GENFI-Cog: Developing a cognitive composite score for presymptomatic genetic FTD therapeutic trials

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Background

Clinical drug trials are likely to have their most profound effect in the presymptomatic phase of neurodegenerative diseases. In monogenic disorders such as familial frontotemporal dementia (FTD) presymptomatic testing of therapies is possible by including at-risk individuals within trials. However, traditional outcome measures such as cognitive tests may not be well suited to trials of this nature due to a lack of sensitivity to change during the presymptomatic period. Cognitive composites which combine multiple tasks are commonly more sensitive and are often used as primary endpoints in such trials but at present none exist in FTD.

The Cohort

We aimed to utilise the cross-sectional and longitudinal neuropsychology data from the GENFI cohort – 177 *GRN* (134 presymptomatic gene carriers; 43 symptomatic gene carriers); 73 *MAPT* (52 presymptomatic gene carriers; 21 symptomatic gene carriers); 171 *C9orf72* (108 presymptomatic gene carriers; 63 symptomatic gene carriers), and 259 gene negative controls – to develop a cognitive composite test, the GENFI-Cog, sensitive to predicting cognitive decline in late presymptomatic FTD.

Methods

Where available we used the baseline and 12 month follow-up data from the 13 cognitive assessments in the GENFI study. Preliminary analysis of the data using independent sample *t*-tests comparing each of the genetic subgroups revealed a significant difference across a number of different cognitive tests (figure 1): in *C9orf72* carriers executive function, naming and social cognition were sensitive to cognitive decline; in *GRN* carriers only tests of executive function were significantly different; and in *MAPT* carriers executive function, episodic memory and semantic knowledge were impaired. Following this, separate logistic regression models were built to classify participants using the results of the *t*-tests. Each model was built using backward elimination. Cognitive assessments were retained if its *p* value was less than 0.1, and these were then used to form the composite (figure 2).

Results

So far we have created a combined symptomatic cognitive composite score consisting of 3 assessments: Digit Span Forwards, Boston Naming Test and Block Design which is able to detect a 50% treatment effect using a sample size of 90 participants. Using this combination of tests together as a composite allows us to test a wide range of cognitive domains which is far superior to one single test.

Discussion

Our work so far shows that the GENFI-Cog has the potential to be used as a primary endpoint in symptomatic clinical trials for genetic FTD. The aim of the composite is to improve power compared to the most sensitive single test items in tracking presymptomatic FTD. Additional work is being performed to create three additional composites for presymptomatic genetic FTD.

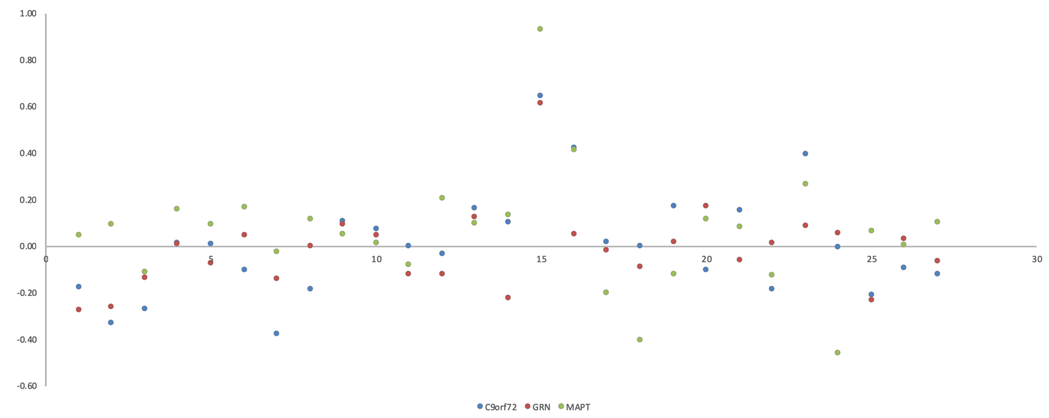

Figure 1. Mean change in z-score between baseline and follow-up on each of the neuropsychological outcome measures (27 from 13 tests) for each of the three genes separately (blue = *C9orf72*, red = *GRN*, green = *MAPT*)

Subjects included in the composite if at least two data points are available
(0 and 12 months)

126 presymptomatic subjects excluded
(52 *GRN*, 59 *C9orf72*, 15 *MAPT*)

68 symptomatic subjects excluded
(23 *GRN*, 36 *C9orf72*, 9 *MAPT*)

All GENFI Neuropsychology assessments considered as candidates for composite

Cognitive Domain	Assessment
Executive Function	Digit Span Backwards / Trail Making Test B / Phonemic Fluency / Stroop – ink colour naming
Speed and Attention	Digit Span Forwards / Trail Making Test A / Digit Symbol / Stroop – colour and word naming
Social Cognition	Faux Pas Test / Ekman Facial Emotion Recognition
Language and Semantics	Boston Naming Test / Modified Camel and Cactus Test / Category Fluency
Episodic Memory	Free Cued Selective Reminding Test / Benson Figure Recall
Visuospatial Function	Benson Figure Copy / Block Design

Independent sample *t*-tests were performed on baseline, follow-up and change scores

Separate logistic regression models were built to classify participants. Each model was built using backward elimination – cognitive assessments were retained if its *p* value was significant

Results from the logistic regression were used to form the basis of the GENFI-Cog

Figure 2. Flowchart showing the steps to create the GENFI-Cog

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