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 significant, 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.

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

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>Assessment</th>
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<tbody>
<tr>
<td>Executive Function</td>
<td>Digit Span Forwards / Trail Making Test B / Phonemic Fluency / Stroop – ink colour naming</td>
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<tr>
<td>Speed and Attention</td>
<td>Digit Span Forwards / Trail Making Test A / Digit Symbol / Stroop – colour and word naming</td>
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<tr>
<td>Social Cognition</td>
<td>False Face Test / Elman Facial Emotion Recognition</td>
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<tr>
<td>Language and Semantics</td>
<td>Boston Naming Test / Modified Camel and Cactus Test / Category Fluency</td>
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<tr>
<td>Episodic Memory</td>
<td>Free Cued Selective Reminding Test / Benton Figure Recall</td>
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<tr>
<td>Visuospatial Function</td>
<td>Benton Figure Copy / Block Design</td>
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</tbody>
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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