Letters

Practice effects in genetic frontotemporal dementia and at-risk individuals: a GENFI study

INTRODUCTION

Frontotemporal dementia (FTD) is a heterogeneous group of neurodegenerative diseases with an onset usually before the age of 65 years even if it can appear also in older ages.[1]

On cognitive tests, patients with FTD show deficits in executive functions, social cognition and language, whereas the initial performances in memory and visuoconstruction tasks usually are preserved.[1] The general approach to detect cognitive decline in dementia is to repeat cognitive testing and observe changes over time. However, exposure to similar tasks could improve performance as the individual gets familiar with both the tasks themselves and the test setting (ie, practice effect or learning effect).[2 3]

Different attempts to adjust for practice effects in repeated testing have been proposed.[4] However, recent research suggests that the phenomenon of practice effects can provide useful information. Patients with neurological and psychiatric conditions show lower practice effects than healthy controls, and individuals with mild cognitive impairment (MCI) that do not show practice effects are more likely to develop Alzheimer disease (AD) within a year than individuals with MCI that have preserved practice effects.[3] In addition to the findings of lower practice effects in patients with dementia, Hassenstab *et al*[5] found that preclinical individuals who later progressed to AD had substantially reduced practice effects in episodic memory compared with cognitively stable individuals. Thus, absence of practice effects might serve as an early marker for cognitive decline.

To our knowledge, practice effects have never been investigated in FTD before. The aim of this study was to examine practice effects in the GENetic Frontotemporal dementia Initiative (GENFI) cohort. More specifically, we investigated whether there is a difference in practice effects between presymptomatic mutation carriers (PMC) and mutation non-carriers (NC).

MATERIALS AND METHODS

Participants

All participants (317 NC, 327 PMC and 159 affected mutation carriers (AMC)) were recruited through GENFI from January 2012 to March 2018 (online supplemental table 1). Of the 803 participants, 471 had two visits; 249 had three visits; and 108 had four visits. After the fourth visit, the number of participants rapidly decreased and only 12 had six test occasions (online supplemental figure 1).

Statistics

A global cognitive score was calculated including the mean z-scores of all tests in the standardised GENFI neuropsychological battery. Additionally, practice effects for different cognitive domains were explored. A linear mixed-effects model was applied to examine potential practice effects. Further details including neuropsychological tests, composite score calculation and model selection criteria are described in the online supplemental materials.

RESULTS

Practice effects

An increase in mean global cognitive test scores was seen in NC over the first five visits (online supplemental figure 2). When investigating different cognitive domains, practice effects were found across visits 1–3 in all domains except for visuoconstruction (online supplemental table 2). The largest practice effect was observed in memory and social cognition. After the third visit, there was a plateau, and the practice effects between visits 3 and 4 as well as visits 4 and 5 were not statistically significant. In contrast, a progressive decline in the mean global score was identified longitudinally in AMC, as could be expected (online supplemental figure 2). PMC carrying a *C9orf72* expansion and with less than 5 years to expected symptom onset (PMC-C9 in proximity to onset) showed no practice effect on their global test score and had the same mean performance at all three visits (figure 1A and online supplemental table 3). Furthermore, PMC-C9 with more than 5 years to expected onset had a lower practice effect between visits 1 and 2 than NC; however, the total practice effect (visits 1–3) was not significantly different from NC.

Similar to PMC-C9, there was a lower practice effect across visits 1–3 in PMC with a proganulin (*GRN*) mutation in proximity to onset compared with NC. However, PMC-GRN in proximity to onset appear to initially have a practice effect but subsequently do not improve their performance at the third visit (figure 1B).

PMC with a *MAPT* mutation (PMC-MAPT) had a similar trajectory in mean cognitive test score across visits 1–3 as NC (figure 1C).

DISCUSSION

In this study, we explored practice effects due to repeated cognitive assessments in

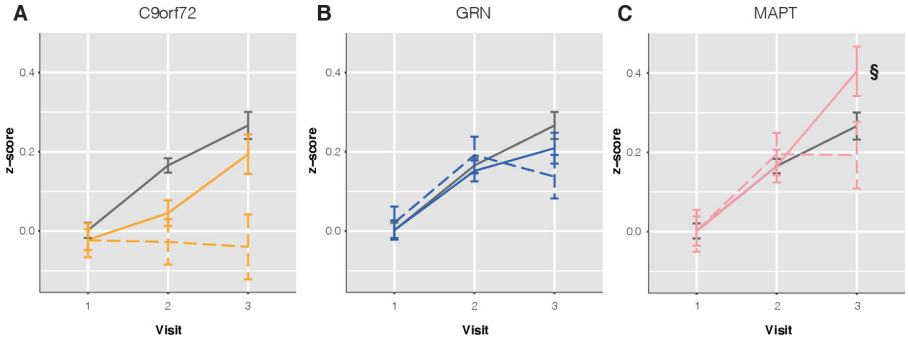

Figure 1 Trajectories of global cognitive test scores in NC and PMC by mutated gene.(A) PMC-C9 and NC (grey line, NC; yellow solid line, PMC-C9 with >5 years to expected symptom onset; yellow dashed line, PMC-C9 with <5 years to expected symptom onset). (B) PMC-GRN and NC (grey line, NC; blue solid line, PMC-GRN with >5 years to expected symptom onset; blue dashed line, PMC-GRN with <5 years to expected symptom onset). (C) PMC-MAPT and NC (grey line, NC; pink solid line, PMC-MAPT with >5 years to expected symptom onset; pink dashed line, PMC-MAPT with <5 years to expected symptom onset). All lines are fitted from the same linear mixed-effect model but plotted in A–C to simplify visualisation. Error bars represent the SEs of the means. §The difference between PMC-MAPT with >5 years to expected symptom onset and NC is no longer observed when PMC-MAPTs are compared with age-matched and family-matched controls. C9, chromosome 9 open reading frame 72; GRN, progranulin; MAPT, microtubule-associated protein tau; NC, non-carrier; PMC, presymptomatic mutation carrier.

a large cohort of individuals with genetic presymptomatic or symptomatic FTD as well as non-mutation carrier family members. Practice effects have been suggested to provide useful information of the progression of cognitive decline but have never been studied in the context of FTD before. Compared with their baseline test scores, NC improved in global cognition at each visit (visits 2 and 3). Presymptomatic individuals carrying the *C9orf72* expansion or a *GRN* mutation had significantly lower practice effects than NC, and this difference was most apparent in PMC-C9 within 5 years of expected symptom onset. However, it is not possible to know if the stable performance over time in PMC in proximity to onset is due to lower practice effects per se or an actual cognitive decline that is masked by practice effects. The question of genuine practice effects applies also to AMC, who showed a progressive decline in global cognitive test scores at each visit. The scores measured after repeated testing in AMC might include a 'hidden' practice effect, and therefore the true cognitive dysfunction would in fact be greater than what was captured in the test scores. Cognitive functions in FTD are expected to decline over the test interval used in this study (mean 1.3 years). Consequently, a potential absence of practice effects in clinical FTD, as reported in AD,[3] cannot be evaluated with the current setup but could be addressed if the retest is performed within days or weeks of the first assessment. Besides the PMC in proximity to onset, also PMC-C9 with more than 5 years to expected symptom onset had lower practice effects than NC which could not be explained by early conversion into a symptomatic stage. Progression of brain atrophy in *C9orf72* expansion carriers can be slow, and some patients have been described with a remarkably long disease duration.[1] Pathological changes in the brain of *C9orf72* expansion carriers are present already in early adulthood, and the potential neurodevelopmental effects could lead to a long prodromal phase in PMC-C9. Previous findings show that cognitive performance in PMC is not different from NC until very close to the disease onset,[1] which is in line with the results of the current study. Nevertheless, an inability to use acquired skills from previous tests might be a marker for very early disease development in PMC-C9. However, the diagnostic potential of practice effects and whether they can be used for differentiating PMC-C9 from NC are yet to be explored.

As the field of FTD research is greatly evolving and treatment opportunities are emerging, knowledge about different stages of the disease is highly required. As we are preparing for clinical trials, several initiatives have been searching for both fluid biomarkers as surrogate endpoints as well as clinical and neuropsychological tests used to evaluate a future treatment response. Practice effects can have implications for the interpretation of longitudinal changes in cognitive performance as it could impact estimations of treatment effects after an intervention, particularly early in the disease course. Furthermore, one could speculate that identifying individuals with lower-than-expected practice effects would be a cost-effective approach for inclusion into clinical trials.[3] The presence of practice effects should thus be considered in future clinical trials especially if neuropsychological measures are included as end points.

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Correction notice This article has been corrected since it was first published online. The 'Results' heading has been added in the text.

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SUPPLEMENTARY MATERIALS

Practice effects in genetic frontotemporal dementia and at-risk individuals: a GENFI study

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1 Supplemental materials

1.1 Participants

The following clinical information was available for each subject: age at testing, date of testing, sex, mutation status (presymptomatic mutation carrier, PMC; affected mutation carrier, AMC; non-carrier, NC) and years of education. In addition, information on mutated gene (chromosome 9 open reading frame 72, *C9orf72*; progranulin, *GRN*; microtubule associated protein tau, *MAPT* or TANK-binding kinase 1, *TBK1*) was available for mutation carriers, and diagnosis as well as age at onset for affected mutation carriers (AMC).

The mean age at onset for mutation carriers has in a recent publication by Moore *et al*., 2019(1) been estimated to be 58.2 years for *C9orf72*, 61.3 years for *GRN* and 49.5 years for *MAPT*. Years to expected onset was calculated based on the age of the participant minus the mean age at

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onset for the specific mutated gene segregating in the family. For example, a 45 years old *C9orf72* mutation carrier was estimated to be 13.2 years from expected symptom onset (45 - 58.2 = -13.2).

1.2 Neuropsychological tests

359 participants were assessed using GENFI 1 protocol (2012-2015) and 444 participants using GENFI 2 protocol (2015-2018)(2). The following tasks were included in both GENFI 1 and GENFI 2 (i.e. all 803 participants performed the tasks): Block design(3), Boston naming test (BNT)(4), Digit symbol(3), Digit span (forward and backward)(3), Trail making test A (TMT A) and B (TMT B)(5) and Verbal fluency test (animals, letters F, A and S)(6). In GENFI 2 (n=444), the following additional tests were administered: Benson figure copy, recall and recognition(7), modified Camel and cactus test (CC)(8), Stroop colour and word test (ink and word naming, interference)(9,10), Free and cued selective reminding test (FCRST)(11), Ekman faces and Faux pas recognition test as part of the mini-SEA(12). All neuropsychological raw scores were converted into z-scores. z-scores were calculated based on mutation negative control data (individual test score minus the mean of non-carriers, divided by the standard deviation of non-carriers) and were corrected for language in language specific tasks (i.e. BNT and Verbal fluency).

1.3 Composite scores

Composite scores were calculated from reflecting different cognitive domains: language, executive function, attention and processing speed, memory, social cognition and visuoconstruction. The composite scores were calculated as the mean of the z-scores of the individual tests included in the composite (13). We treat the composite value as an estimate of a standardised score, meaning that a value of 1 is approximately 1 standard deviation (SD). The composite score of language included BNT, CC and Verbal fluency animals; executive function included TMT B, Verbal fluency letters, Digit span backward and Stroop interference; attention and processing speed included TMT A, Digit symbol, Digit span forward and Stroop ink and word naming; memory included Digit span (forward and backward) and FCRST; social cognition included Ekman faces and Faux pas recognition test (mini-SEA); and visuoconstruction included Block design and Benson figure. If there were missing data from a specific task (if a participant did not complete the whole test battery), the domain composite score was calculated based on the remaining test scores for that domain, i.e. the sum of the z-scores divided by the number of completed tests. As a sensitivity analysis, we excluded the individuals with less

than two thirds of completed tests (n=5) and re-ran the mixed effect model of global cognitive score. The results were the same and did not change the conclusion.

1.4 Statistical analysis

All statistical analyses and visual illustrations were performed using R version 4.0.3. P-values below 0.05 were considered statistically significant and baseline p-values were adjusted for multiple comparisons using Bonferroni corrections (number of comparisons = 63). Assumptions were assessed visually by residual plots (independence and equal variance) and normal probability plots (normality).

When assessing mean differences in numeric variables between NC, PMC and AMC, One-way ANOVA with Bonferroni post hoc tests was used (age, years of education). Chi-square tests were used for assessing sex distribution in NC, PMC and AMC.

Model selection(14) was based upon clinical relevance and Bayesian information criterion (BIC), where lower BIC was preferred. A stepwise backward selection was performed for the fixed effects using R package lmerTest v2.0-36. Mutation group (AMC, PMC or NC) or mutated gene (*C9orf72*, *GRN*, *MAPT*, NC), visit, years from baseline visit, age, age^2, education, sex and baseline score were included as fixed effects (independent variables) in the final models. In addition, the interaction between gene and visit was included to investigate whether the trajectories for neuropsychological test scores were different over time depending on which gene was mutated. Site and individual were included as random effects to account for within-subject correlations.

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Supplementary Table 1. Demographic data. *NC, non-carriers; PMC, presymptomatic mutation carriers; AMC, affected mutation carriers; C9orf72, chromosome 9 open reading frame 72; GRN, progranulin; MAPT, microtubule associated protein tau; TBK1, TANK-binding kinase 1; SD, standard deviation.*

	Mutation group				Test statistic	
	NC	PMC	AMC	Total	p value	
N	317	327	159	803		
Age (Years)					< 0.001[a]	AMC > PMC = NC
Mean (SD)	46.2 (14.0)	44.4 (12.0)	62.6 (8.0)	48.7 (14.0)		
Range	19.4 - 85.7	20.1 - 75.5	37.9 - 78.7	19.4 - 85.7		
Sex					0.01[b]	
Females (%)	182 (57.4)	198 (60.6)	65 (40.9)	445 (55.4)		
Education (Years)					< 0.001[c]	AMC < PMC = NC
Mean (SD)	11.0 (3.5)	11.3 (3.3)	9.2 (3.9)	10.8 (3.6)		
Range	2.0 - 21.0	2.0 - 21.0	1.0 - 19.0	1.0 - 21.0		
Mutated gene (%)						
C9orf72		121 (37.0)	79 (49.7)	200 (24.9)		
GRN		148 (45.3)	52 (32.7)	200 (24.9)		
MAPT		58 (17.7)	27 (17.0)	85 (10.6)		
TBK1		0 (0.0)	1 (0.6)	1 (0.1)		

[a] ANOVA. Differences in age between AMC vs PMC and AMC vs NC. No difference between PMC and NC.

[b] Pearson's Chi-squared test.

[c] ANOVA. Difference in years of education between AMC vs PMC and AMC vs NC. No difference between PMC and NC.

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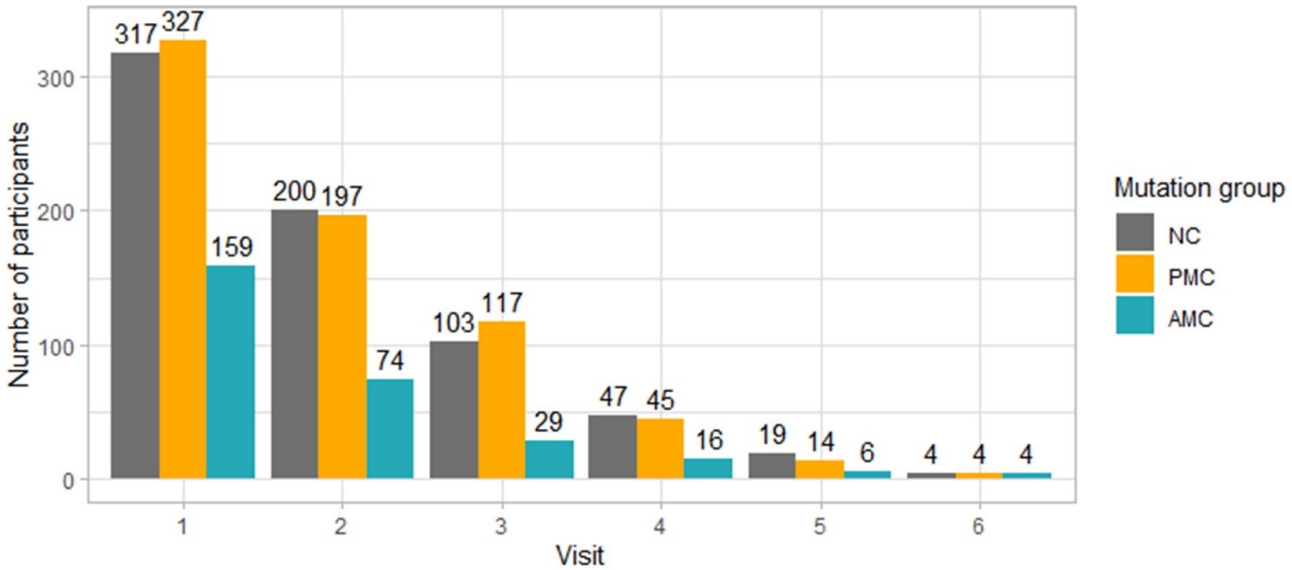
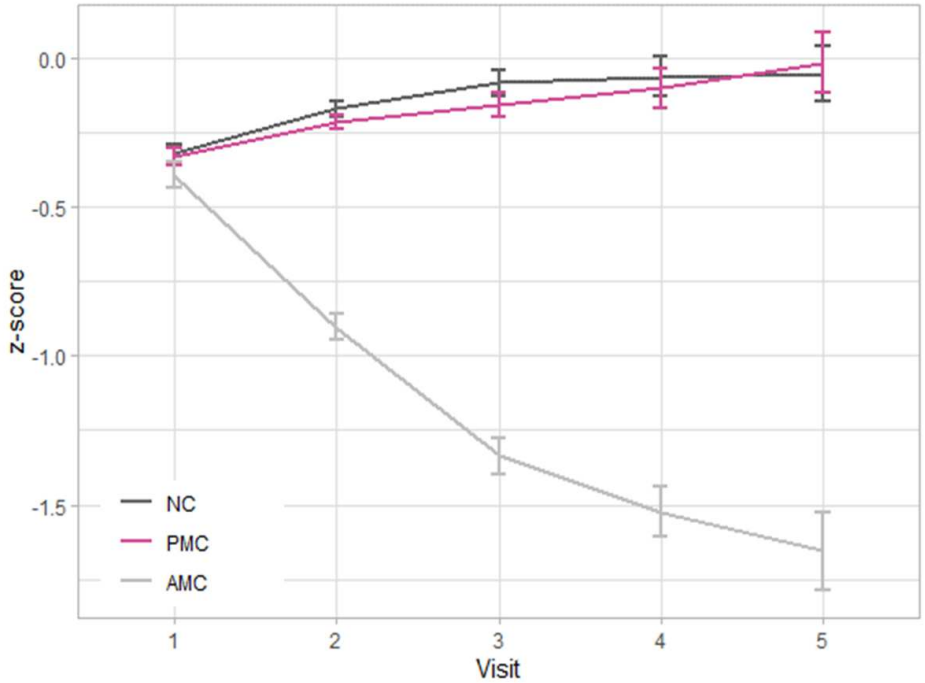


Supplementary Figure 1. *Bar chart illustrating the number of participants at each visit. NC, non-carriers; PMC, presymptomatic mutation carriers; AMC, affected mutation carriers.*

SUPPLEMENTARY MATERIALS



Supplementary Figure 2. *Trajectories of global cognitive test scores, fitted line from mixed effect model. The model included mutation group (AMC, PMC, NC), visit (1-5), mutation group:visit, years from baseline visit, age, age^2, education, sex and baseline score as fixed effects and site and individual as random effects. NC, non-carriers; PMC, presymptomatic mutation carriers; AMC, affected mutation carriers. Error bars represent the standard errors of the means.*

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***Supplementary Table 2**. Estimates, standard errors and p-values from linear mixed-effects models for the different cognitive domains. Distant PMC, presymptomatic mutation carriers with MORE than 5 years to expected symptom onset; Proximity PMC, presymptomatic mutation carriers with LESS than 5 years to expected onset. Values for the following fixed effects are displayed: mutated gene (including distant vs proximity PMC). visit (1-3) and the interaction between mutated gene and visit. Other fixed effects in model: years from baseline visit. age. age^2. education. sex and baseline score. Random effects: site and individual. The reference is a female, non-carrier at baseline. Ref = estimates, SE and p-value for each genetic group without interaction with visit. SE=standard error. C9, chromosome 9 open reading frame 72; GRN, progranulin; MAPT, microtubule associated protein tau.*

			Global			**Language**			**Executive function**			**Attention and processing speed**			**Memory**			**Social cognition**			**Visuoconstruction**		
			Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
	Intercept		0.001	0.077	0.992	-0.130	0.148	0.378	-0.179	0.112	0.110	-0.025	0.103	0.807	0.264	0.155	0.090	-0.279	0.223	0.211	0.171	0.146	0.242
	Visit2		0.164	0.026	**0.000**	0.105	0.051	**0.040**	0.083	0.038	**0.029**	0.207	0.036	**0.000**	0.267	0.057	**0.000**	0.362	0.146	**0.013**	0.134	0.055	**0.015**
	Visit3		0.264	0.045	**0.000**	0.278	0.087	**0.001**	0.187	0.066	**0.004**	0.297	0.061	**0.000**	0.430	0.098	**0.000**	0.721	0.264	**0.007**	0.067	0.094	0.477
C9	Distant PMC	Ref	-0.024	0.025	0.348	-0.019	0.049	0.693	-0.020	0.036	0.586	-0.038	0.034	0.264	-0.030	0.053	0.576	-0.074	0.069	0.282	-0.034	0.050	0.496
		Visit 2	-0.097	0.040	**0.017**	-0.092	0.080	0.254	-0.024	0.057	0.676	-0.101	0.055	0.066	-0.168	0.087	0.055	-0.037	0.132	0.779	-0.140	0.084	0.096
		Visit 3	-0.049	0.052	0.353	-0.141	0.104	0.173	0.052	0.074	0.484	0.033	0.071	0.644	0.009	0.112	0.940	-0.132	0.323	0.684	-0.165	0.107	0.123
	Proximity PMC	Ref	-0.025	0.042	0.547	-0.089	0.081	0.271	-0.054	0.060	0.367	-0.008	0.056	0.884	-0.015	0.087	0.864	0.008	0.105	0.937	-0.062	0.083	0.455
		Visit 2	-0.168	0.067	**0.013**	-0.047	0.134	0.726	-0.021	0.095	0.828	-0.158	0.092	0.086	-0.314	0.146	**0.031**	0.230	0.182	0.208	-0.450	0.139	**0.001**
		Visit 3	-0.281	0.089	**0.002**	-0.410	0.175	**0.020**	-0.255	0.126	**0.043**	-0.147	0.120	0.224	-0.387	0.190	**0.042**	0.348	0.280	0.215	-0.371	0.180	**0.040**
GRN	Distant PMC	Ref	0.001	0.023	0.978	-0.004	0.045	0.930	-0.001	0.033	0.977	-0.014	0.031	0.644	0.062	0.049	0.206	-0.009	0.066	0.890	0.005	0.046	0.920
		Visit 2	-0.014	0.035	0.681	0.017	0.070	0.804	0.045	0.049	0.359	-0.049	0.047	0.300	-0.057	0.076	0.456	-0.065	0.109	0.551	0.004	0.073	0.961
		Visit 3	-0.058	0.042	0.168	-0.060	0.083	0.473	-0.092	0.059	0.121	-0.009	0.057	0.874	-0.102	0.091	0.258	0.107	0.154	0.489	-0.136	0.086	0.117
	Proximity PMC	Ref	0.019	0.039	0.627	0.012	0.077	0.874	0.020	0.056	0.720	0.052	0.053	0.327	-0.019	0.083	0.817	0.045	0.129	0.728	-0.012	0.078	0.878
		Visit 2	0.007	0.057	0.900	0.200	0.113	0.076	-0.021	0.080	0.794	-0.065	0.077	0.400	-0.121	0.122	0.321	0.340	0.205	0.099	-0.049	0.117	0.676
		Visit 3	-0.148	0.059	**0.013**	-0.260	0.118	**0.028**	-0.285	0.084	**0.001**	-0.223	0.081	**0.006**	-0.089	0.128	0.486	0.188	0.259	0.470	0.029	0.122	0.813
MAPT	Distant PMC	Ref	0.000	0.036	0.992	-0.008	0.069	0.912	0.018	0.051	0.723	-0.013	0.048	0.787	0.045	0.075	0.548	-0.028	0.102	0.780	-0.013	0.071	0.859
		Visit 2	0.000	0.052	0.992	-0.053	0.103	0.607	-0.059	0.073	0.418	0.120	0.070	0.087	-0.039	0.112	0.726	-0.034	0.154	0.824	-0.067	0.108	0.537
		Visit 3	0.138	0.068	**0.042**	-0.022	0.135	0.873	0.010	0.096	0.915	0.197	0.092	**0.033**	0.298	0.146	**0.042**	0.232	0.253	0.360	0.156	0.139	0.263
	Proximity PMC	Ref	0.000	0.052	0.995	-0.045	0.102	0.660	0.003	0.075	0.973	0.027	0.071	0.703	-0.011	0.110	0.918	0.013	0.150	0.931	-0.019	0.104	0.852
		Visit 2	0.030	0.070	0.672	-0.007	0.141	0.960	0.108	0.099	0.275	0.009	0.096	0.922	0.067	0.154	0.665	0.086	0.217	0.693	0.015	0.150	0.919
		Visit 3	-0.074	0.093	0.428	-0.282	0.185	0.127	-0.142	0.131	0.281	-0.027	0.126	0.830	-0.167	0.201	0.405	0.210	0.458	0.646	0.400	0.191	**0.036**

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Supplementary Table 3. *Mixed effects model for global cognitive test scores.*

The reference is a female, non-carrier at baseline. The global practice effect in NC was approximately 0.15 SD per visit. We included baseline scores in our statistical models to eliminate the effect of novelty to a task (i.e. stress response at first testing causing interference with performance), and the dilemma of regression to the mean often seen in repeated testing situations. C9, chromosome 9 open reading frame 72; GRN, progranulin; MAPT, microtubule associated protein tau; NC, non-carriers; PMC, presymptomatic mutation carriers; AMC, affected mutation carriers.

Fixed effects	Estimate	Standard Error	p-value
Intercept	0.000	0.076	0.996
Visit 2	0.167	0.026	**<0.001**
Visit 3	0.270	0.044	**<0.001**
PMC-C9	-0.025	0.023	0.279
PMC-GRN	0.005	0.021	0.825
PMC-MAPT	-0.002	0.030	0.959
Years from baseline	-0.085	0.013	**<0.001**
Male	-0.016	0.013	0.229
Age	0.003	0.003	0.416
Age^2	0.000	0.000	0.057
Education (years)	0.003	0.002	0.151
Baseline global score	0.888	0.013	**<0.001**
Visit 2*PMC-C9	-0.114	0.036	**0.002**
Visit 3*PMC-C9	-0.104	0.047	**0.027**
Visit 2*PMC-GRN	-0.008	0.032	0.790
Visit 3*PMC-GRN	-0.086	0.037	**0.021**
Visit 2*PMC-MAPT	0.011	0.043	0.795
Visit 3*PMC-MAPT	0.064	0.057	0.264
Random effects	**Variance**		
Individual variance of intercept	0.006		
Site variance of intercept	0.00002		
Residual variance	0.04		

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1.5 References

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SUPPLEMENTARY MATERIALS

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1 Supplemental materials

1.1 Participants

The following clinical information was available for each subject: age at testing, date of testing, sex, mutation status (presymptomatic mutation carrier, PMC; affected mutation carrier, AMC; non-carrier, NC) and years of education. In addition, information on mutated gene (chromosome 9 open reading frame 72, *C9orf72*; progranulin, *GRN*; microtubule associated protein tau, *MAPT* or TANK-binding kinase 1, *TBK1*) was available for mutation carriers, and diagnosis as well as age at onset for affected mutation carriers (AMC).

The mean age at onset for mutation carriers has in a recent publication by Moore *et al*., 2019(1) been estimated to be 58.2 years for *C9orf72*, 61.3 years for *GRN* and 49.5 years for *MAPT*. Years to expected onset was calculated based on the age of the participant minus the mean age at

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onset for the specific mutated gene segregating in the family. For example, a 45 years old *C9orf72* mutation carrier was estimated to be 13.2 years from expected symptom onset (45 - 58.2 = -13.2).

1.2 Neuropsychological tests

359 participants were assessed using GENFI 1 protocol (2012-2015) and 444 participants using GENFI 2 protocol (2015-2018)(2). The following tasks were included in both GENFI 1 and GENFI 2 (i.e. all 803 participants performed the tasks): Block design(3), Boston naming test (BNT)(4), Digit symbol(3), Digit span (forward and backward)(3), Trail making test A (TMT A) and B (TMT B)(5) and Verbal fluency test (animals, letters F, A and S)(6). In GENFI 2 (n=444), the following additional tests were administered: Benson figure copy, recall and recognition(7), modified Camel and cactus test (CC)(8), Stroop colour and word test (ink and word naming, interference)(9,10), Free and cued selective reminding test (FCRST)(11), Ekman faces and Faux pas recognition test as part of the mini-SEA(12). All neuropsychological raw scores were converted into z-scores. z-scores were calculated based on mutation negative control data (individual test score minus the mean of non-carriers, divided by the standard deviation of non-carriers) and were corrected for language in language specific tasks (i.e. BNT and Verbal fluency).

1.3 Composite scores

Composite scores were calculated from reflecting different cognitive domains: language, executive function, attention and processing speed, memory, social cognition and visuoconstruction. The composite scores were calculated as the mean of the z-scores of the individual tests included in the composite (13). We treat the composite value as an estimate of a standardised score, meaning that a value of 1 is approximately 1 standard deviation (SD). The composite score of language included BNT, CC and Verbal fluency animals; executive function included TMT B, Verbal fluency letters, Digit span backward and Stroop interference; attention and processing speed included TMT A, Digit symbol, Digit span forward and Stroop ink and word naming; memory included Digit span (forward and backward) and FCRST; social cognition included Ekman faces and Faux pas recognition test (mini-SEA); and visuoconstruction included Block design and Benson figure. If there were missing data from a specific task (if a participant did not complete the whole test battery), the domain composite score was calculated based on the remaining test scores for that domain, i.e. the sum of the z-scores divided by the number of completed tests. As a sensitivity analysis, we excluded the individuals with less

than two thirds of completed tests (n=5) and re-ran the mixed effect model of global cognitive score. The results were the same and did not change the conclusion.

1.4 Statistical analysis

All statistical analyses and visual illustrations were performed using R version 4.0.3. P-values below 0.05 were considered statistically significant and baseline p-values were adjusted for multiple comparisons using Bonferroni corrections (number of comparisons = 63). Assumptions were assessed visually by residual plots (independence and equal variance) and normal probability plots (normality).

When assessing mean differences in numeric variables between NC, PMC and AMC, One-way ANOVA with Bonferroni post hoc tests was used (age, years of education). Chi-square tests were used for assessing sex distribution in NC, PMC and AMC.

Model selection(14) was based upon clinical relevance and Bayesian information criterion (BIC), where lower BIC was preferred. A stepwise backward selection was performed for the fixed effects using R package lmerTest v2.0-36. Mutation group (AMC, PMC or NC) or mutated gene (*C9orf72*, *GRN*, *MAPT*, NC), visit, years from baseline visit, age, age^2, education, sex and baseline score were included as fixed effects (independent variables) in the final models. In addition, the interaction between gene and visit was included to investigate whether the trajectories for neuropsychological test scores were different over time depending on which gene was mutated. Site and individual were included as random effects to account for within-subject correlations.

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Supplementary Table 1. Demographic data. *NC, non-carriers; PMC, presymptomatic mutation carriers; AMC, affected mutation carriers; C9orf72, chromosome 9 open reading frame 72; GRN, progranulin; MAPT, microtubule associated protein tau; TBK1, TANK-binding kinase 1; SD, standard deviation.*

	Mutation group				Test statistic	
	NC	PMC	AMC	Total	p value	
N	317	327	159	803		
Age (Years)					< 0.001[a]	AMC > PMC = NC
Mean (SD)	46.2 (14.0)	44.4 (12.0)	62.6 (8.0)	48.7 (14.0)		
Range	19.4 - 85.7	20.1 - 75.5	37.9 - 78.7	19.4 - 85.7		
Sex					0.01[b]	
Females (%)	182 (57.4)	198 (60.6)	65 (40.9)	445 (55.4)		
Education (Years)					< 0.001[c]	AMC < PMC = NC
Mean (SD)	11.0 (3.5)	11.3 (3.3)	9.2 (3.9)	10.8 (3.6)		
Range	2.0 - 21.0	2.0 - 21.0	1.0 - 19.0	1.0 - 21.0		
Mutated gene (%)						
C9orf72		121 (37.0)	79 (49.7)	200 (24.9)		
GRN		148 (45.3)	52 (32.7)	200 (24.9)		
MAPT		58 (17.7)	27 (17.0)	85 (10.6)		
TBK1		0 (0.0)	1 (0.6)	1 (0.1)		

[a] ANOVA. Differences in age between AMC vs PMC and AMC vs NC. No difference between PMC and NC.

[b] Pearson's Chi-squared test.

[c] ANOVA. Difference in years of education between AMC vs PMC and AMC vs NC. No difference between PMC and NC.

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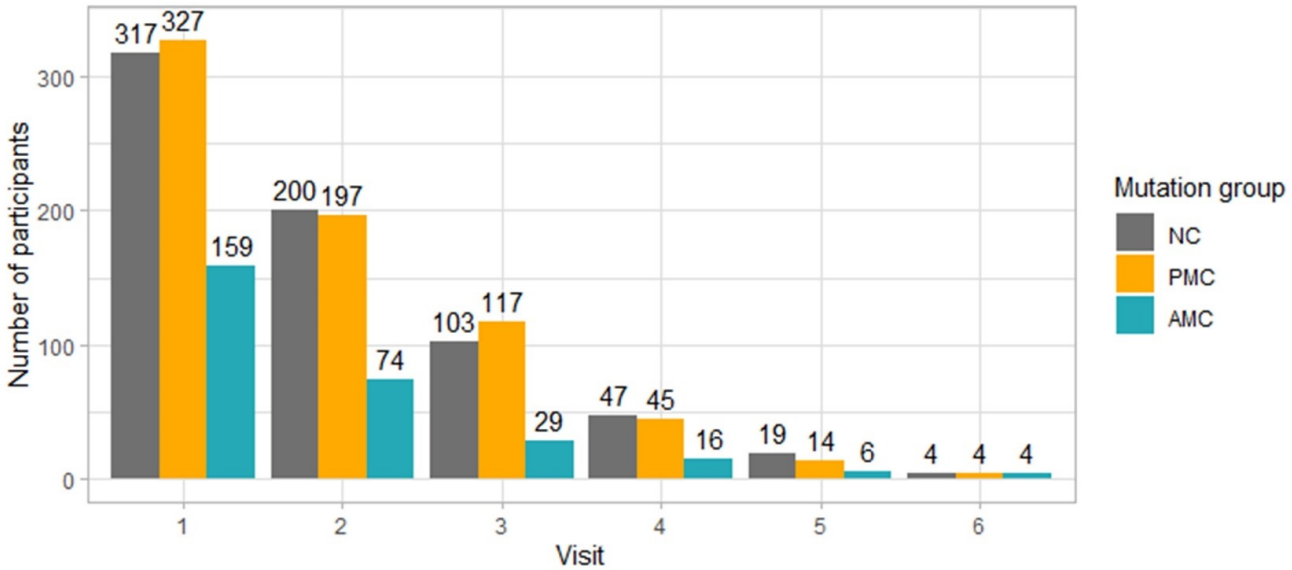
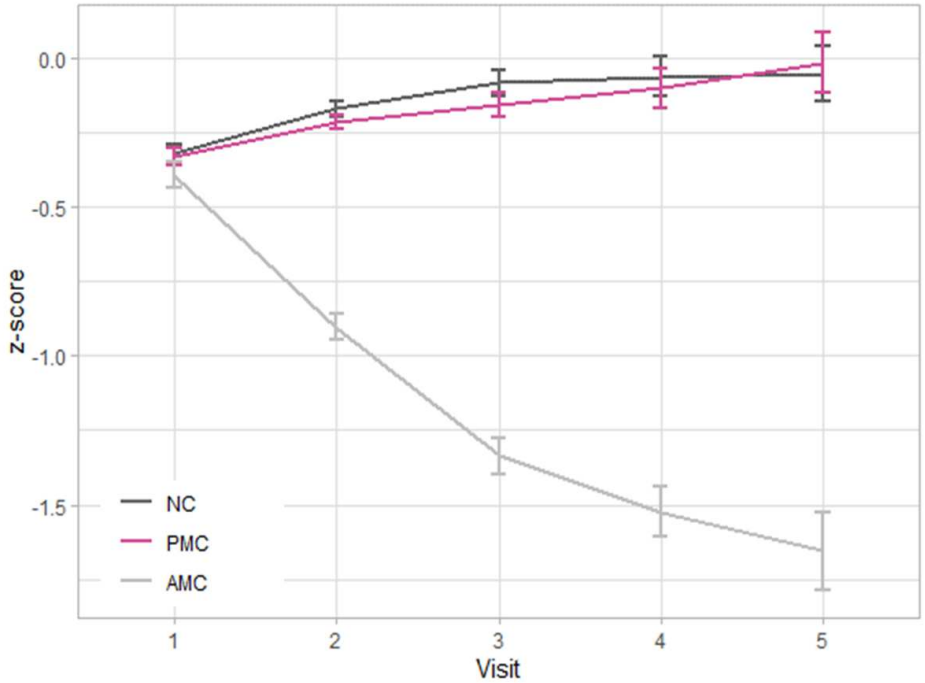


Supplementary Figure 1. *Bar chart illustrating the number of participants at each visit. NC, non-carriers; PMC, presymptomatic mutation carriers; AMC, affected mutation carriers.*

SUPPLEMENTARY MATERIALS



Supplementary Figure 2. *Trajectories of global cognitive test scores, fitted line from mixed effect model. The model included mutation group (AMC, PMC, NC), visit (1-5), mutation group:visit, years from baseline visit, age, age^2, education, sex and baseline score as fixed effects and site and individual as random effects. NC, non-carriers; PMC, presymptomatic mutation carriers; AMC, affected mutation carriers. Error bars represent the standard errors of the means.*

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***Supplementary Table 2**. Estimates, standard errors and p-values from linear mixed-effects models for the different cognitive domains. Distant PMC, presymptomatic mutation carriers with MORE than 5 years to expected symptom onset; Proximity PMC, presymptomatic mutation carriers with LESS than 5 years to expected onset. Values for the following fixed effects are displayed: mutated gene (including distant vs proximity PMC). visit (1-3) and the interaction between mutated gene and visit. Other fixed effects in model: years from baseline visit. age. age^2. education. sex and baseline score. Random effects: site and individual. The reference is a female, non-carrier at baseline. Ref = estimates, SE and p-value for each genetic group without interaction with visit. SE=standard error. C9, chromosome 9 open reading frame 72; GRN, progranulin; MAPT, microtubule associated protein tau.*

			Global			**Language**			**Executive function**			**Attention and processing speed**			**Memory**			**Social cognition**			**Visuoconstruction**		
			Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p	Estimate	SE	p
	Intercept		0.001	0.077	0.992	-0.130	0.148	0.378	-0.179	0.112	0.110	-0.025	0.103	0.807	0.264	0.155	0.090	-0.279	0.223	0.211	0.171	0.146	0.242
	Visit2		0.164	0.026	**0.000**	0.105	0.051	**0.040**	0.083	0.038	**0.029**	0.207	0.036	**0.000**	0.267	0.057	**0.000**	0.362	0.146	**0.013**	0.134	0.055	**0.015**
	Visit3		0.264	0.045	**0.000**	0.278	0.087	**0.001**	0.187	0.066	**0.004**	0.297	0.061	**0.000**	0.430	0.098	**0.000**	0.721	0.264	**0.007**	0.067	0.094	0.477
C9	Distant PMC	Ref	-0.024	0.025	0.348	-0.019	0.049	0.693	-0.020	0.036	0.586	-0.038	0.034	0.264	-0.030	0.053	0.576	-0.074	0.069	0.282	-0.034	0.050	0.496
		Visit 2	-0.097	0.040	**0.017**	-0.092	0.080	0.254	-0.024	0.057	0.676	-0.101	0.055	0.066	-0.168	0.087	0.055	-0.037	0.132	0.779	-0.140	0.084	0.096
		Visit 3	-0.049	0.052	0.353	-0.141	0.104	0.173	0.052	0.074	0.484	0.033	0.071	0.644	0.009	0.112	0.940	-0.132	0.323	0.684	-0.165	0.107	0.123
	Proximity PMC	Ref	-0.025	0.042	0.547	-0.089	0.081	0.271	-0.054	0.060	0.367	-0.008	0.056	0.884	-0.015	0.087	0.864	0.008	0.105	0.937	-0.062	0.083	0.455
		Visit 2	-0.168	0.067	**0.013**	-0.047	0.134	0.726	-0.021	0.095	0.828	-0.158	0.092	0.086	-0.314	0.146	**0.031**	0.230	0.182	0.208	-0.450	0.139	**0.001**
		Visit 3	-0.281	0.089	**0.002**	-0.410	0.175	**0.020**	-0.255	0.126	**0.043**	-0.147	0.120	0.224	-0.387	0.190	**0.042**	0.348	0.280	0.215	-0.371	0.180	**0.040**
GRN	Distant PMC	Ref	0.001	0.023	0.978	-0.004	0.045	0.930	-0.001	0.033	0.977	-0.014	0.031	0.644	0.062	0.049	0.206	-0.009	0.066	0.890	0.005	0.046	0.920
		Visit 2	-0.014	0.035	0.681	0.017	0.070	0.804	0.045	0.049	0.359	-0.049	0.047	0.300	-0.057	0.076	0.456	-0.065	0.109	0.551	0.004	0.073	0.961
		Visit 3	-0.058	0.042	0.168	-0.060	0.083	0.473	-0.092	0.059	0.121	-0.009	0.057	0.874	-0.102	0.091	0.258	0.107	0.154	0.489	-0.136	0.086	0.117
	Proximity PMC	Ref	0.019	0.039	0.627	0.012	0.077	0.874	0.020	0.056	0.720	0.052	0.053	0.327	-0.019	0.083	0.817	0.045	0.129	0.728	-0.012	0.078	0.878
		Visit 2	0.007	0.057	0.900	0.200	0.113	0.076	-0.021	0.080	0.794	-0.065	0.077	0.400	-0.121	0.122	0.321	0.340	0.205	0.099	-0.049	0.117	0.676
		Visit 3	-0.148	0.059	**0.013**	-0.260	0.118	**0.028**	-0.285	0.084	**0.001**	-0.223	0.081	**0.006**	-0.089	0.128	0.486	0.188	0.259	0.470	0.029	0.122	0.813
MAPT	Distant PMC	Ref	0.000	0.036	0.992	-0.008	0.069	0.912	0.018	0.051	0.723	-0.013	0.048	0.787	0.045	0.075	0.548	-0.028	0.102	0.780	-0.013	0.071	0.859
		Visit 2	0.000	0.052	0.992	-0.053	0.103	0.607	-0.059	0.073	0.418	0.120	0.070	0.087	-0.039	0.112	0.726	-0.034	0.154	0.824	-0.067	0.108	0.537
		Visit 3	0.138	0.068	**0.042**	-0.022	0.135	0.873	0.010	0.096	0.915	0.197	0.092	**0.033**	0.298	0.146	**0.042**	0.232	0.253	0.360	0.156	0.139	0.263
	Proximity PMC	Ref	0.000	0.052	0.995	-0.045	0.102	0.660	0.003	0.075	0.973	0.027	0.071	0.703	-0.011	0.110	0.918	0.013	0.150	0.931	-0.019	0.104	0.852
		Visit 2	0.030	0.070	0.672	-0.007	0.141	0.960	0.108	0.099	0.275	0.009	0.096	0.922	0.067	0.154	0.665	0.086	0.217	0.693	0.015	0.150	0.919
		Visit 3	-0.074	0.093	0.428	-0.282	0.185	0.127	-0.142	0.131	0.281	-0.027	0.126	0.830	-0.167	0.201	0.405	0.210	0.458	0.646	0.400	0.191	**0.036**

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Supplementary Table 3. *Mixed effects model for global cognitive test scores.*

The reference is a female, non-carrier at baseline. The global practice effect in NC was approximately 0.15 SD per visit. We included baseline scores in our statistical models to eliminate the effect of novelty to a task (i.e. stress response at first testing causing interference with performance), and the dilemma of regression to the mean often seen in repeated testing situations. C9, chromosome 9 open reading frame 72; GRN, progranulin; MAPT, microtubule associated protein tau; NC, non-carriers; PMC, presymptomatic mutation carriers; AMC, affected mutation carriers.

Fixed effects	Estimate	Standard Error	p-value
Intercept	0.000	0.076	0.996
Visit 2	0.167	0.026	**<0.001**
Visit 3	0.270	0.044	**<0.001**
PMC-C9	-0.025	0.023	0.279
PMC-GRN	0.005	0.021	0.825
PMC-MAPT	-0.002	0.030	0.959
Years from baseline	-0.085	0.013	**<0.001**
Male	-0.016	0.013	0.229
Age	0.003	0.003	0.416
Age^2	0.000	0.000	0.057
Education (years)	0.003	0.002	0.151
Baseline global score	0.888	0.013	**<0.001**
Visit 2*PMC-C9	-0.114	0.036	**0.002**
Visit 3*PMC-C9	-0.104	0.047	**0.027**
Visit 2*PMC-GRN	-0.008	0.032	0.790
Visit 3*PMC-GRN	-0.086	0.037	**0.021**
Visit 2*PMC-MAPT	0.011	0.043	0.795
Visit 3*PMC-MAPT	0.064	0.057	0.264
Random effects	**Variance**		
Individual variance of intercept	0.006		
Site variance of intercept	0.00002		
Residual variance	0.04		

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1.5 References

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