudinal studies in presymptomatic FTD provide a unique opportunity to determine the age at which atrophy rates start to deviate from normal.[17] Identifying a potential change point at which the atrophy rate accelerates compared with the normal aging process is essential for upcoming clinical trials because 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,[7,8,11,13,18] which has been shown to be unreliable in *C9orf72* and *GRN* because there is large variation between and within families.[19] Only a few studies so far have investigated atrophy rates longitudinally.[5,10] For example, One of these studies showed that the first changes occurred approximately 2 years before actual symptom onset in 8 FTD converters.[5] However, it remains unclear at what age atrophy starts to accelerate compared with 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 with a group of age-matched and sex-matched cognitively healthy individuals.[20,21] These approaches are interesting for presymptomatic cohorts because there is evidence that they could lead to an earlier identification of atrophy than visual rating scales and can improve the accuracy of dementia diagnosis.[21-23] 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 up on a 1-year or 2-year basis.[13] Participants for this study were recruited between December 2009 and October 2019.[13] DNA genotyping at study entry assigned participants to either the PVC group or the noncarrier group. Inclusion criteria of the current study were as follows: 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,[2] PPA,[3] and/or ALS[24]), and had a Clinical Dementia Rating scale plus National Alzheimer Coordinating Center Frontotemporal Lobar Degeneration (CDR plus NACC FTLD) of 0, and 3) had undergone at least 1 MRI scan.[25] Exclusion criteria for this study were as follows: 1) other neurologic that can affect brain volumetry and/or primary psychiatric disorders, and 2) presymptomatic PVCs

younger than 45 years because the reference population in Quantib ND consists of cognitively healthy individuals aged between 45 and 95 years[26] This resulted in the inclusion of 34 *GRN*, 8 *MAPT*, and 14 *C9orf72* PVCs at baseline and 33 *GRN*, 5 *MAPT*, and 11 *C9orf72* PVCs underwent 2 or more MRI scans (Table 1). Six PVCs developed clinical symptoms during the follow-up (*C9orf72*: one ALS and one FTD-ALS; *GRN*: one bvFTD and 2 nfvPPA; *MAPT*: one bvFTD) and progressed on the CDR plus NACC FTLD global score (eFigure 1, links.lww.com/WNL/C369). 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, neurologic 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[27]), Cambridge Behavioral Inventory—Revised (CBI-R[28]), and Frontotemporal dementia Rating Scale (FRS[29]). The Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB) were used as global cognitive and frontal executive screeners, respectively.[30,31] Neuropsychological assessment consisted of tests assessing language (60-item version Boston Naming Test, categorical fluency), attention and mental processing speed (Trail Making Test (TMT)—part A, Stroop Color-Word Interference Test (SCWIT) word and color naming card, Wechsler Adult Intelligence Scale (WAIS)-III, and digit span forward), executive functioning (TMT—part B, SCWIT ink naming card, modified Wisconsin Card Sorting Test, letter fluency, and WAIS-III digit span backward), 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 and 2016 and a 32-channel SENSE head coil from 2016 onward. Owing to ongoing recruitment, not all participants have the same number of scans made with either the 8-channel or 32-channel head coil (for numbers per visit, see eTable 1, links.lww.com/WNL/C369). 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 × 177 × 168 mm, flip angle = 8, slices = 140, voxel size = 0.88x0.88x1.20 mm, SENSE = none, total acquisition time = 4.56 minutes. All scans underwent extensive visual quality check. Images were analyzed using Quantib ND software.

Normative Volumetric Image Data Processing

Quantib® ND (quantib.com) is a postprocessing image analysis tool for T1-weighted images, which 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 studies conducted by Vrooman et al.[20] and Fortunati et al.[21] 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 with reference centile curves based on a large population of cognitively healthy individuals.[26] The reference population consisted of 4,951 people aged 45–95 years from the Rotterdam study, the largest Dutch prospective cohort study, whose scans were acquired on 1.5T MRI (GE Healthcare, US) between 2005 and 2015. The Rotterdam study is described elsewhere in more detail.[26] See, for an example, output file from Quantib® ND eAppendix 1, links.lww.com/WNL/C369.

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 the 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, links.lww.com/WNL/C369).

Because this is an ongoing study, participants varied in the number of visits that were completed, and 7 individuals had only 1 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® ND software. For 5 converters, all MRI scans up until the clinical diagnosis were included, and for 1 converter, 1 MRI scan 1 year after diagnosis was included. A mixed-effects model with

Table 1 Available Longitudinal Data

Number of MRI scans	1	2	3	4	5	6
C9orf72	3	3	6	2	0	0
GRN	1	4	8	5	7	9
MAPT	3	2	2	0	1	0
Total	7	9	16	7	8	9

Participants were followed up on a 1-year or 2-year basis. The mean interval between MRI scans was 22.5 ± 5.3 mo (median = 22.5; range 11.7–40.5).

Table 2 Sociodemographic, Cognitive, and Clinical Data at Baseline

	C9orf72	*GRN*	*MAPT*	*p* Value
n	14	34	8	—
Sex, %female	79	65	50	0.38
Age	52.5 (8.5) [45.0 to 67.0]	53.2 (6.7) [45.0 to 67.0]	46.4 (3.5) [45.0 to 55.0]	0.05
Education level[a]	5.7 (0.9) [4.0 to 7.0]	5.6 (0.9) [3.0 to 7.0]	5.0 (1.8) [1.0 to 7.0]	0.27
MMSE	29.4 (0.9) [27.0 to 30.0]	29.2 (1.3) [24.0 to 30.0]	29.0 (1.1) [27.0 to 30.0]	0.70
FAB	16.7 (1.2) [15.0 to 18.0]	17.3 (1.6) [13.0 to 18.0]	17.5 (0.8) [16.0 to 18.0]	0.40
NPI-Q	2.6 (4.1) [0.0 to 12.0]	1.2 (3.4) [0.0 to 13.0]	3.0 (3.0) [0.0 to 6.0]	0.48
CBI-R	6.0 (10.1) [0.0 to 30.0]	1.2 (2.2) [0.0 to 5.0]	4.3 (3.5) [0.0 to 8.0]	0.54
FRS	96.4 (4.8) [88.0 to 100.0]	99.1 (2.1) [93.0 to 100.0]	99.0 (2.0) [96.0 to 100.0]	0.14
Language	0.00 (0.86) [−1.29 to 1.35]	0.00 (0.81) [−1.78 to 1.56]	0.11 (0.86) [−1.22 to 1.28]	0.92
Attention	0.10 (0.62) [−1.02 to 0.35]	0.14 (0.72) [−1.37 to 1.77]	0.38 (0.66) [−1.02 to 1.35]	0.49
Executive function	0.07 (0.59) [−1.44 to 0.83]	−0.01 (0.65) [to 1.35 to 1.41]	0.24 (0.61) [−0.64 to 1.08]	0.42
Memory	0.12 (0.43) [−0.55 to 0.83]	−0.22 (0.90) [to 2.05 to 1.07]	0.04 (1.02) −2.14 to 1.07]	0.24
Social cognition	−0.36 (0.67) [to 1.71 to 0.70]	0.07 (0.76) [−1.62 to 1.25]	0.02 (0.91) [−1.37 to 1.57]	0.17
Visuoconstruction	−0.09 (0.65) [to 1.71 to 0.41]	−0.08 (1.22) [to 3.12 to 1.12]	0.06 (1.00) [−1.71 to 1.12]	0.95

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

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 1 MRI scan). In each model, %ICV of the brain structure of interest was used as a dependent variable, and we specified the following fixed effects: age, gene group, age × gene group, sex, and scanner software update. Time interval between MRI scans was not included as a covariate because 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)[13] and subtracting the beta coefficient from the %ICV. We tested the best-fitting model by comparing models with random intercepts and/or slopes with 2 or 3 splines. An overview of the best-fitting models per brain structure is summarized in eTable 2, links.lww.com/WNL/C369. 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® 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 on 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

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
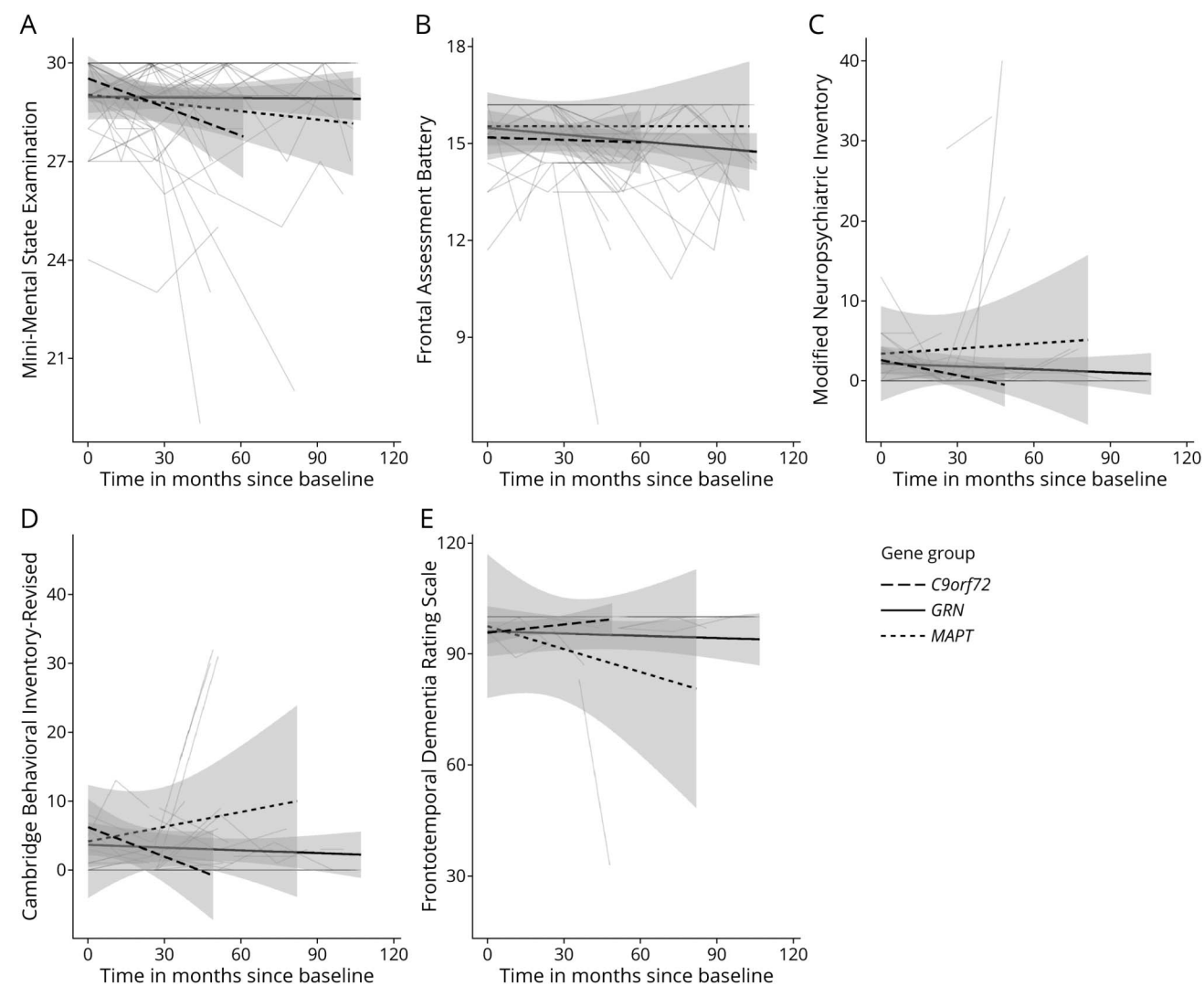
was no main effect of time on any of the cognitive domains (language: $F(1,133) = 0.16$, $p = 0.69$, Figure 2A; attention: $F(1,132) = 2.16$, $p = 0.14$, Figure 2B; executive function: $F(1,130) = 1.19$, $p = 0.28$, Figure 2C; memory: $F(1,131) = 0.57$, $p = 0.45$, Figure 2D; social cognition: $F(1,131) = 2.01$, $p = 0.16$, Figure 2E; and 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 with *GRN* PVCs (Figure 2A).

Brain Volume Trajectories

There were interaction effects between age and gene group in the %ICV of the total brain ($LR = 17.03$, $p = 0.002$), frontal lobe ($LR = 25.00$, $p < 0.001$), 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 summarized in eTable 3, links.lww.com/WNL/C369.

In *GRN* PVCs, a faster decline than the reference centile curves was visible in Figure 3A-3D for total brain volume and frontal, temporal, and parietal lobe volume from age 45 years onward, though all brain structures' percentile scores remained in the normal range between ages 45 and 70 years. For the occipital lobe, cerebellar, and hippocampal volumes, a faster decline than the reference centile curves was visible from age 60 years onward. A steeper decline in brain volume was visible for the left than for the right temporal lobe (eTable 3, links.lww.com/WNL/C369).

The total brain volume in *MAPT* PVCs showed the fastest decline compared with the other gene groups because it already crossed the 5th percentile at approximately age 50 years (Figure 3A), whereas at age 45 years, it was still in the normal range. Frontal lobe volume was at the 5th percentile at age 45 years, showing a further decline between ages 50 and 60 years (Figure 3B). The temporal lobe volume was still around the 50th percentile at age 45 years but subsequently showed the

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
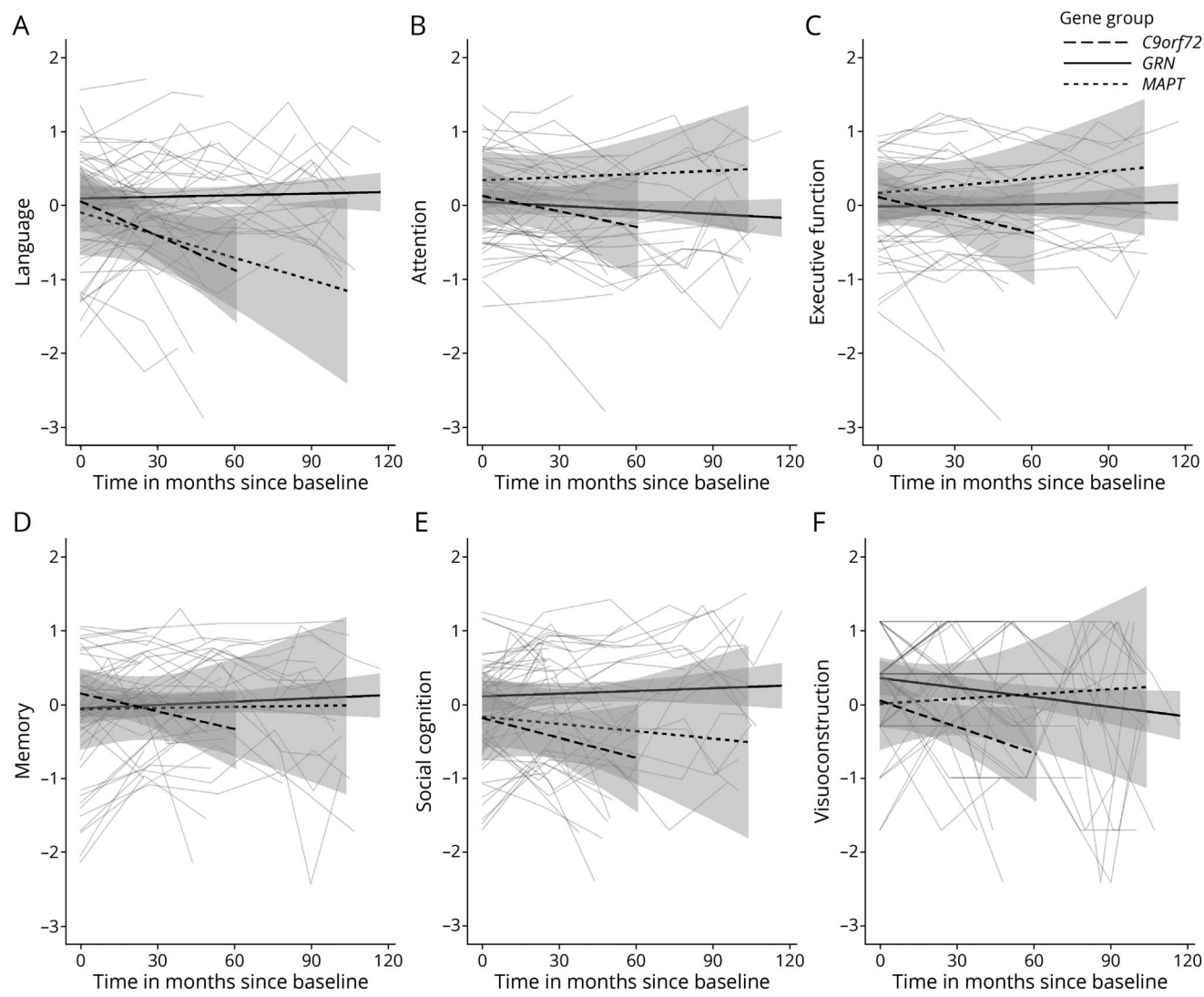
fastest decline compared with the other brain structures (Figure 3C). This decline was more pronounced in the left than in the right temporal lobe. Parietal lobe volume declined less steeply than the frontal and temporal structures, albeit still steeper than the reference centile curves, crossing the 5th percentile at approximately age 60 years (Figure 3D). Occipital lobe, cerebellar, and hippocampal volumes 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 with reference/normative data at age 45 years, though with minimal decline over time until age 60 years (Figure 3A). Frontal lobe volume was the lowest, being already below the 5th percentile at age 45 years (Figure 3B), and the temporal and parietal lobes and cerebellum largely followed the 5th reference centile curve between ages 45 and 70 years (Figure 3C-3E). Occipital lobe and hippocampal volumes 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, links.lww.com/WNL/C369). Intraindividual 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 6 individual converters can be found in eFigures 1–2, links.lww.com/WNL/C369.

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 with a large normative population-

Figure 3 Atrophy Rates Compared With Reference Centile Curves for (A) Total Brain, (B) Frontal Lobe, (C) Temporal Lobe, (D) Parietal Lobe, and (E) Cerebellum
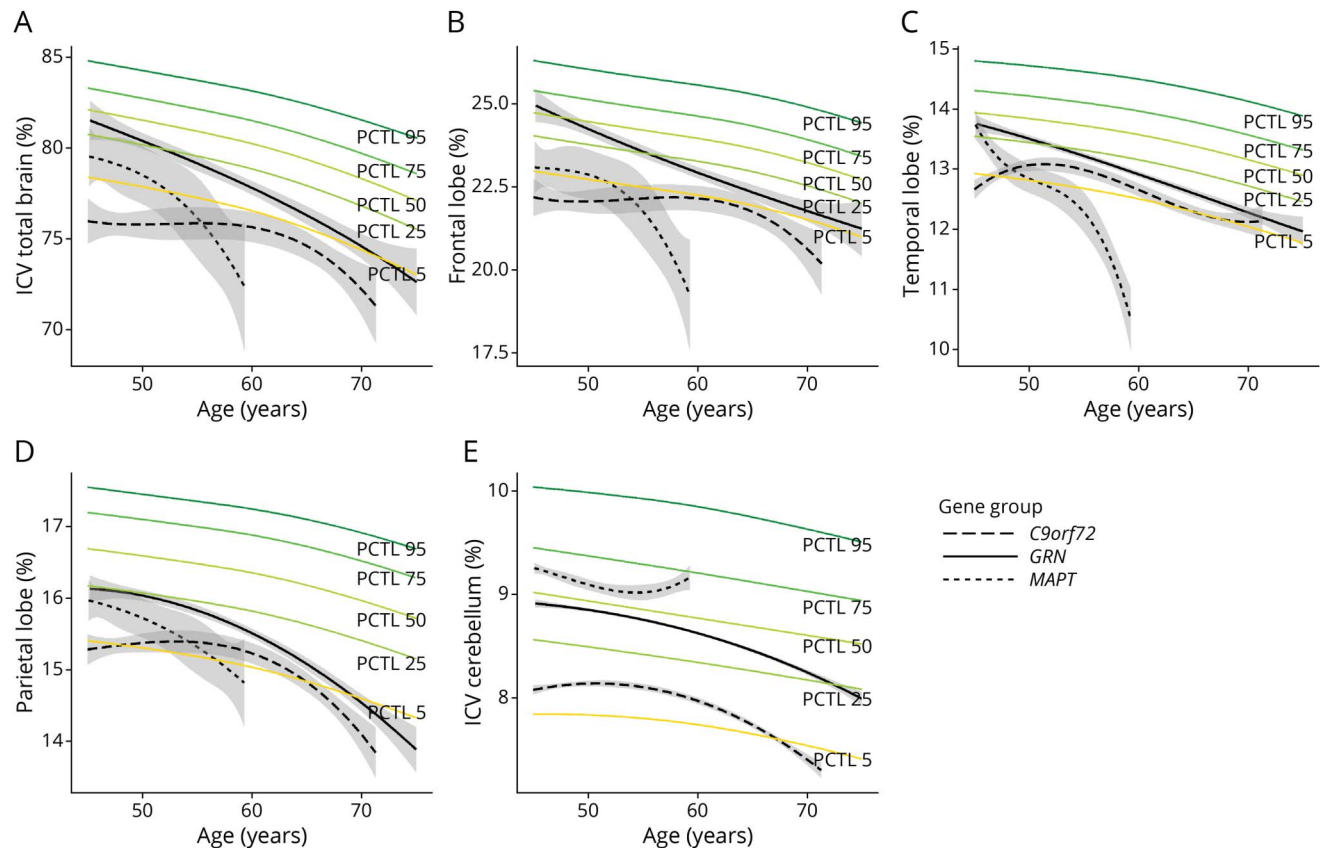
Abbreviations: PCTL = Percentile.

derived reference dataset. We compared atrophy rates over time in lobar volumes, hippocampus, and cerebellum between gene groups and found gene-specific differences for 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 and the speed of change over time, these results hold important potential for upcoming gene-specific clinical trials because they provide insight into the best time window to start treatment in the different PVCs.

GRN PVCs showed brain structure volumes between the 5th and 75th age-specific and sex-specific normative percentile over an age range of 45–70 years, but showed more progressive decline than the reference centile curves for frontal, temporal, and parietal lobe volume from age 45 years onward, and for occipital lobe, cerebellum, and hippocampus from age 60 years, without evidence of cognitive decline. This means that although on group level, presymptomatic *GRN* PVCs were never in the absolute "abnormal" range compared with 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 *GRN* PVCs and controls[8,10] and highlights the value of multitime point data. A study on the temporal ordering of biomarker changes indeed showed that structural MRI biomarkers are relatively late to change in *GRN*-related FTD, when compared with, for example, language functioning and neurofilament light chain.[32] This coincides with other studies on cognitive and fluid biomarkers, which similarly showed no decline compared with controls in the presymptomatic stage, with rapid changes occurring in a short time frame before overt disease onset.[6,9,10] A longitudinal imaging study demonstrated a time window of approximately 2 years before symptom onset in which brain volume deteriorated rapidly in 8 *GRN* PVCs.[5] The volume loss in 3 *GRN* converters from this study similarly showed a steep decline over time from approximately the 80th percentile to below the 5th percentile in a 5-year 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.[8,33,34] A second hypothesis is the asymmetry often seen in *GRN*, which can variably affect the right or left hemisphere and thereby mediate effects found on group level.[5,14,33] Nonetheless, in our study, a more progressive

decline was visible from the fourth decade of life compared with 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 *GRN* PVCs, including atrophy of dorsolateral and ventromedial prefrontal, superolateral temporal, and lateral parietal lobe areas, anterior cingulate, insula, precuneus, and striatum.[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.[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 a follow-up of 2 or 4 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 5th percentile at age 45 years in *MAPT* PVCs, with progressive decline over time in the frontal and parietal lobes, but most notably temporal lobe, crossing the 5th reference centile curve at age 55 years. 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 *MAPT* PVCs, showing anteromedial temporal lobe atrophy as the key neuroimaging feature and as a result semantic and/or episodic memory problems.[8,14,35] Mild impairments have even been demonstrated as early as the presymptomatic stage.[36,37] However, cross-sectional studies investigating presymptomatic *MAPT* PVCs have not been able to demonstrate differences that survived multiple testing correction compared with controls, while uncorrected results indicated similar temporal areas to be affected first.[8,10,35] Rohrer et al.[7] found decline in the temporal lobe and hippocampus approximately 10–15 years before estimated symptom onset. Following this, a 4-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 2 years before symptom onset in *MAPT* converters.[5] The progressive decline that is already seen from the age of 45 years onward in this study is probably because the *MAPT* PVCs are closer to symptom onset due to the younger average age at symptom onset in this group.[19] Most of the *MAPT* PVCs in our cohort come from families with a *P301L* variant, and previous studies have shown an average age at symptom onset of 51 years,[38] explaining why our results indicate a fast decline in the frontal and temporal lobes in the first 10-year age bracket of our study (i.e. between ages 45 and 55 years).

C9orf72 PVCs had lower volumes of the frontal lobe, temporal lobe, and cerebellum at age 45 years compared with the other 2 gene groups, and these were already below the 5th percentile compared with the age-matched healthy controls.

Notably, a decline in language functioning, but not any of the other cognitive domains, was observed compared with that in *GRN* PVCs. Brain volume remained quite stable below the 5th percentile between ages 45 and 70 years, showing minimal volume decline with increasing age. Previous cross-sectional studies investigating brain changes in presymptomatic *C9orf72* PVCs have indeed shown differences in frontal, temporal, and cerebellar structures compared with controls.[7,8,10,18] A two-year follow-up study showed cross-sectional differences between presymptomatic *C9orf72* PVCs and noncarriers in GM volume of the cerebellum and frontal and planum temporale, but without significant change over time.[10] Lee et al.[39] showed focal GM and structural and functional connectivity deficits from the fourth decade of life, similar to what the results of this study showed. In addition, this is accompanied by early changes in other modalities, such as reduced WM integrity[5,39] and reduced cerebral blood flow.[12] These deficits may represent the earliest signs of neurodegeneration that already start before the fourth decade of life. Our data suggest that brain volume loss already occurs before the age of 45 years, but there is relatively minimal decline or cognitive deterioration over time. It could be that the neurodegenerative process associated with the *C9orf72* repeat expansion can be very slowly progressive in nature. An alternative hypothesis suggests that early deficits in *C9orf72* PVCs might be caused by abnormal brain development. The *C9orf72* protein is believed to play an essential role in the development of the central nervous system, and loss of the protein because of altered expression affects brain development.[39-41] 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.[39,40] It has been suggested that presymptomatic *C9orf72* PVCs exert a lifelong neuropsychiatric vulnerability that manifests as personality and behavioral changes early on in life.[42] Recent studies investigating the neuroanatomical associations of psychiatric symptoms in *C9orf72* PVCs have indeed shown a widespread pattern of cortical (i.c. frontal, temporal, parietal, and occipital lobes and insula) and subcortical (i.c. basal ganglia, thalamus, and cerebellum) GM volume loss similar to the widespread atrophy profile found in this study.[43]

Over the past decade, automated normative quantification of brain morphology, function, connectivity, and pathology has improved considerably with machine and deep learning techniques.[44] Different types of approaches have been investigated in the detection and classification of dementia and proven sensitive, but most often in Alzheimer dementia.[21,22,44,45] Studies in FTD are more limited in number and focus on diagnostic accuracy and classification between different types of dementia.[46-48] Our study has investigated brain volume loss in presymptomatic genetic FTD with up to 9 years of follow-up, using software for automated normative brain volumetry. Future work could combine this work with machine learning classification techniques, toward 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 3 major genetic causes of FTD, the long follow-up time, the use of nonlinear modeling, and automated software for normative volumetry, allowing a direct comparison of the gene-specific model predictions with a very large reference population. Thus far, most studies in genetic FTD have compared with much smaller sample sizes of noncarrying family members with the same number of follow-ups, instead of comparing with 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 nonlinear change of brain volume over time could be modeled without making assumptions about the shape of this change.[49] Previous longitudinal neuroimaging studies in genetic FTD have typically used linear models,[5,10,11] 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. Nonlinear models might be more suitable for the analysis of longitudinal atrophy rates, similar to what has been shown in presymptomatic atrophy in genetic Alzheimer dementia.[17] A limitation of our study is the relatively small sample size of the *MAPT* and *C9orf72* cohorts and should therefore be carefully interpreted. Replication in larger cohorts, such as GENFI, is therefore warranted. This is partly due to the age range of 45–95 years of the reference population used in Quantib ND. As a result, we had to exclude presymptomatic PVCs younger than 45 years, resulting in smaller sample sizes. This is unfortunate because our data suggest 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 provides segmentation only for the (lateralized) lobes, cerebellum, and hippocampus and no other substructures. Furthermore, 6 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. Last, a seemingly paradoxical increase in occipital lobe volume was visible for *MAPT* and *C9orf72* PVCs and to a lesser extent in the hippocampus for *MAPT* PVCs, between ages 45 and 60 years. This seems 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.[50] Panman et al.[50] 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.[50]

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 lobes, 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.

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Disclosure

Publication History

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Appendix *(continued)*

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Appendix *(continued)*

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