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

Farley, S.[1], Blesius, A.[1], Bouzigues, A.[1], Ferry-Bolder, E.[1], Cullen, E.[1], Russell, L.L.[1], Foster, P.H.[1], van Swieten, J.C.[2], Jiskoot, L.C.[2], Seelaar, H.[2], Galimberti, D.[3], Vandenberghe, R.[4], Laforce, R.[5], Finger, E.[6], Bruffaerts, R.[7], Bertoux, M.[8], Lebouvier, T.[8], Solje, E.[9], Levin, J.[10], di Fede, G.[11], Thompson, A.[12], Le Ber, I.[13], Migliaccio, R.L.[13], Körtvélyessy, P.[14], Schroeter, M.L.[15], Logroscino, G.[16], Otto, M.[17], Uzelac, Z.[18], Illán-Gala, I.[19], Krüger, J.[20], Nacmias, B.[21], Gerhard, A.[22], Langheinrich, T.[22], Ducharme, S.[23], Santana, I.[24], Tartaglia, M.C.[25], Masellis, M.[26], de Mendonça, A.[27], Rowe, J.B.[28], Graff, C.[29], Moreno, F.[30], Synofzik, M.[31], Borroni, B.[32], Sanchez-Valle, R.[33], Convery, RS.[1], Rohrer, J.D.[1]

1Dementia Research Centre, UCL Queen Square Institute of Neurology, London,. (see GENFI website www.genfi.or for more details on affiliations)

BACKGROUND

Apathy is a core symptom of frontotemporal dementia (FTD), affecting daily functioning and quality of life. However, its emergence and progression across disease stages and genetic groups remain poorly characterised. The brief-Dimensional Apathy Scale (b-DAS) is a brief, study partner-rated measure, but its utility in FTD remains underexplored.

We investigated whether apathy emerges before symptom onset, increases with disease severity, and is associated with clinical decline in genetic FTD.

METHODS

Participants were recruited from the GENFI cohort and included 341 mutation carriers and 174 non carriers. All underwent standardised clinical assessment at their annual GENFI visit and were classified by FTLD-CDR-NM global score as asymptomatic (0), prodromal (0.5), or symptomatic (≥1).

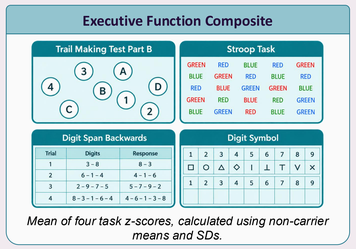
	Non-carriers (N=174)	C9orf72 (N=184)	GRN (N=104)	MAPT (N=53)
CDR = 0	-	90	67	19
CDR = 0.5	-	47	18	13
CDR ≥ 1	-	47	19	21
Age	49.5 (13.8)	49.5 (14.3)	53.4 (11.8)	49.0 (13.2)
Education	15.9 (3.11)	14.6 (3.06)	15.2 (3.58)	14.3 (3.23)
Male (%)	73 (42.0%)	77 (41.8%)	43 (41.3%)	27 (50.9%)
FTLD-CDR-NM SOB	0.15 (0.41)	3.19 (5.72)	1.75 (3.88)	4.24 (6.12)

Table 1) *Demographics*

Apathy was assessed within three months of clinical assessment using the **9-item b-DAS scale,** with higher scores reflecting greater apathy. Subscale structure was evaluated using **exploratory** and **confirmatory factor analysis** (WLSMV estimator), with reliability (McDonald's ω) and discriminant validity (HTMT) assessed for each subscale.

b-DAS total scores were compared across individual disease stages and genetic groups using **linear regression** adjusted for age, sex and education, with bootstrapping for non-normality.

Spearman's correlations assessed associations between b-DAS total score and an executive function composite, measures of social functioning (Revised Self-Monitoring Scale [RSMS]; modified Interpersonal Reactivity Index [mIRI]), and neurofilament light chain (NfL) as a marker of neurodegeneration.



Mean of four task z-scores, calculated using non-carrier means and SDs.

RESULTS

1 Proposed b-DAS subscales showed substantial overlap

- High reliability: total ω = .92; subscales ω = .69-.86.
- Item 6 loaded weakly on its subscale (λ = .15) and showed little relationship with other items (Figure 1).
- Subscales overlapped substantially (r = .90-.94; Figure 2); HTMT = .59-.91, with initiation-emotional exceeding .90.
- **b-DAS total score used for analyses**.

Figure 1) *Inter-item polychoric correlation matrix for the b-DAS*

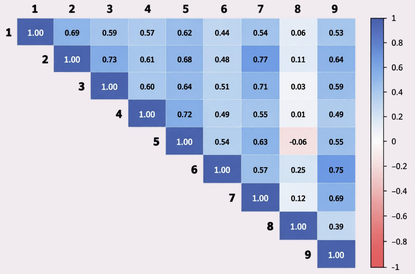
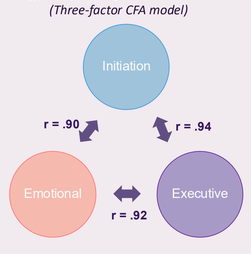


Figure 2) *Latent factor correlations (Three-factor CFA model)*



Values are standardised latent factor correlations from the three-factor CFA model

Brief-Dimensional Apathy Scale (b-DAS)
9-item study partner questionnaire

1. He/she thinks of new things to do during the day
2. He/she is concerned about how his/her family feel
3. He/she is able to focus on a task until it is finished
4. He/she sets goals for him/herself
5. Before he/she does something he/she thinks about how others would feel about it
6. When doing a demanding task, he/she has difficulty working out what he/she has to do
7. He/she acts on things he/she has thought about during the day
8. He/she is indifferent to what is going on around him/her
9. He/she finds it difficult to keep his/her mind on things

2 Higher apathy in some mutation carriers before symptom onset

Figure 3) b-DAS by genetic group stratified by FTLD-CDR-NM global score

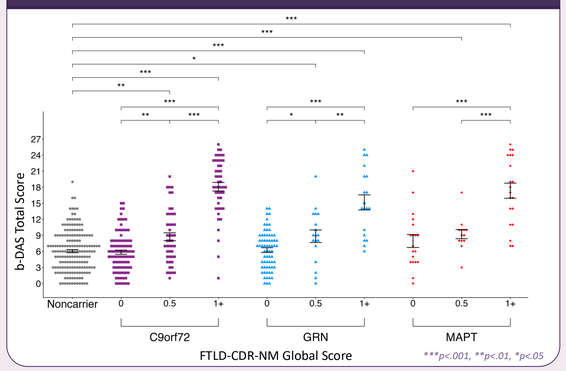
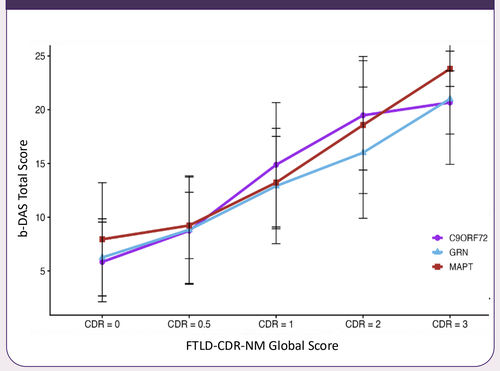


Figure 4) b-DAS in each genetic group by FTLD-CDR-NM global score

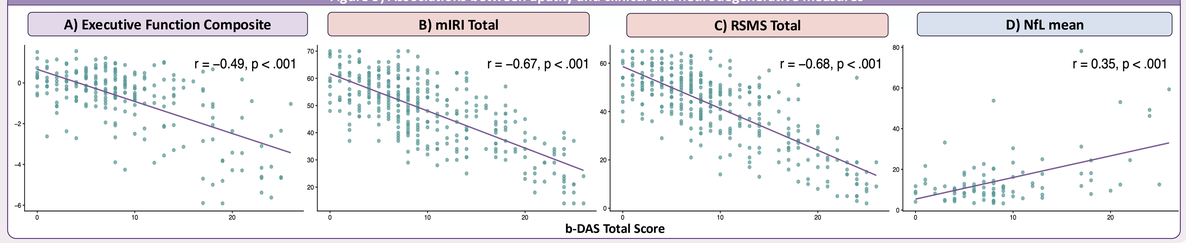


- **Apathy emerges before symptom onset:** Higher b-DAS scores were observed in prodromal carriers compared with non-carriers across all genetic groups (C9orf72: p = .004; GRN: p = .015; MAPT: p = .001; Figure 3).
- **Apathy increases with disease severity**: b-DAS increased further at the symptomatic stage (all p < .001) (Figure 1) and with advancing CDR® plus NACC FTLD+NM score across C9orf72, GRN and MAPT groups (Figure 4).

3 Apathy correlates with clinical and neurodegenerative markers

- Higher apathy was associated with poorer executive function (r = −.49), poorer social functioning (RSMS r = −.68; mIRI r = −.67), and higher NfL (r = .35) (Figure 5; A-D)
- **All associations p < .001.**

Figure 5) Associations between apathy and clinical and neurodegenerative measures



CONCLUSIONS

Apathy is elevated during the prodromal phase of familial FTD and increases with advancing disease stage. Associations with executive dysfunction, social changes and NfL suggest apathy is closely related to clinical disease state. These findings highlight apathy as a potential early clinical marker in familial FTD, although its prognostic value requires further longitudinal investigation in larger cohorts.

sophie.farley.23@ucl.ac.uk
PhD student
University College London, Dementia Research Centre

Acknowledgements: We thank the research participants for their contribution to the study. RSC and JDR acknowledge the support of the Rosetrees Trust, the National Brain Appeal, the Kissick Family Foundation and the NIHR UCL/H Biomedical Research Centre. This work was also supported by the MRC UK GENFI grant (MR/M023664/1), the Bluefield Project, and the JPND GENFI-PROX grant (2019-02248). Please see GENFI website (www.genfi.org) for further acknowledgements.

The National Brain Appeal
GENFI GENETIC FTD INITIATIVE
PRINTED BY SCIENCEPOSTERS.co.uk
Scan to keep up to date with the FTD Talk team
FTDtalk