Performance on gene specific cognitive composites (GENFI-Cog) in the Genetic FTD Initiative

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Background

Familial frontotemporal dementia (fFTD) shows gene-specific patterns of cognitive decline (Poos et al., 2025). Conventional neuropsychological testing batteries may lack the sensitivity to detect these differences. The GENFI-Cog addresses this by integrating multiple cognitive domains into a single weighted metric.

Aim: Determine whether cognitive composite scores distinguish clinical disease stages and are associated with gold standard markers of disease severity.

Methods

We analysed neuropsychological data from 1,245 GENFI participants (mean age 46.6 years [12.8]; 44% male; education 14.8 years [3.2].) Mutation carriers were stratified by disease stage using CDR+NACC FTLD-NM, asymptomatic (0), prodromal (0.5), or symptomatic (≥1).

Group	N	CRD 0	CDR 0.5	CDR 1	CDR >1
C9orf72	372	198	92	36	46
GRN	262	184	57	14	7
MAPT	134	61	39	18	16
Non-carrier	610	-	-	-	-

Raw test scores were converted into W-scores adjusted for age, sex, education, and language. These scores were then combined into previously derived composites (GENFI-Cog), using linear regression coefficients to weight test contributions.

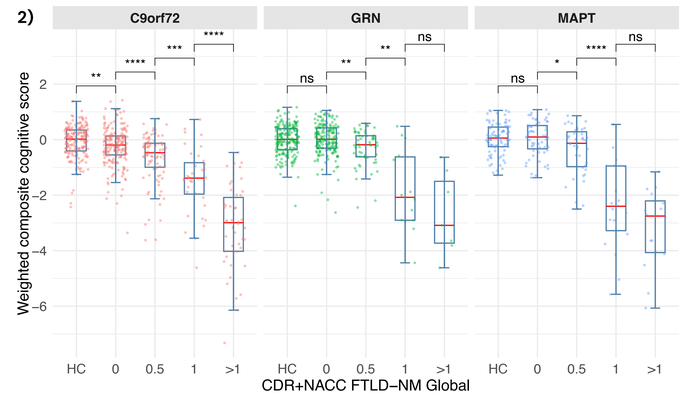
Bootstrapped linear regression models were used to assess score differences across disease stages. Spearman's and Pearson's correlation coefficients examined relationships between weighted composite scores, CDR+NACC FTLD-NM Sum of Boxes scores and neurofilament light levels (NfL; log-transformed due to non-normal distribution).

C9orf72	GRN	MAPT
Category fluency	Camel and Cactus Test	Camel and Cactus Test
Color Word Interference Test – color and word naming	Color Word Interference Test – ink naming	Boston Naming Test
Color Word Interference Test – ink naming	Trail Making Test – part B	Color Word Interference Test – color naming
Trail Making Test – part B	Benson Figure recall	Benson Figure recall
Benson Figure Copy	FCSRT immediate total recall and delayed free recall	FCSRT immediate free and total recall
FCSRT immediate free recall	Facial Emotional Recognition Test	Facial Emotional Recognition Test
Facial Emotional Recognition Test		

Figure 1. Breakdown of GENFI-Cog measures by cognitive domain. Adapted from Poos et al., (2022)

Results

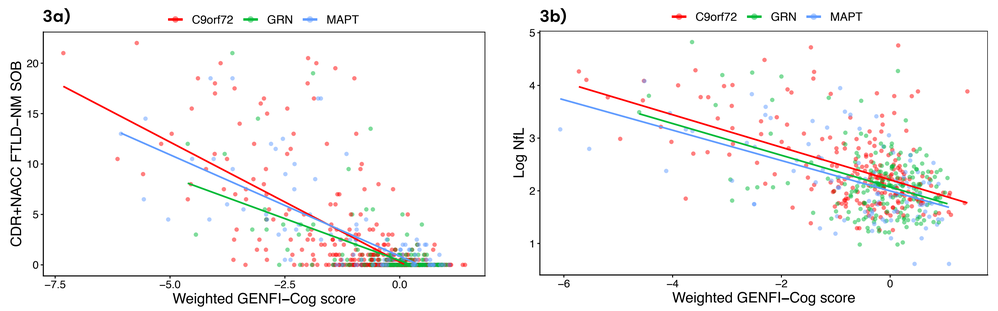
Figure 2. Boxplot comparing cognitive performance across CDR+NACC FTLD-NM stages against healthy controls (HC), within gene groups. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, ns = not significant.



Across all genetic groups, composite scores declined significantly with increasing disease stage.

All mutation carrier groups at the prodromal stage performed significantly worse than the non-carrier group (p<0.005).

Small but significant difference in composite scores in asymptomatic C9orf72 expansion carriers (CDR 0) as a group compared with non-carrier controls (p<0.001).



Composite scores correlated negatively with both CDR-SOB (r = -0.60 to -0.67, p<0.001) and NfL levels (r = -0.46 to -0.48, p<0.001).

Figure 3 a and b. Correlations between composite scores, CDR+NACC FTLD-NM Sum of Boxes, and log-transformed neurofilament light protein concentrations (NfL).

Key Takeaways

- GENFI-Cog composite scores sensitively capture gene-specific patterns of cognitive decline
- Findings support composite scores as robust measures of preclinical cognitive change
- Longitudinal analysis will allow for an improved understanding of disease progression and more accurate fFTD prognostic models

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1. Poos JM, et al., on behalf of GENFI. Cognitive composites for genetic frontotemporal dementia: GENFI-Cog. *Alzheimers Res Ther.* 2022;14(1):10.
2. Poos JM, van den Berg E, de Boer L, et al. Neuropsychological profiles in genetic frontotemporal dementia: a meta-analysis and systematic review. *Aging Dis.* 2025;16(3):1378–1396.

Acknowledgements: We thank the research participants for their contribution to the study. JDR has current funding from the Bluefield Project, the National Brain Appeal, the Rosetrees Trust, the Kissick Family Foundation and the NIHR UCL/H Biomedical Research Centre and has previously received funding from a Miriam Marks Brain Research UK Senior Fellowship, an MRC Clinician Scientist Fellowship (MR/M008525/1), the NIHR Rare Disease Translational Research Collaboration (BRC149/NS/MH), the MRC UK GENFI grant (MR/M023664/1), and the JPND GENFI-PROX grant (2019-02248). LCR is supported by a Career Progression Award from Alzheimer's Society UK (grant number 639). RC is supported by the Rosetrees Trust. PF is supported by an Alzheimer's Society PhD studentship. AB is supported by a GENFI studentship in association with the National Brain Appeal.

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