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

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.

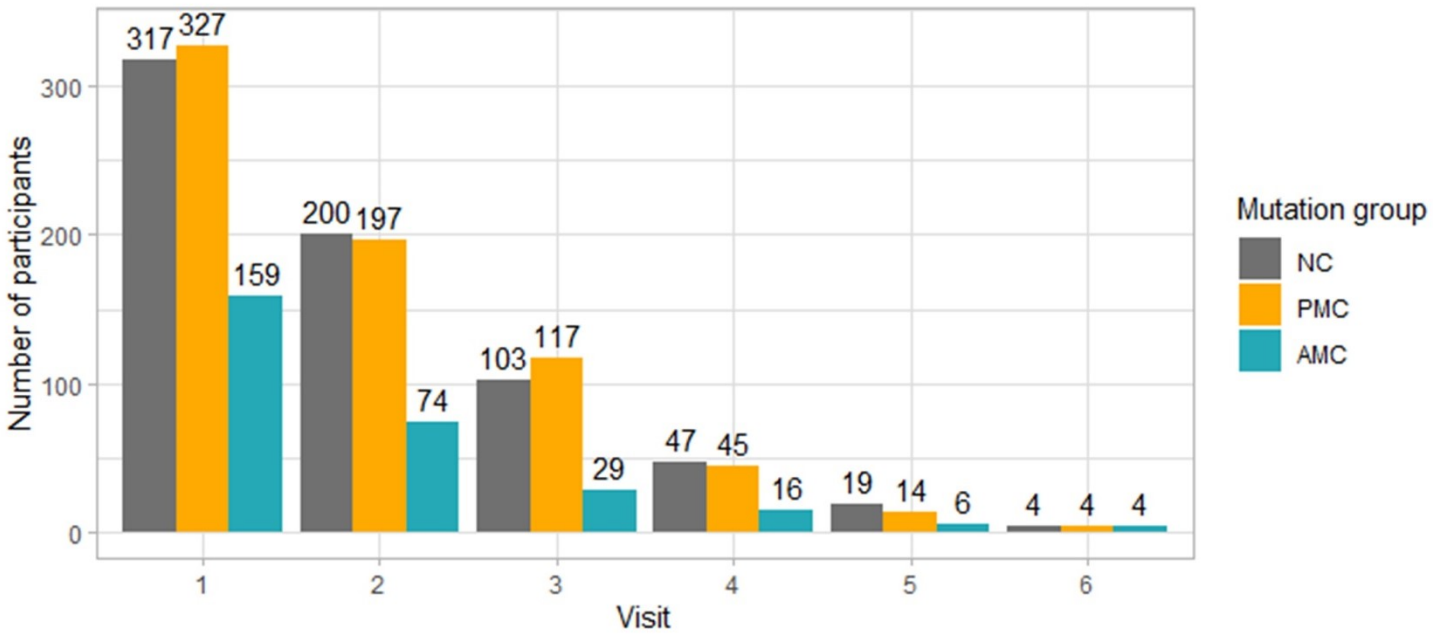
Supplementary Table 1. Demographic data. *NC, non-carriers; PMC, presymptomatic mutation carriers; AMC, affected mutation carriers; C9orf72, chromosome 9 open reading frame 72; GRN, progranulin; MAPT, microtubule associated protein tau; TBK1, TANK-binding kinase 1; SD, standard deviation.*

	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)		

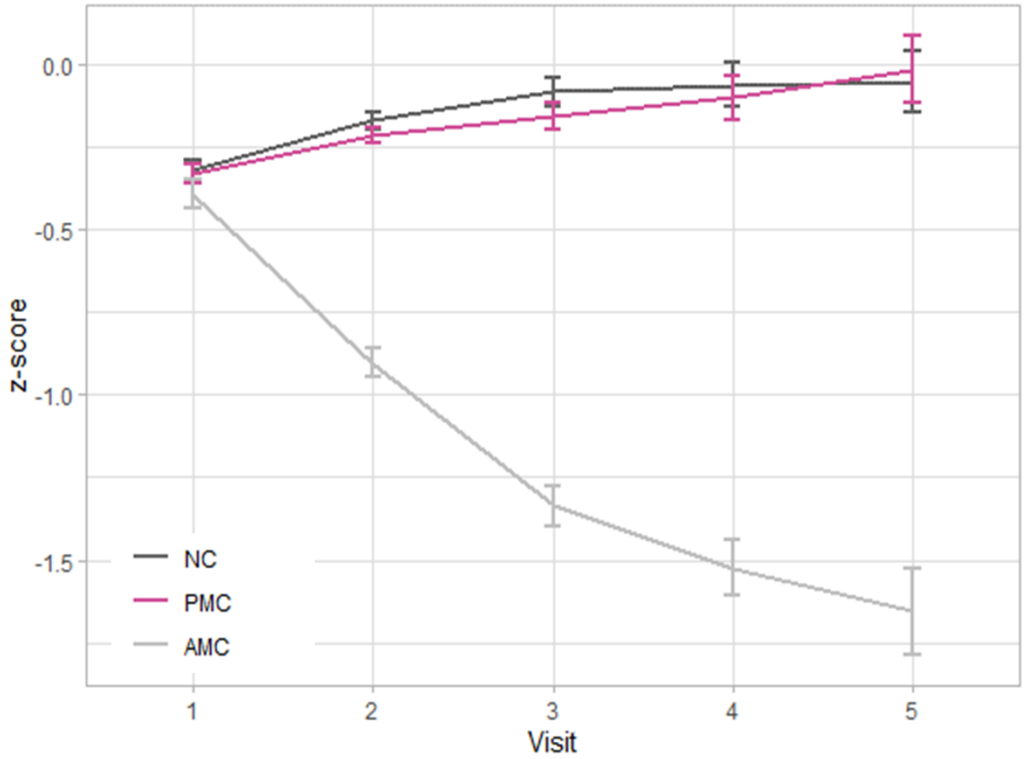
[a] ANOVA. Differences in age between AMC vs PMC and AMC vs NC. No difference between PMC and NC.

[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.



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 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.*

***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**

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		

1.5 References

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