Practice effects are reduced within prodromal and symptomatic FTD mutation carriers using the Ignite app

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Background

Practice effects can be observed on repeated cognitive testing and are often viewed as potential sources of bias. However, there is mounting evidence that their absence or reduction can indicate early changes in cognition, with decreased 'learning over repeated exposure' seen in those with mild cognitive impairment.

A recent GENetic FTD Initiative (GENFI) study demonstrated practice effects are diminished in *C9orf72* and *GRN* mutation carriers proximal to disease onset compared to controls at testing intervals of one year *(Öijerstedt et al, 2022)*.

The aim of this study is to explore how practice effects differ in the GENFI cohort at shorter time intervals using *Ignite,* an iPad-based set of cognitive tests, with the aim of exploiting this understanding to detect subtle cognitive impairment within clinical trials.

Methods

Ignite, an iPad based cognitive app

- 20-25 min test of cognitive function, repeated 4 x over 4 weeks
- Speed-accuracy trade off scores calculated by dividing the total correct by average response time
- Outcomes converted to z-scores using normative data from >2000 individuals, adjusting for age, sex and education
- Composite cognitive scores calculated as the mean score of tests assessing the same cognitive domain

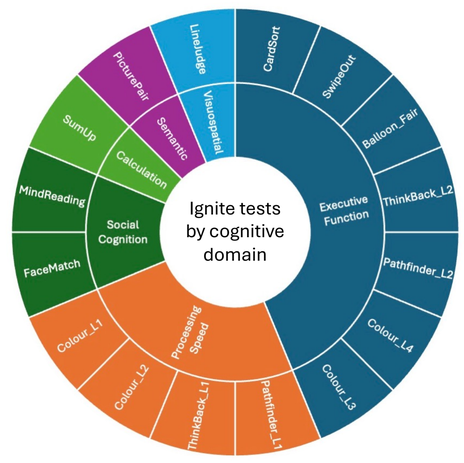
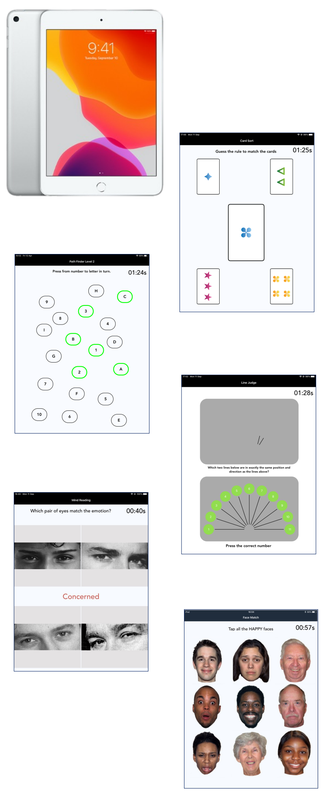


Figure 1: Ignite tests by cognitive domain. Composite scores are calculated for Executive function, Processing speech and Social Cognition, by calculating the mean.



Participants

- 73 GENFI participants with plasma neurofilament light chain (NfL) data were included in this preliminary analysis. 47 were mutation carriers (29 C9orf72, 16 MAPT, 2 GRN), and 26 were mutation negative controls.
- Mutation carriers were split into 3 groups:
  - **SCs (Symptomatic Carriers):** 7 carriers with bvFTD.
  - **PCs (Prodromal Carriers):** 10 were deemed prodromal on the basis of a CDR® plus NACC FTLD global score of 0.5 and raised plasma NfL. Raised NfL was defined as ≥ 13.6pg/ml, a level associated with increased risk of phenoconversion over 2 years (Rojas et al 2021).
  - **ACs (Asymptomatic Carriers):** The remaining 30 carriers.

Analysis

- A Mixed Model for Repeated Measures (MMRM) analysis was performed in Stata and RStudio to examine change over time.

Results (1)

Prodromal carriers show altered practice effects in a burst testing protocol using *Ignite*

	Controls	Asymptomatic Carriers	Prodromal Carriers	Symptomatic Carriers
Number at baseline	26	30	10	7
Age in years, mean (sd)	49.7 (13.9)	40.7 (9.2)	53.4 (9.2)	63.7 (3.5)
Female, n (%)	13 (50%)	14 (47%)	6 (60%)	2 (29%)
Education in years, mean (sd)	16 (2.3)	15.5 (2.1)	15 (2.6)	12.9 (3.0)
Plasma NfL pg/ml, mean (sd)	11.8 (8.3)	8.9 (2.7)	24.9 (9.1)	26.4 (16.0)
Completed all 4 assessments	77% (20)	77% (23)	80% (8)	57% (4)
Completed ≥ 3 assessments	92% (24)	93% (28)	90% (9)	86% (6)
Completed ≥ 2 assessments	100% (26)	100% (30)	90% (9)	100% (7)

Table 1: Baseline characteristics of the four groups

- Controls and ACs both showed significant improvements ($p<0.05$) across all 16 tests between timepoint 1 and 4. PCs showed significant improvements across 10/16 tests. SCs showed significant improvements on only 2/16 tests.
- Controls showed greatest improvement between the first and second timepoint. Because of this, maximal differences between groups were observed in a cross-sectional analysis at timepoint 2 (table 2).

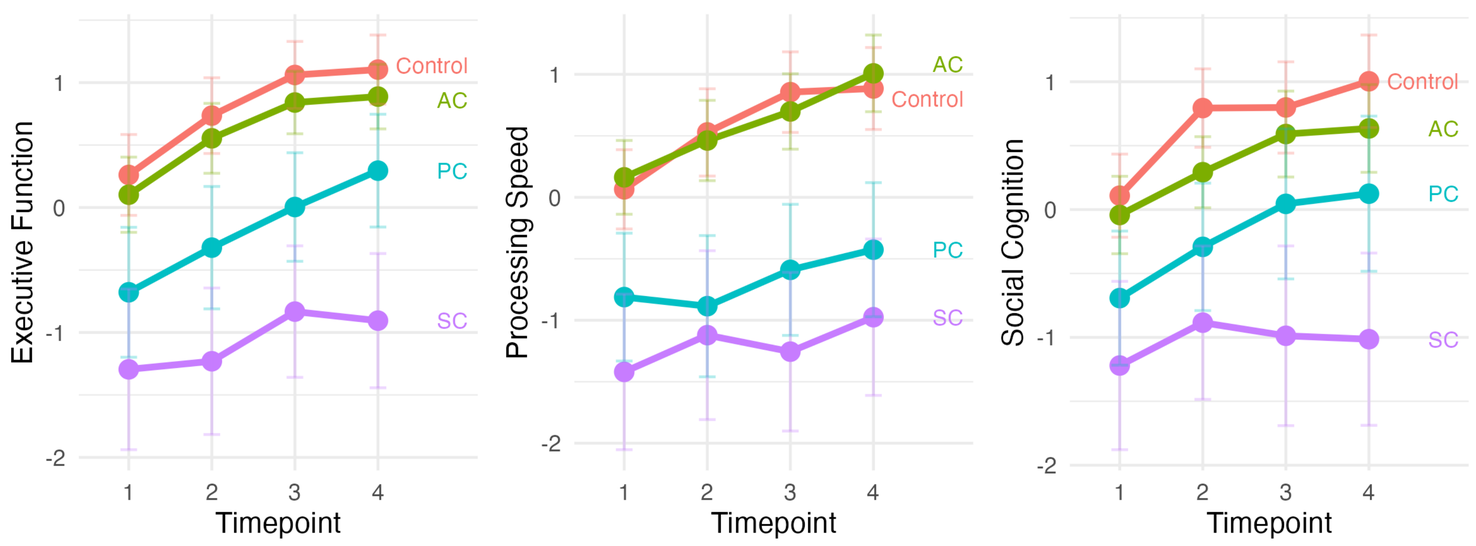


Figure 2: Change over 4 timepoints by group, with each graph representing the 3 major cognitive domains assessed by Ignite. Estimated means and error bars with 95% confidence interval, derived from MMRM analysis, are plotted.

Results (2)

Between group differences are enhanced by practice effects at Timepoint 2

Group Comparisons at Timepoint 2

	AC vs Controls				PC vs Controls				SC vs Controls			
Variable	Estimate	Lower CL	Upper CL	p-value	Estimate	Lower CL	Upper CL	p-value	Estimate	Lower CL	Upper CL	p-value
Executive Function	−0.18	−0.73	0.36	0.816	**−1.06**	**−1.82**	**−0.30**	**0.003**	**−1.97**	**−2.84**	**−1.10**	**< 0.001**
Processing Speed	−0.07	−0.70	0.57	0.993	**−1.41**	**−2.30**	**−0.52**	**< 0.001**	**−1.65**	**−2.67**	**−0.63**	**< 0.001**
Social Cognition	−0.50	−1.05	0.04	0.083	**−1.09**	**−1.86**	**−0.31**	**0.002**	**−1.68**	**−2.57**	**−0.79**	**< 0.001**
Calculation	−0.06	−0.87	0.76	0.998	**−1.33**	**−2.46**	**−0.19**	**0.016**	**−1.87**	**−3.17**	**−0.57**	**0.002**
Semantic Knowledge	−0.69	−1.80	0.41	0.357	**−2.44**	**−4.02**	**−0.87**	**< 0.001**	**−4.62**	**−6.42**	**−2.82**	**< 0.001**
Visuospatial	−0.26	−0.96	0.45	0.775	−0.95	−1.94	0.04	0.064	**−1.80**	**−2.94**	**−0.67**	**< 0.001**

Table 2: Score differences by cognitive domain between groups at timepoint 2. Highlighted rows reach statistical significance ($p<0.05$). ACs = Asymptomatic Carriers, PCs = Prodromal Carriers, SCs = Symptomatic Carriers. CL = Confidence Level.

Conclusions

- Early data from the UCL GENFI cohort demonstrates significant differences in cognition in the prodromal FTD mutation carriers compared to controls, detected using the iPad test *Ignite*.
- Cross-sectional differences are maximal at timepoint 2, given differential practice effect trajectories of each group.
- All groups showed a degree of practice effect on composite cognitive scores when comparing the 1st and the 3rd, and the 1st and the 4th timepoint, but this was greatest in the Control group, and smaller in the Prodromal and Symptomatic Carrier groups.
- Only Asymptomatic Carriers benefitted significantly from a 4th timepoint.

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