Lifestyle activity and clinical severity in familial frontotemporal dementia

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Introduction

Lifestyle activities such as physical and cognitive activity have been shown to influence cognitive decline trajectories and mitigate disease progression in various forms of neurodegeneration. This has led to suggestions that such lifestyle factors may contribute to **cognitive reserve**, with increased reserve conferring a protective influence (Premi et al., 2017).

Prior work showed that in **genetic frontotemporal dementia (FTD)**, participants with more active lifestyles showed less functional decline over time (Casaletto et al., 2020). However, follow-up sample size was limited.

This study aimed to examine whether lower levels of physical and/or cognitive activity were associated with **greater clinical impairment** in presymptomatic familial FTD, and to characterise longitudinal relationships between **activity and clinical progression** to assess potential cognitive reserve in familial FTD.

Methods

- Symptomatic and asymptomatic C9orf72, GRN, or MAPT mutation carriers and non-carrier family members from the GENFI cohort completed the Physical Activity Scale for the Elderly (PASE) and Cognitive Activity Scale (CAS).
- The CDR+NACC FTLD-NM was used as a marker of clinical progression.

Table 1. Demographic data grouped by carrier status, continuous variables presented as mean ± SD

	Non-carrier	Mutation carrier	
		Asymptomatic	Symptomatic
N	193	285	59
C9orf72, n	73	151	38
GRN, n	87	96	7
MAPT, n	33	38	14
Age, years	49.2±13.8	45.7±12.6	62.3±7.2
Sex, F	54%	60%	36%
Education, years	15.7±3.1	15.3±3	13.2±3.5
CDR+NACC FTLD-NM SOB	0.2±0.6	0.5±1.2	10.2±5.6

Statistical analyses

1) **Baseline asymptomatic comparisons** – Pearson's correlation and multiple linear regression (adjusted for age, sex, site, education covariates) were used to assess associations between activity levels and CDR score at baseline.
2) **Baseline asymptomatic high vs low activity groups** – participants were divided according to high and low activity levels and Wilcoxon rank-sum tests were used to compare the groups' CDR scores.
3) **Longitudinal CDR trajectories in all mutation carriers** – CDR change over time was examined using linear mixed effects models, adjusting for covariates.

Table 2. Participants with longitudinal data (*N*)

	Baseline	Visit 2	Visit 3
Non-carrier	51	51	7
Asymptomatic	86	86	15
Symptomatic	14	14	4

Results

Significant differences observed between symptomatic carriers and controls in physical & cognitive activity levels ($p < .05$), but not asymptomatic carriers & controls, or genetic groups.

1) Baseline asymptomatic comparisons

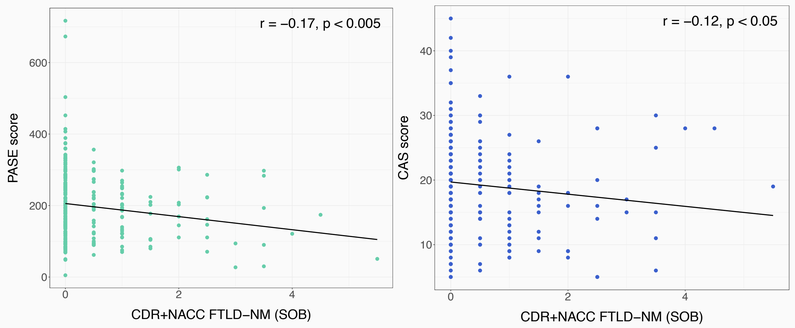

Figure 1. Higher a) physical and b) cognitive activity levels were significantly correlated with lower CDR scores (p<.001 and p<.05, respectively)

2) Baseline asymptomatic high vs low activity groups

- The low PASE group had significantly higher CDR +NACC FTLD-NM scores (mean±SD: 0.59±1.04) compared to the high group (0.29±0.67; $p = .005$).
- The low CAS group had significantly higher CDR +NACC FTLD-NM scores (mean ± SD: 0.60 ± 0.88) than the high group (0.38 ± 0.90; $p < .05$).

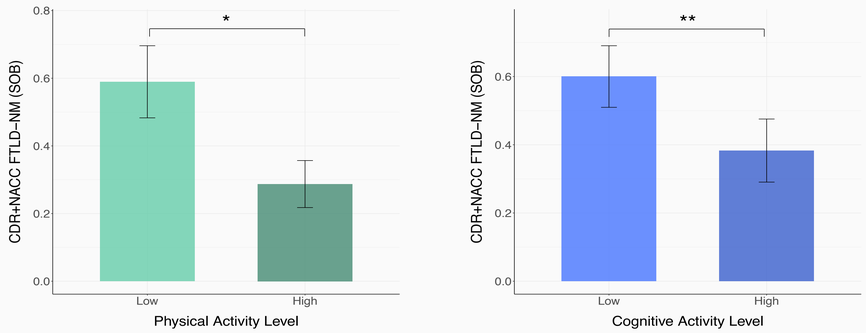

Figure 2. CDR scores were significantly different between low vs high physical and cognitive activity groups * p < 0.05, ** p < 0.01

3) Longitudinal CDR trajectories in all mutation carriers

- Higher PASE score was associated with slower clinical decline ($p < .05$), and with lower baseline CDR severity ($p < .05$).
- PASE did not significantly modify slope in asymptomatic carriers alone.
- Higher CAS score was associated with lower baseline clinical severity ($p < .05$) and with significantly slower clinical decline in asymptomatic carriers alone ($p = .005$).
- The global Time × CAS interaction was not significant in carriers.

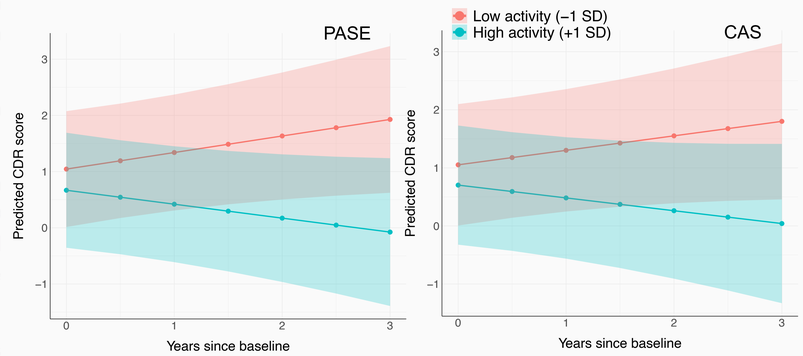

Figure 3. Model-based predicted CDR trajectory by activity level

Conclusions

- No differences in activity levels were observed between non-carriers and asymptomatic participants or C9orf72, MAPT, and GRN mutation carriers.
- Lower levels of physical and cognitive activity were associated with greater clinical impairment in asymptomatic familial FTD.
- Physical activity was associated with slower clinical progression in carriers but did not modify trajectory in asymptomatic mutation carriers alone.
- Cognitive activity was associated with significantly slower clinical decline in the asymptomatic group alone.

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