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Longitudinal Cognitive Changes in Genetic Frontotemporal Dementia Within the GENFI Cohort

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Handling Editor Statement:

Abstract

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

Methods: *C9orf72*, *GRN* and *MAPT* pathogenic variant carriers as well as controls underwent a yearly neuropsychological assessment covering eight cognitive domains, as part of the Genetic FTD Initiative (GENFI), a prospective multicenter cohort study. Pathogenic variant carriers were stratified

according to disease stage using the global CDR® plus NACC FTLD score (0, 0.5 and ≥1). Linear mixed-effects models were used to investigate differences between genetic groups and disease stages, as well as the three-way interaction between time, genetic group and disease stage.

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

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

Introduction

Frontotemporal dementia (FTD) is a common cause of dementia, often presenting at a young age with devastating effects on daily living[1]. The typical cause of FTD is neurodegeneration of the frontal and temporal lobes resulting in behavioural disturbances (behavioural variant FTD (bvFTD)), and/or language impairment (primary progressive aphasia (PPA))[2, 3]. FTD is highly heritable and is

autosomal dominantly inherited in up to ~30% of cases. The most common causes are pathogenic variants in the microtubule-associated protein tau (*MAPT*), progranulin (*GRN*), or chromosome 9 open reading frame 72 (*C9orf72*) genes[4]. Deficits in executive function, language and social cognition are often predominant, but may vary in severity and progression due to the heterogeneous nature of the disease [1-3, 5].

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

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

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

Larger international cohort studies with longer follow-up time are crucial to identify cognitive markers that signify disease onset at the earliest stage and can measure changes during disease progression. In addition, clinical instruments for disease severity, such as the Clinical Dementia

Rating (CDR)® scale plus National Alzheimer's Coordinating Center (NACC) frontotemporal lobar degeneration (FTLD) module[29], could stratify pathogenic variant carriers and provide valuable insight into cognitive decline during the different stages of the disease per genetic group.

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

Methods

Participants

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

Standard Protocol Approvals, Registrations, and Patient Consents

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

Procedures

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

Statistical analysis

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

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

domains, as the free recall scores are a part of the total recall scores. The memory encoding, social cognition and visuoconstruction domains are represented by only one test.

As this is a prospective cohort study, not all pathogenic variant carriers had completed all study visits which resulted in missing data. We used linear mixed-effects models for each cognitive domain to examine whether differences existed between *C9orf72, GRN, MAPT* pathogenic variant carriers and controls in cognitive decline since baseline. This type of model allows for the analysis of longitudinal data with unbalanced time points and missing data[39]. Age and years of education were included in all models as covariates. In each model a different cognitive outcome was used as the dependent variable and we specified the following fixed effects: time since baseline in years, gene group, CDR category at baseline, age at baseline, years of education, the two-way interactions between time and group, time and CDR category, and gene group and CDR category and the three-way interaction between time, group and CDR category. We included random intercepts for participants who were nested within families, but not random slopes as this did not improve model fit. A natural cubic splines model did not improve model fit. We performed post-hoc pairwise comparisons in intercepts and slopes between genetic groups within CDR categories. Results are shown as a difference between pathogenic variant group and the control group, or a different pathogenic variant group if stated. The letter β indicates an estimated difference in z-score at baseline, β_1 indicates a difference in change over time (slope). An example of the model and its outputs is shown in eAppendix 1 in the Supplement.

Data Availability

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

Results

Demographics

There were more females in CDR categories 0 and 0.5, and more males in CDR category≥1 for *C9orf72* ($\chi^2(2)=9.8$, $p=0.007$) and *MAPT* ($\chi^2(2)=6.6$, $p=0.036$) pathogenic variant carriers (Table 2).

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

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

Attention

We found strong evidence for differences in the attention domain between CDR categories ($\chi^2(2)=23.2$, p<0.001) and between gene groups ($\chi^2(3)=26.0$, p<0.001) at baseline. *C9orf72* (β=-2.2, SE=0.14, p<0.001), *GRN* (β=-2.2, SE=0.16, p<0.001) and *MAPT* (β=-1.1, SE=0.21, p<0.001) pathogenic variant carriers with CDR category ≥1 all performed worse than controls, with both *C9orf72* (β=-1.1, SE=0.23, p<0.001) and *GRN* (β=-1.2, SE=0.25, p<0.001) pathogenic variant carriers performing worse than *MAPT* pathogenic variant carriers. *C9orf72* pathogenic variant carriers with CDR category 0 also performed worse at baseline than *GRN* (β=-0.3, SE=0.13, $p=0.010$) and *MAPT* (β=-0.4, SE= 0.16, $p=0.030$) pathogenic variant carriers, and controls (β=-0.4, SE= 0.11, $p<0.001$; Figure 1A). In addition, we found an interaction effect between time and gene group ($\chi^2(3)=37.1$, $p<0.001$). All gene groups with CDR category ≥1 declined over time compared to controls (*C9orf72*: $\beta_1=-0.3$, SE=0.07, $p<0.001$; *GRN*: $\beta_1=-0.4$, SE=0.10, $p<0.001$; *MAPT*: $\beta_1=-0.3$, SE=0.09, $p=0.004$).

There was some weak evidence that *C9orf72* pathogenic variant carriers with CDR category 0 declined over time compared to controls (β_1=-0.4, SE=0.11, p=0.086; Figure 1A).

Executive function

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

Language

Language differed between CDR categories (χ^2(2)=96.7, p<0.001) and between gene groups (χ^2(3)=21.5, p<0.001) at baseline. Again, all gene groups with CDR category ≥1 performed worse than controls (*C9orf72:* β=-3.2, SE=0.28, p<0.001; *GRN:* β=-2.9, SE=0.31, p<0.001; *MAPT*: β=-5.0, SE=0.41, p<0.001) at baseline, but in this case *MAPT* pathogenic variant carriers performed worse than *C9orf72* (β=-1.7, SE=0.34, p=0.002) and *GRN* (β=-1.3, SE=0.33, p=0.009) pathogenic variant carriers (Figure 1C). We also found interaction effects between time and gene group (χ^2(3)=104.8,

p<0.001), time and CDR category (X^2(2)=14.0, p=0.001) and time, gene group and CDR category (X^2(4)=25.5, p<0.001). *MAPT* pathogenic variant carriers with CDR category 0.5 (β_1=-0.5, SE=0.17, p=004) and ≥1 (β_1=-0.5, SE=0.15, p=0.003) as well as *C9orf72* (β_1=-0.6, SE= 0.11, p<0.001) and *GRN* (β_1=-1.3, SE=0.14, p<0.001) pathogenic variant carriers with CDR category ≥1 declined over time compared to controls. In CDR category ≥1, *GRN* pathogenic variant carriers demonstrated steeper decline over time than *C9orf72* (β_1=-0.7, SE=0.17, p<0.001) and *MAPT* (β_1=-0.0.9, SE=0.20, p<0.001) pathogenic variant carriers (Figure 1C).

Verbal fluency

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

Memory – immediate recall

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

performing worse than *C9orf72* (β=--3.0, SE=0.47, p<0.001) and *MAPT* pathogenic variant carriers (β=-1.2, SE=0.62, p=0.032; Figure 2A).

Memory – delayed recall

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

Social cognition

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

variant carriers with CDR category ≥1 showed steeper decline over time compared *C9orf72* pathogenic variant carriers (β_1=-0.3, SE=0.16, p=0.047; Figure 2C).

Visuoconstruction

We found differences between gene groups on visuoconstruction ($\chi^2(3)$=11.0, p=0.012) at baseline. All gene groups with CDR category ≥1 performed worse than controls (*C9orf72*: β=-2.0, SE=0.22, p<0.001; *GRN*: β=-1.6, SE=0.26, p<0.001; *MAPT*: β=-0.9, SE=0.32, p=0.004), with *C9orf72* (β=-1.2, SE=0.33, p=0.002) and *GRN* (β=-1.0, SE=0.36, p=0.008) performing worse than *MAPT* pathogenic variant carriers. *GRN* pathogenic variant carriers with CDR category 0.5 (β_1=-0.5, SE=0.23, p=0.050) showed steeper decline over time than controls (Figure 2D).

Discussion

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

Asymptomatic *C9orf72* pathogenic variant carriers performed worse at baseline than controls on attention/mental processing speed, executive function and verbal fluency. In the prodromal stage, social cognition was also lower at baseline, whereas at the fully symptomatic stage all cognitive domains were lower at baseline. There was no decline over time in the asymptomatic stage or prodromal stage, but attention/mental processing speed, language and verbal fluency declined over time in the symptomatic stage, although less rapidly than in other gene groups. The other cognitive domains remained relatively stable, and of note, there were signs of possible practice effects for memory and social cognition. This is largely in line with previous studies demonstrating widespread cognitive impairment in *C9orf72* pathogenic variant carriers with relatively minimal decline over time[5, 40, 41]. It is further corroborated by the fact that the neurodegenerative process associated with the *C9orf72* pathogenic variant is widespread, with neurodegeneration in the frontal and temporal cortices but also in more posterior cortical, subcortical and cerebellar regions[40, 42]. Interestingly, this group performed lowest compared to the other groups on a wide range of neuropsychological tests, specifically tests for attention/mental processing speed and executive function, at the asymptomatic stage. Although these performances were not at an 'impaired' level (i.e. Z-score ≤ -2), these deficits might represent the earliest signs of neurodegeneration with very slow decline over time. Alternatively, the lack of decline over time in all three disease stages raises the intriguing possibility that these deficits are not merely preclinical signs of FTD as a result of early neurodegeneration, but might be indicative of a neurodevelopmental disorder in *C9orf72* which at a certain age is superimposed by additional neurodegeneration. This hypothesis has been suggested by several previous studies that found gray and white matter deficits and connectivity disruption as well as psychiatric conditions and cognitive deficits many years before the estimated age of symptom onset without evidence of disease progression over time[43, 44]. Future studies should focus on ascertaining early-life radiological and clinical assessments to test this hypothesis.

In *MAPT* pathogenic variant carriers, there was a trend towards lower memory performance than controls at baseline in the asymptomatic stage, which became significant at the prodromal stage. All

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

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

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

This is to our knowledge the first study to longitudinally investigate a large cohort of all three major causes of genetic FTD over a 5-year period. A major strength of this study is the use of the CDR plus NACC FTLD to stratify pathogenic variant carriers from asymptomatic to prodromal and fully symptomatic (i.e., 0, 0.5, ≥1). Most previous studies have stratified pathogenic variant carriers as either presymptomatic or symptomatic according to whether they fulfilled diagnostic criteria for FTD syndromes, but this does not fully grasp the clinical trajectory of FTD. Importantly, the cognitive profile between the presymptomatic and symptomatic phase has not been well-characterized. Some other studies have used estimated years to symptom onset based on mean family age at onset, but a recent paper demonstrated that the correlations between age at symptom onset and mean family age at symptom onset were weak for *C9orf72* and *GRN* pathogenic variant carriers, indicating that this might

not be a reliable proxy[28]. By stratifying according to CDR plus NACC FTLD, we have provided insight into cognitive decline during different disease stages. There are, however, a few limitations to this study. Firstly, the sample size at the CDR plus NACC FTLD 0.5 stage was smaller than the other stages, which probably influenced the statistical power in this specific group. Secondly, due to ongoing recruitment within GENFI, participants varied in the number of completed visits resulting in missing data at later time points. Therefore, we analyzed the data with linear mixed-effects model as these models allow for unbalanced time points and missing data[39]. We could not use a non-linear mixed effects model (e.g. natural cubic splines) due to the limited number of follow-up visits. However, similar to what has been performed in studies of familial AD[48], non-linear models might be more suitable for the analysis of clinical progression in FTD. Future studies with longer follow-up should therefore investigate the use of non-linear models in analyzing clinical disease progression in FTD. Thirdly, we did not take progression over time on the CDR plus NACC FTLD into account, but stratified groups according to their global score at baseline. Future research should investigate the cognitive trajectories of progressors compared to non-progressors on the CDR plus NACC FTLD more in depth. Importantly, individual trajectories demonstrated high variability between individuals in each group. A possible explanation for this inter-individual variability could be that some individuals with a CDR plus NACC FTLD global score of 0 might be closer to symptom onset than others. Similarly, individuals with a CDR plus NACC FTLD score of 0.5 or ≥1 at baseline might vary in time since progression to that CDR category (i.e. individuals that had a global score of 0.5 for several years at inclusion will likely progress faster than individuals that progressed to a score of 0.5 more recently). Validation in other cohorts such as ALLFTD or DINAD is warranted. Fourthly, practice effects were strikingly visible for the FCSRT and Facial Emotion Recognition Test stressing the need for different test versions in the former, but more sensitive tasks for emotion recognition (e.g. the use of morphed facial expressions[22]) and social cognition in general. Lastly, in the interpretation of the memory – immediate recall, social cognition and visuoconstruction results it should be taken into account that they were represented by only a single cognitive test, and those individual tests might not be a representation of the entire cognitive domain.

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

WNL-2022-200571_sup -- http://links.lww.com/WNL/B987

WNL-2022-200571_coinvestigator_appendix --http://links.lww.com/WNL/B988

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Tables and Figures

Table 1. Cumulative frequency of the number of participants at each yearly follow-up. Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau.

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

Table 2. Demographics and neuropsychological data per genetic group and FTLD CDR global score category at baseline. Values are represented as mean Z-score compared to controls (standard deviation) unless otherwise specified. Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration; y = years; MMSE = Mini-Mental State Examination.

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

Visuoconstruction	-0.1 (1.2)	-0.2 (1.6)	-2.3 (2.9)	0.2 (0.8)	0.2 (1.0)	-1.9 (3.2)	-0.2 (0.9)	-0.2 (0.9)	-1.3 (2.7)	-

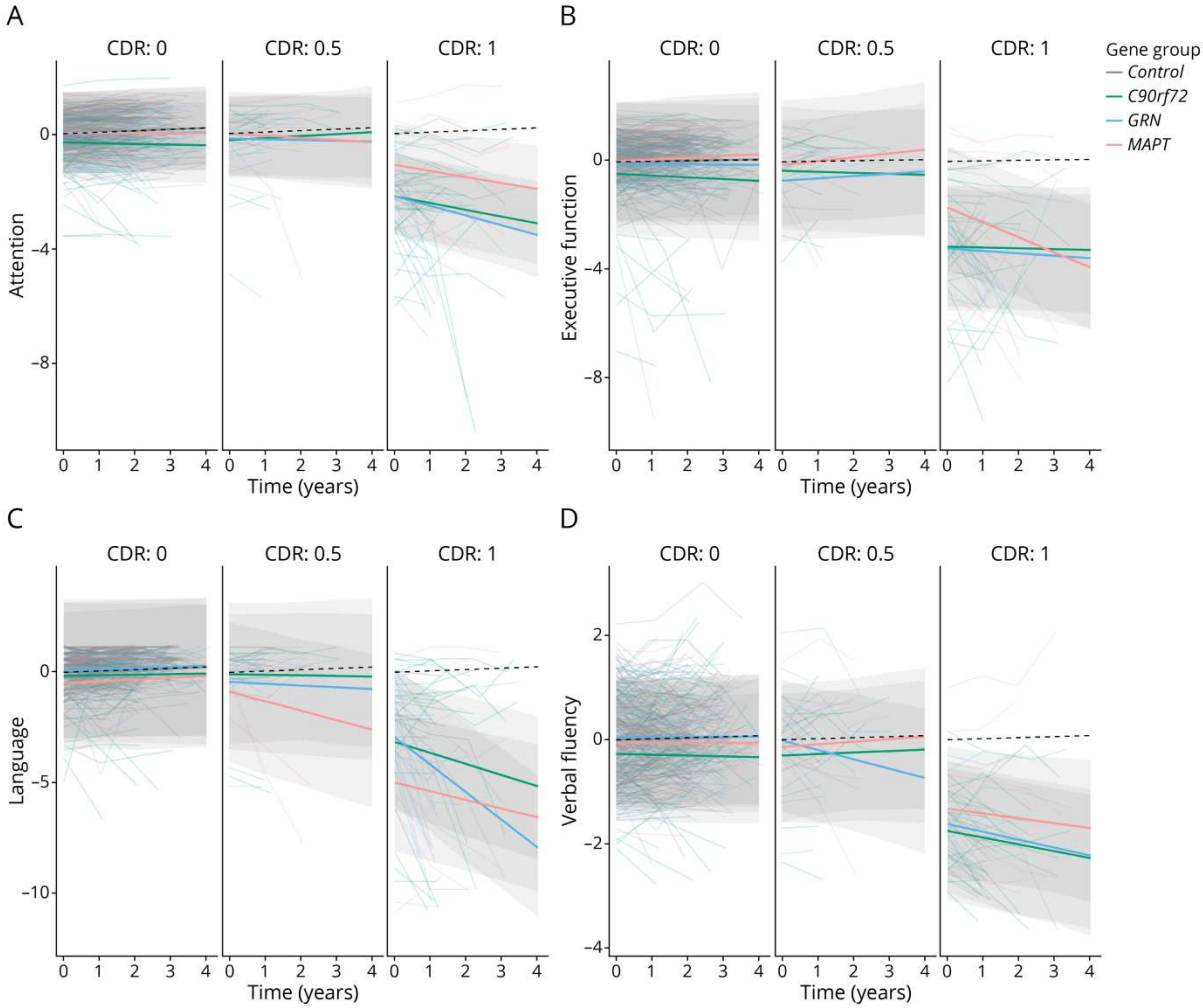
Table 3. Slopes and confidence interval stratified by genetic group and CDR plus NACC FTLD global score for each cognitive domain. Abbreviations: C9orf72 = chromosome 9 open reading frame 72; GRN = progranulin; MAPT = microtubule-associated protein tau; CDR® plus NACC FTLD = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration

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

Controls			
	β	95%CI	
Language	0.06	-0.02	0.13
Attention	0.05	0.00	0.10
Verbal fluency	0.02	-0.02	0.05
Executive function	0.02	-0.03	0.08
Memory - immediate recall	0.00	-0.11	0.22

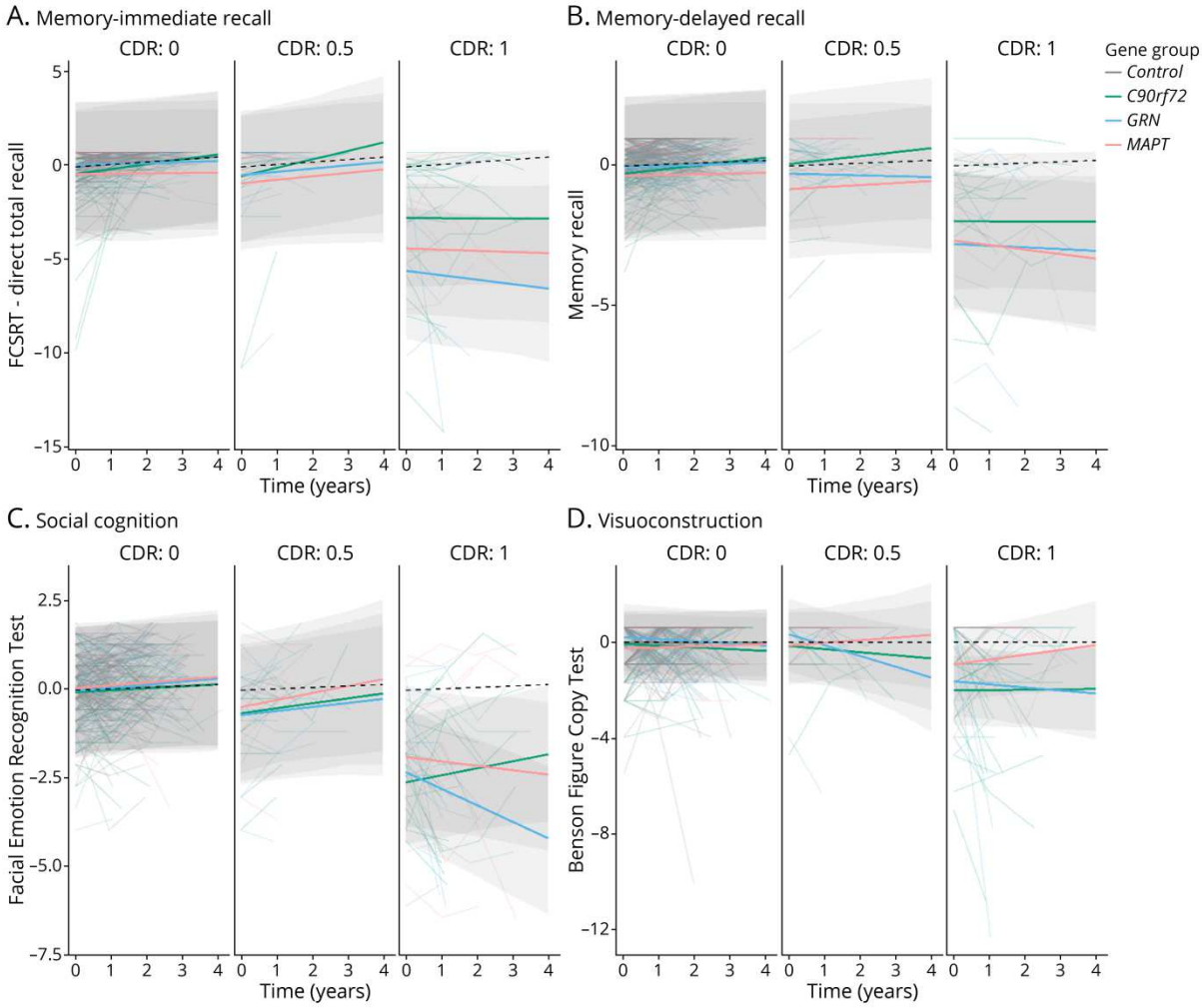
Memory - delayed recall	0.05	-0.01	0.10
Social cognition	0.04	-0.03	0.12
Visuoconstruction	0.13	0.04	0.12

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



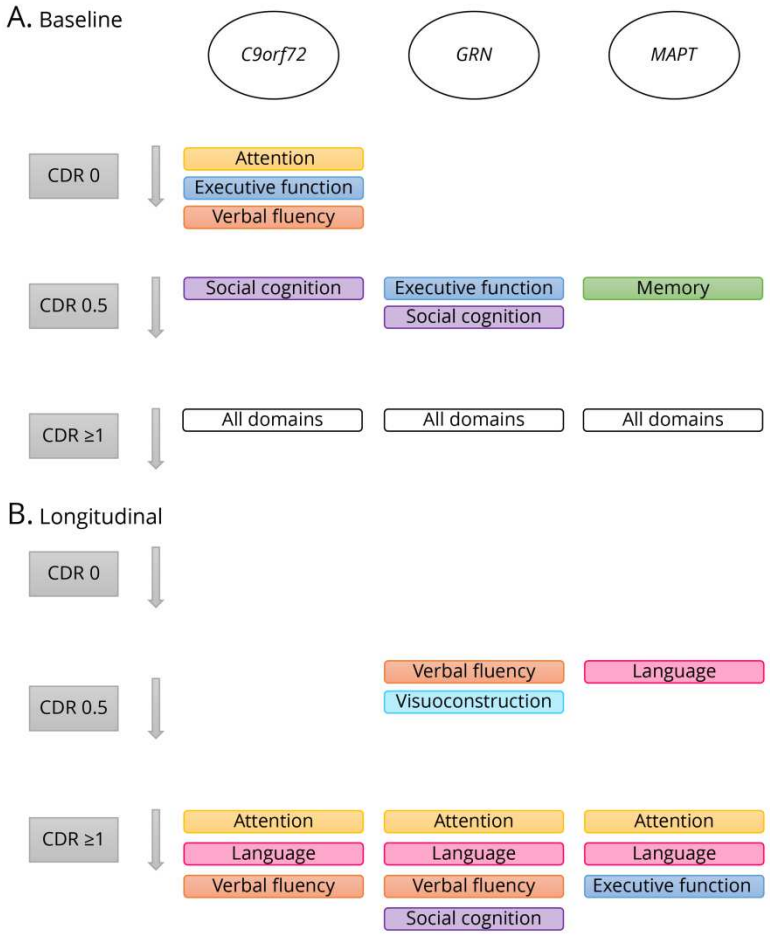
Abbreviations: *C9orf72* = chromosome 9 open reading frame 72; *GRN* = progranulin; *MAPT* = microtubule-associated protein tau; CDR = Clinical Dementia Rating scale plus National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration.

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



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

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



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

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