

# Investigating apathy across disease stages and genetic groups in frontotemporal dementia (FTD)

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### BACKGROUND

Apathy is a core symptom of frontotemporal dementia (FTD) and has a substantial impact on patients and caregivers. Research into apathy profiles in the presymptomatic stages of FTD is relatively limited. One scale used to assess apathy severity, is the brief version of the informant-rated Dimensional Apathy Scale (b-DAS). However, its application in FTD remains limited, and the trajectories of apathy across disease stages and genetic subtypes remain poorly characterised.

### METHODS

Participants were recruited as part of the GENetic Frontotemporal dementia Initiative (GENFI). A total of 515 individuals were included in the analyses, including 174 non-carrier controls, and 341 mutation carriers with C9orf72, GRN, or MAPT mutations (Table 1).

All participants underwent a standardised clinical assessment during their annual GENFI visit, including the CDR+NACC FTLD scores, incorporating neuropsychiatric and motor components (+NM). Participants were stratified using this into presymptomatic (CDR=0), prodromal (CDR=0.5), or symptomatic (CDR≥1).

|           | Non-carriers | Mutation carriers |             |             |             |             |            |             |             |            |
|-----------|--------------|-------------------|-------------|-------------|-------------|-------------|------------|-------------|-------------|------------|
|           |              | C9orf72 (n=184)   |             |             | GRN (n=104) |             |            | MAPT (n=53) |             |            |
|           |              | CDR=0             | CDR=0.5     | CDR≥1       | CDR=0       | CDR=0.5     | CDR≥1      | CDR=0       | CDR=0.5     | CDR≥1      |
| N         | 174          | 90                | 47          | 47          | 67          | 18          | 19         | 19          | 13          | 21         |
| Male (%)  | 42           | 37                | 36          | 57          | 39          | 28          | 63         | 58          | 46          | 48         |
| Age       | 49.5 (13.8)  | 42.1 (10.9)       | 50.2 (14.5) | 63.1 (10.9) | 52.0 (11.0) | 49.4 (13.4) | 61.2 (9.1) | 42.9 (10.7) | 44.2 (16.2) | 57.4 (8.3) |
| Education | 15.9 (3.11)  | 15.6 (2.5)        | 14.3 (2.9)  | 12.8 (3.5)  | 15.7 (3.7)  | 15.3 (2.7)  | 13.4 (3.4) | 14.3 (3.7)  | 15.2 (2.1)  | 13.7 (3.4) |

Table 1. Demographics

Apathy was assessed using the brief Dimensional Apathy Scale (b-DAS), a 9-item informant-rated scale with higher scores indicating greater apathy. Cross-sectional analyses compared b-DAS total scores across disease stages and genetic groups using linear regression, adjusted for age, sex, and education, with bootstrapping applied to account for non-normality. Associations between apathy and other indicators of disease were also assessed.

To assess apathy trajectories across the full disease course, b-DAS scores were examined across increasing CDR stages and genetic groups, (CDR 1-3 indicating increasing symptom severity; Table 2).

Further analyses evaluated the relationship between apathy and other disease markers, including an executive function composite score.

Clinician-rated apathy assessed during the clinical evaluation was compared with informant-reported b-DAS score to explore potential discrepancies between rating sources.

#### Executive Function Composite

Trail Making Test Part B

Stroop Task

Digit Span Backwards

Digit Symbol

Time (s)

Length

### CONCLUSION

Apathy emerges early in genetic FTD, is detectable at the prodromal stage, and increases with disease progression across all genetic groups. It is associated with executive dysfunction, with clinician- and informant-rated measures demonstrating overall consistency, despite some discrepancies.

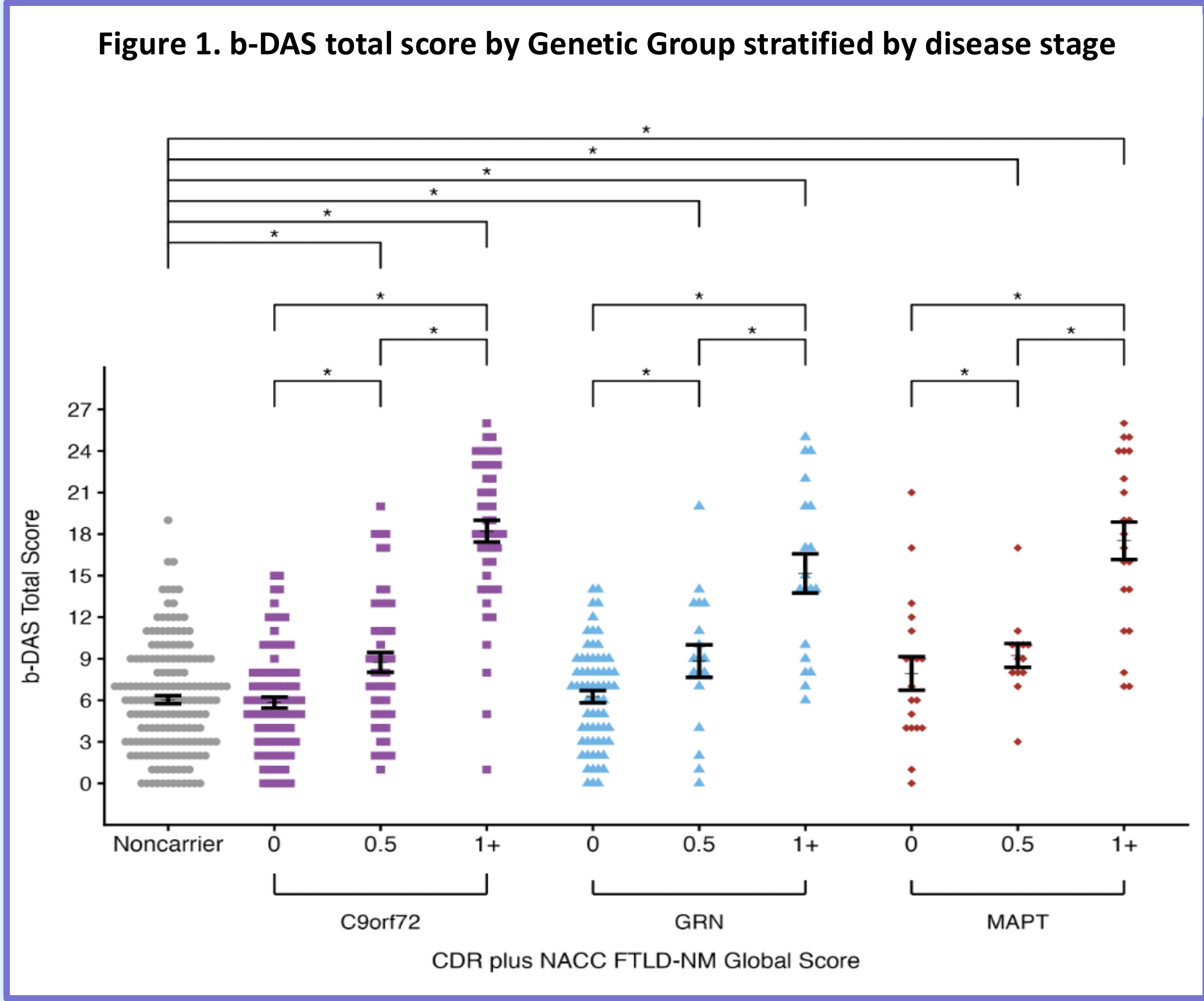
These findings indicate that the b-DAS is sensitive to early behavioural change and suitable for longitudinal monitoring in familial FTD. Apathy represents a progressive disease feature and a potential marker of progression and clinical trial outcome measure.

Future longitudinal analyses will clarify whether apathy predicts subsequent subclinical decline and how it relates to other disease features.

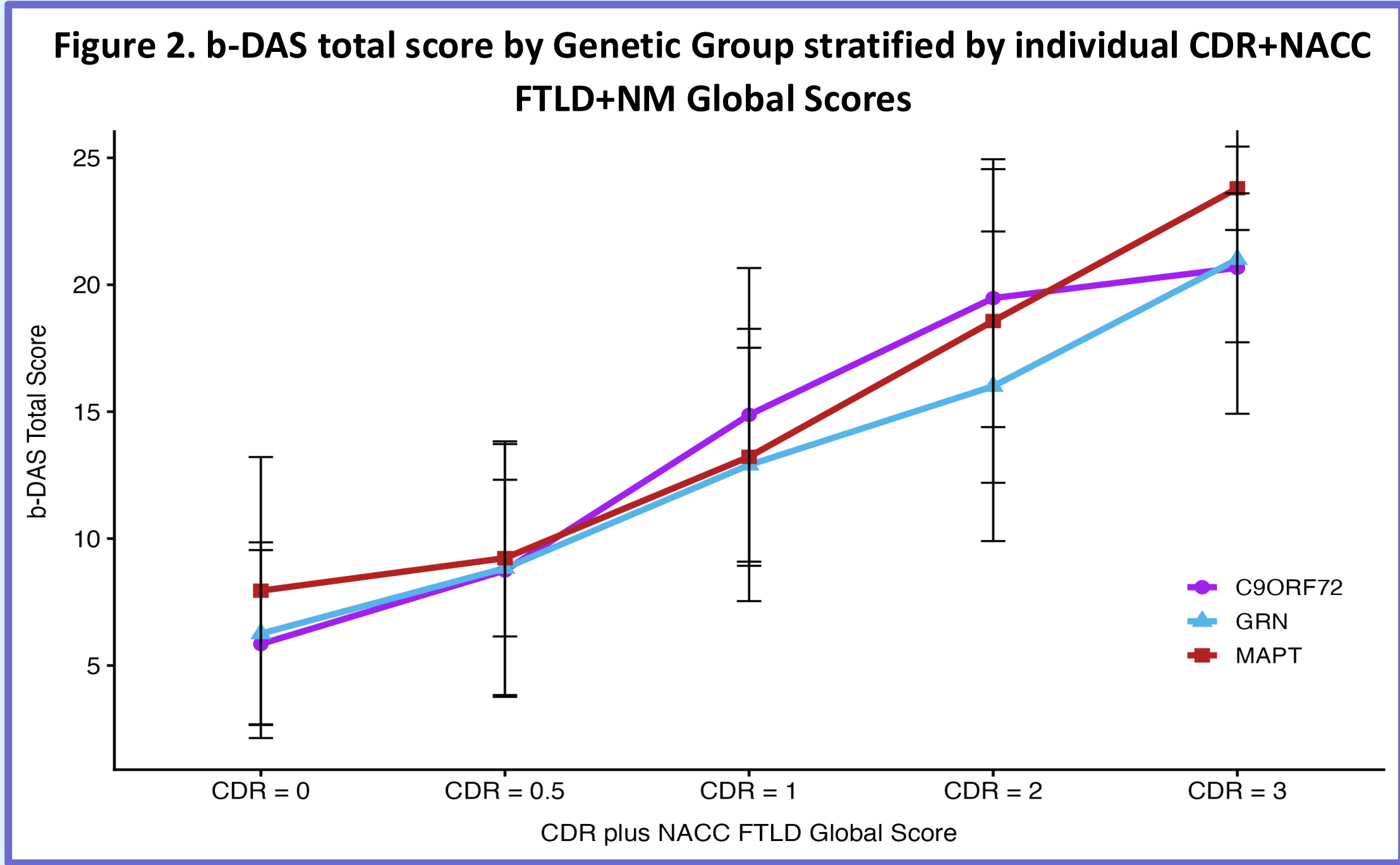
### RESULTS

#### Apathy Across Disease Stages and Genetic Groups:

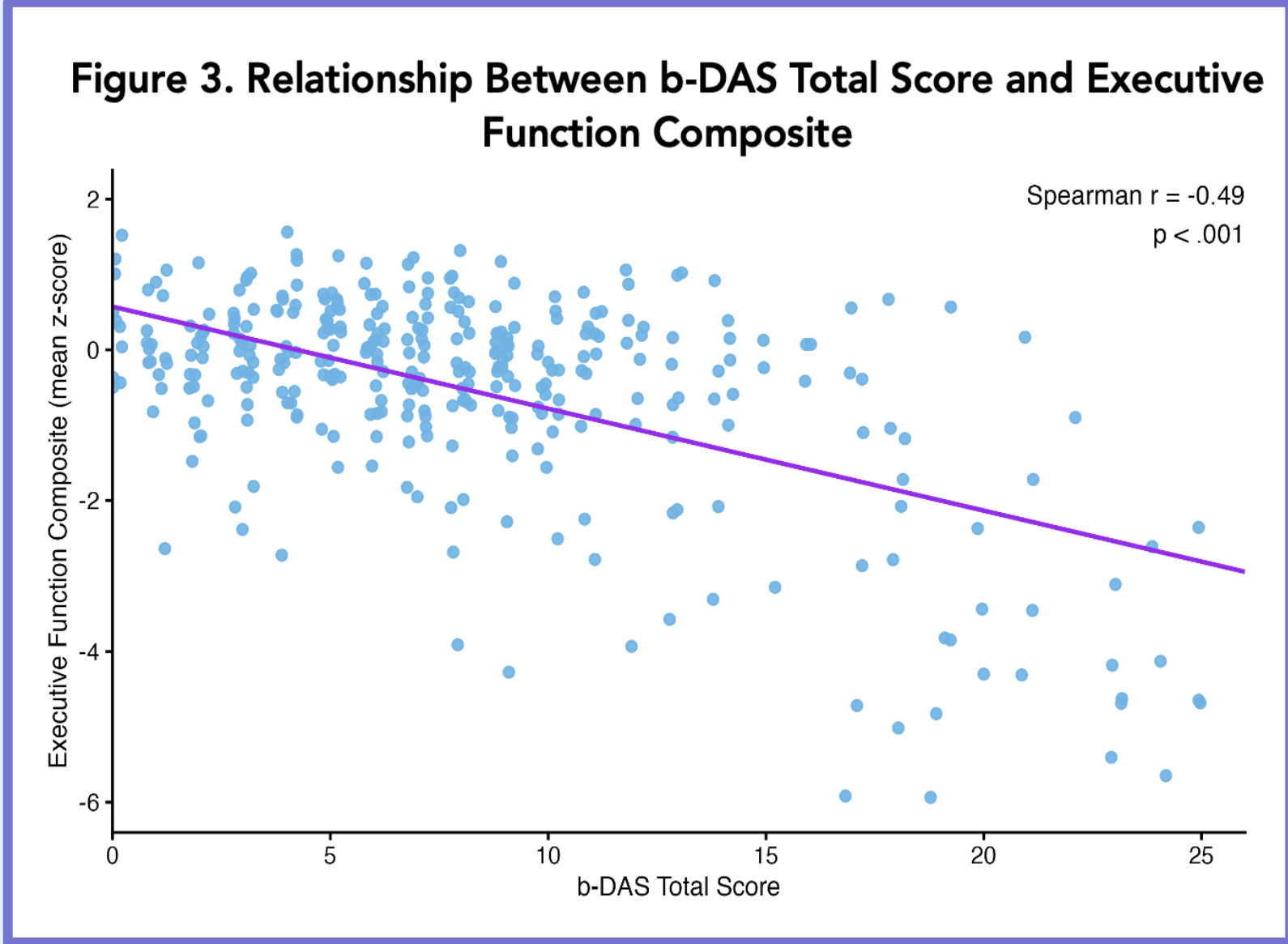
Apathy increased progressively with advancing disease stage across all mutation groups. Symptomatic carriers showed significantly higher b-DAS total scores, and prodromal carriers also exhibited elevated scores compared with non-carriers (Figure 1). No significant differences were observed between asymptomatic carriers and controls, and no mutation-specific differences were identified within disease stages.



When stratified by individual CDR® plus NACC FTLD+NM global scores, all genetic groups demonstrated increasing b-DAS total scores with advancing CDR stage, including beyond symptom onset (Figure 2).



#### Association of b-DAS with Executive Function and Clinician Rating:



A significant moderate negative association was observed between executive function and b-DAS total score (Spearman  $r = -0.49$ ,  $p < .001$ ), with higher apathy associated with poorer executive performance (Figure 3), suggesting there is an association found between motivational and executive processes.

Results show that clinician-rated apathy increased progressively across disease stages in all mutation groups. Discrepancies between clinician and informant ratings were evident, with some informants reporting high apathy despite clinicians rating it as absent (Figure 4).

