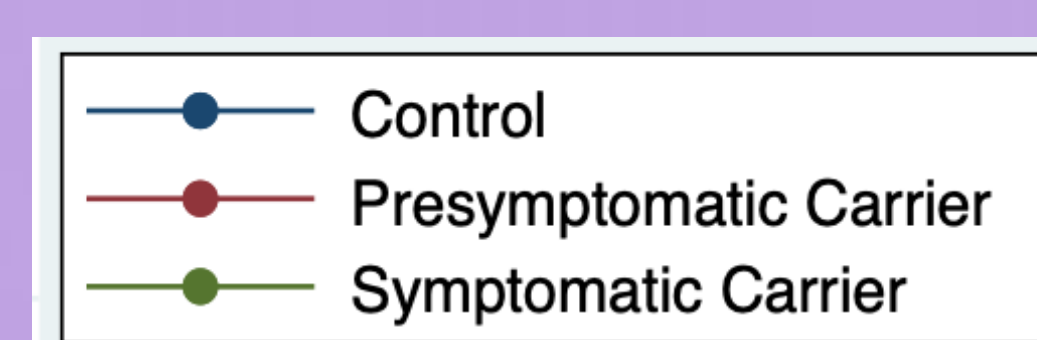
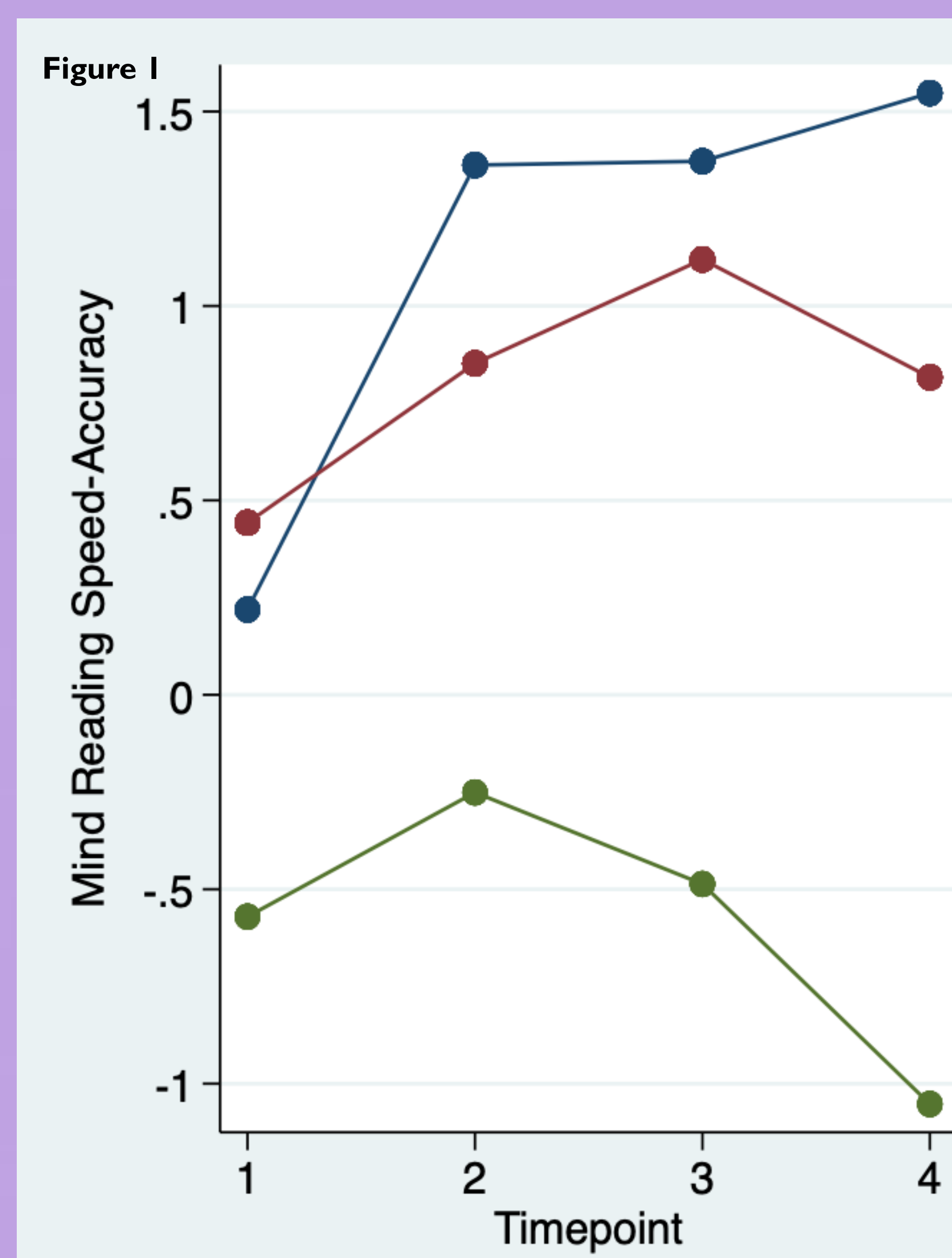


Examining practice effects within the GENFI presymptomatic FTD cohort using computerised cognitive testing

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Practice effects are diminished within a presymptomatic genetic FTD group compared to controls



Across tests of social cognition, calculation, working memory, and executive function

1. 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.

2. Methods

Participants

36 individuals from the GENFI cohort (24 presymptomatic, gene carriers, 3 symptomatic participants, and 9 controls) undertook a 'burst testing' protocol, completing *Ignite* across 4 timepoints: baseline, 1 week, 2 weeks and 4 weeks.

Computerised testing

Ignite includes 16 computerised tasks designed to test executive function and processing speed, semantic knowledge, social cognition, calculation and visuospatial skills. Tests are adapted from traditional neuropsychology tests such as the Stroop test, Wisconsin Card Sorting, N-back, Camel and Cactus, Reading the Mind in the Eyes, and the Ekman Faces Emotion Recognition Task. For the 11 tests that output total correct and reaction time, a single speed-accuracy trade-off score was calculated by dividing the total number of correct items by average reaction time.

Statistical analysis

Z-scores were calculated across tasks, adjusting for age, sex and education, using reference data from a normative sample of >2000 individuals. A Mixed Models for Repeated Measures (MMRM) approach was used in Stata v17 to analyse the results, examining both within group and between group practice effects. This method was chosen as it is robust to data missing at random and it does not assume a linear trajectory of change.

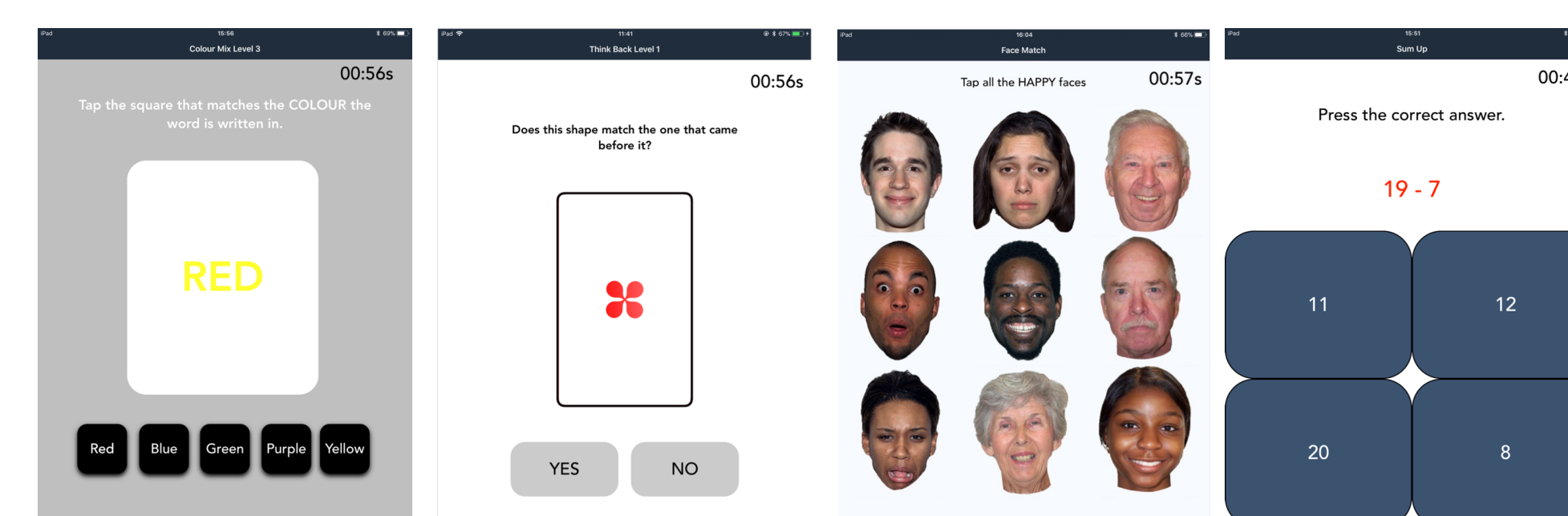


Figure 2 – *Ignite* tests from left to right: Colour Mix (Stroop test), Think Back (N-back task), Face Match (Ekman Faces Emotion Recognition task), Sum Up (Graded Difficulty Arithmetic Test)

3. Results

• Within group practice effects

- Significant overall improvement was observed across:
 - 13/16 tasks in the presymptomatic group
 - 11/16 in the control group, with a trend towards improvement across all tasks
 - 3/16 tasks in the symptomatic group

• Between group comparisons of practice effect

- The control group showed a significantly greater improvement on the Mind Reading task between timepoints 1 and 4 compared to both the presymptomatic and symptomatic gene carrier groups.
- A proportion of the control group showed a decline in performance between week 2 and 4. When excluding this timepoint and comparing change between baseline and timepoint 3, several other tests showed significant differences between the control and presymptomatic groups, and these are depicted in table 1.

	Difference in change score	p value	95% Confidence Interval	
Colour Mix Level 1	-0.7157039	0.018	-1.30675	-0.1246547
Think Back Level 1	-0.7194692	0.025	-1.35064	-0.0883017
Balloon Score	-0.7699946	0.038	-1.49916	-0.0408278
Sum Up	-0.4249755	0.009	-0.74308	-0.1068689

Table 1 – Differences in change scores (control group change score subtracted from presymptomatic group change score), with negative differences representing a diminished practice effect in the presymptomatic group compared to the control group

4. Conclusions

- The control and presymptomatic groups had significant practice effects across the timepoints, whereas the symptomatic group showed improvement across just 3 tasks. However this group was small (n=3).
- Significant differences in practice effect, with the control group improving to a greater degree than the presymptomatic group, emerged on the Mind Reading, Colour Mix Level 1, Think Back Level 1, Balloon Score, and Sum Up tasks. These are tests of social cognition, executive function, working memory, and calculation.
- Work is ongoing to expand this burst testing protocol to a wider group within GENFI, and the presymptomatic group will be stratified according to proximity markers such as plasma NfL.