

# Performance on gene specific cognitive composites (GENFI-Cog) in the Genetic Frontotemporal dementia (GENFI) study

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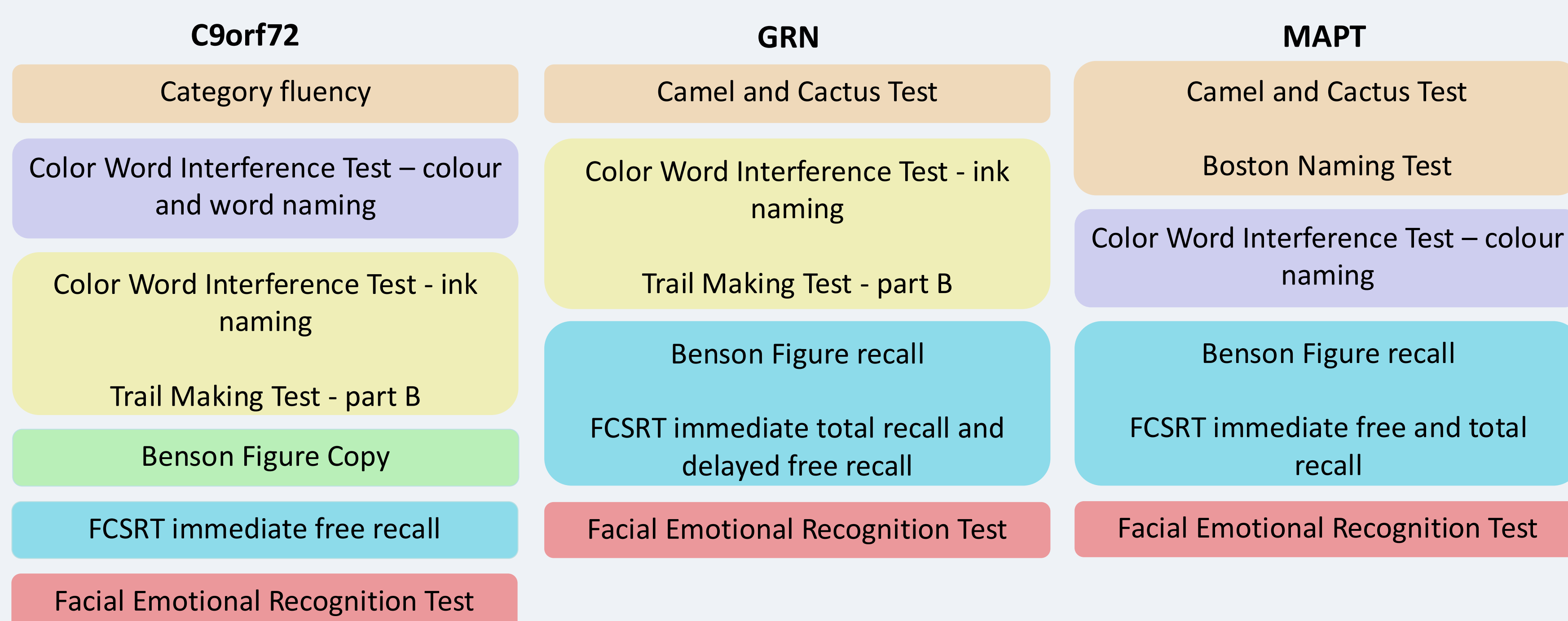
## Background

Understanding early cognitive changes in familial frontotemporal dementia (fFTD) remains a major challenge, particularly distinguishing the timing of onset and progression profiles of genetic subtypes. While neuropsychological testing is used in both research and clinical settings, conventional testing batteries may lack the sensitivity to detect gene-specific patterns of decline. The GENFI-Cog addresses this by integrating multiple cognitive domains into one weighted metric. Here, we aimed to characterise gene-specific cognitive trajectories in asymptomatic and symptomatic *C9orf72*, *GRN*, and *MAPT* mutation carriers by comparing GENFI-Cog composite scores across disease stages.

## Methods

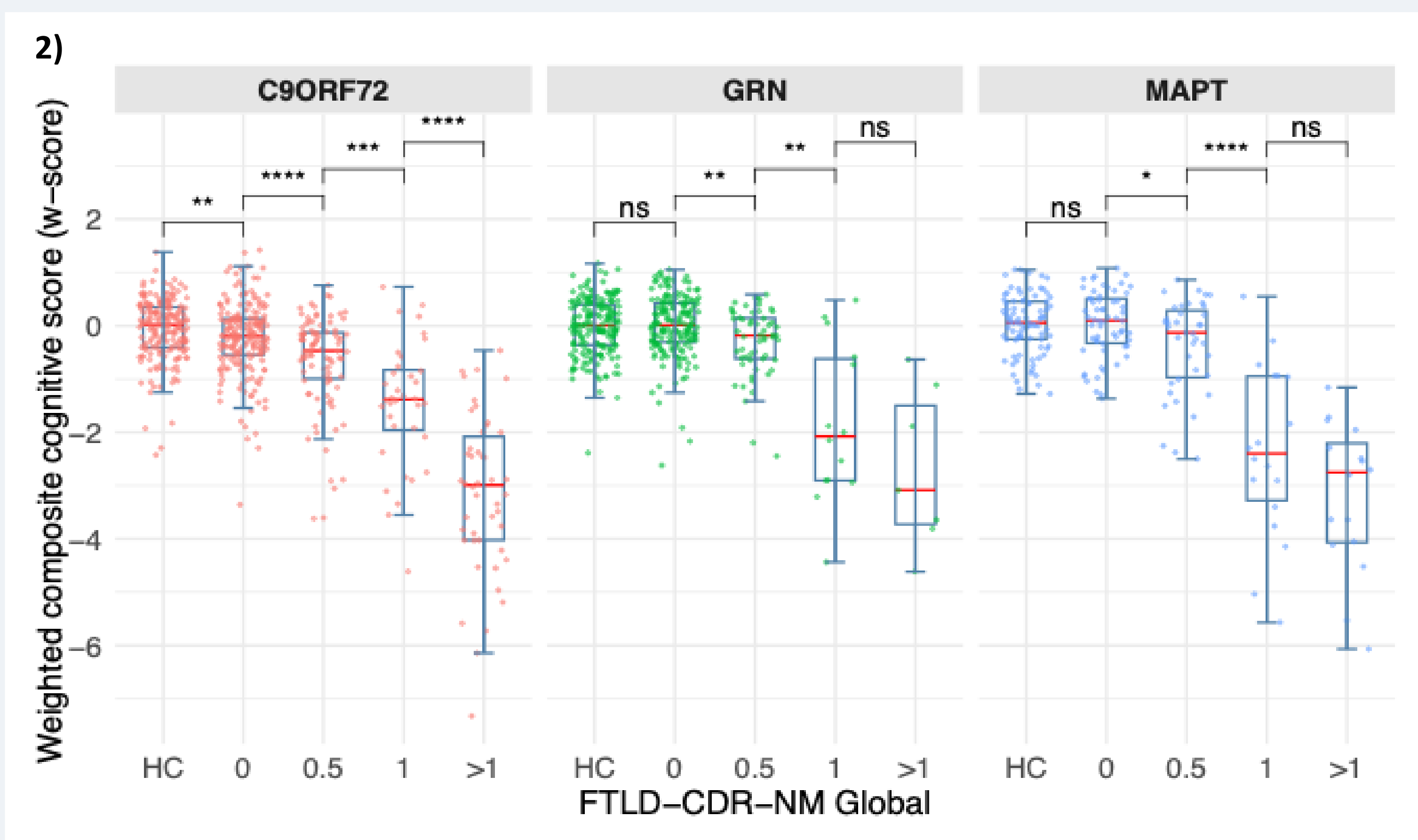
We analysed neuropsychological data from 1,245 GENFI participants (mean age 46.6 years [12.8]; 44% male; education 14.8 years [3.2]), including 372 *C9orf72*, 262 *GRN*, and 134 *MAPT*, and 610 non-carriers. Mutation carriers were stratified by disease stage using CDR+NACC FTLD-NM, asymptomatic (0), prodromal (0.5), or symptomatic ( $\geq 1$ ). Raw test scores were converted into W-scores adjusted for age, sex, education, and language. These scores were then combined based on previously derived gene-specific composite scores (GENFI-Cog), using linear regression coefficients to weight individual test contributions.

Cross-sectional differences in composite scores were assessed across disease stages using bootstrapped linear regression models. In addition, Spearman's correlation coefficients were performed to assess associations between weighted composite scores and CDR+NACC FTLD-NM Sum of Boxes scores, separately for each genetic group.



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

## Results



**Figure 2.** Boxplot comparing cognitive performance across CDR+NACC FTLD-NM stages against healthy controls, within gene groups.

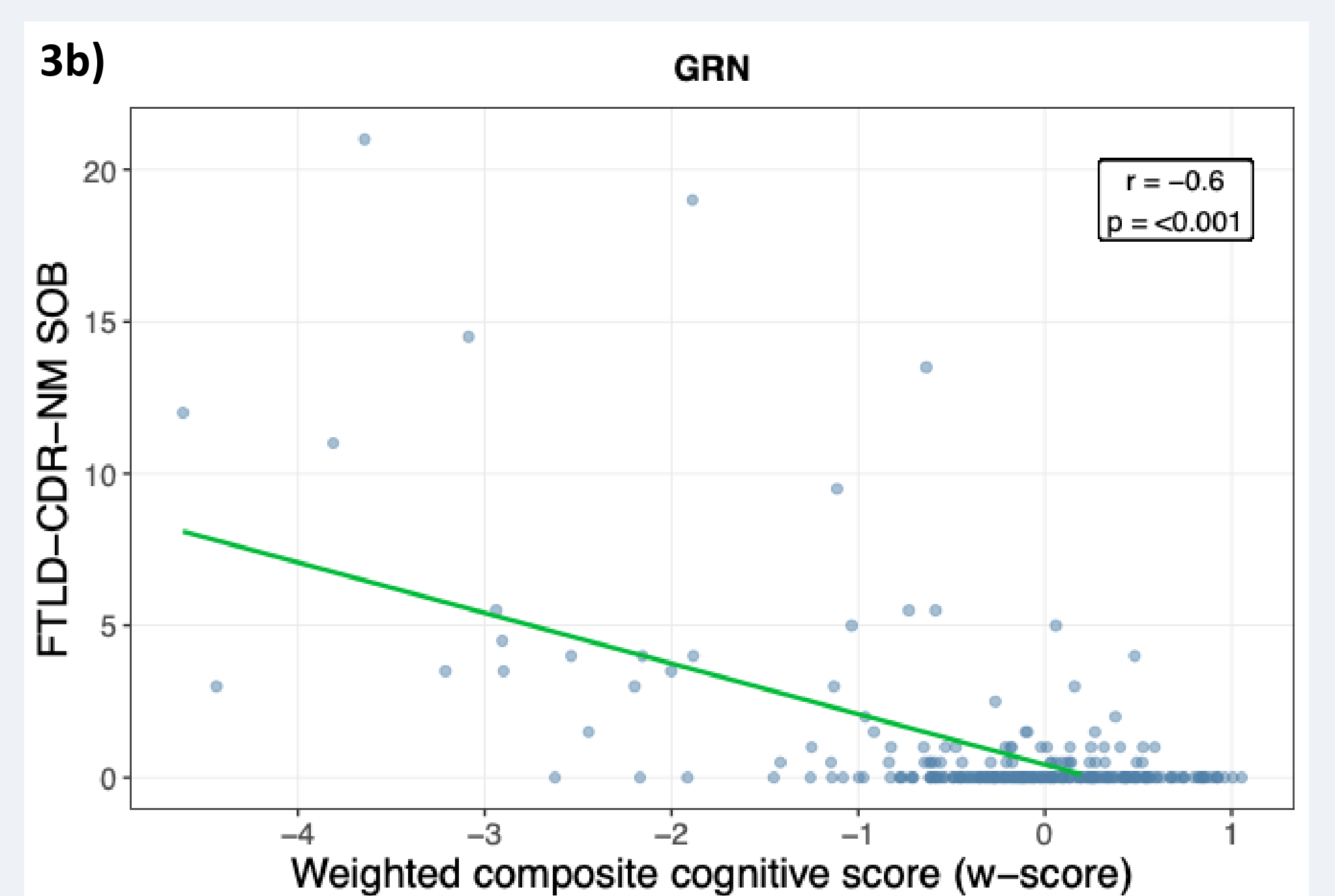
Across all genetic groups, cognitive composite scores significantly declined as disease severity increased. All mutation carriers, with a CDR score of 0.5 or above, performed worse than non-carriers ( $p < 0.005$ ). Notably, asymptomatic *C9orf72* carriers (CDR 0), also performed significantly worse than non-carriers ( $p < 0.001$ ). In *GRN* and *MAPT* carriers, composite scores declined more abruptly from the prodromal stage (CDR 0.5) onwards, and post-conversion variability was notably higher.

## Results

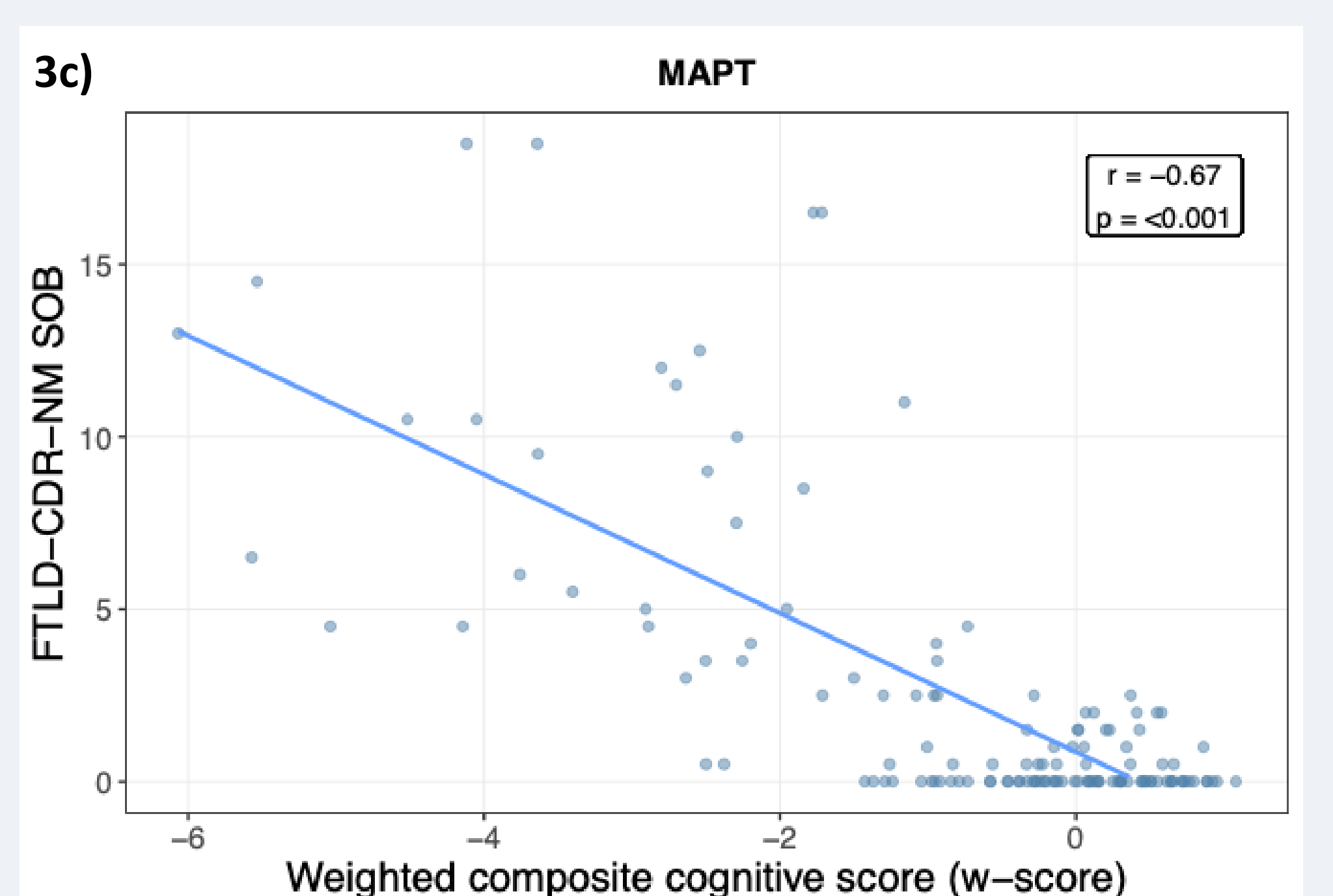
**Figure 3 a to c.** Correlations between weighted composite cognitive score and CDR+NACC FTLD-NM, by gene group.



In *C9orf72* expansion carriers, weighted composite cognitive scores demonstrated a strong negative correlation with CDR+NACC FTLD-NM Sum of Boxes scores ( $r = -0.65$ ,  $p < 0.001$ ), reflecting progressively poorer cognitive performance with greater clinical disease severity.



A significant negative association was also observed in *GRN* mutation carriers ( $r = -0.60$ ,  $p < 0.001$ ). Cognitive scores were more variable, particularly among individuals with higher Sum of Boxes scores



In *MAPT* carriers, composite scores showed the strongest negative correlation ( $r = -0.67$ ,  $p < 0.001$ ). The distribution reflected a more abrupt drop in cognitive performance with advancing clinical severity.

## Conclusion

GENFI-Cog composite scores sensitively capture gene-specific patterns of cognitive decline. The results also suggest early sensitivity to cognitive impairment, particularly in asymptomatic *C9orf72* expansion carriers, supporting the use of weighted composite measures to detect subtle, preclinical cognitive changes in fFTD. However, further longitudinal analysis of the GENFI-Cog will allow for an improved understanding of disease progression and more accurate fFTD prognostic models.

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