Examining empathy deficits across familial forms of frontotemporal dementia within the GENFI cohort

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Background

Reduced capacity for empathy is a common symptom in frontotemporal dementia (FTD). Although empathy deficits and the corresponding patterns of atrophy have been extensively researched in sporadic cases, few studies have explored the differences in familial forms of FTD.

Methods

Empathy was examined using the modified Interpersonal Reactivity Index (mIRI) in participants from the Genetic FTD Initiative. Demographics of the participants are displayed in table 1.

The mIRI Total score, as well as the subscores of emotional concern (EC) and perspective taking (PT) were assessed. Bootstrapped linear regressions (2000 repetitions) were used to assess empathy ratings across the genetic groups, as well as across phenotypes in the symptomatic carriers, covarying for gender and language. Spearman's rank correlation was conducted to examine the relationship between mIRI total and disease severity using the CDR® plus NACC FTLD sum of boxes score.

To elucidate the brain the regions associated with scores on the mIRI, participants underwent T1 weighted MRI scans, analysed using voxel-based morphometry.

Table 1: Participant demographics including mean and standard deviation scores for age at visit, years spent in education, as well as Mini-Mental State Examination (MMSE), and CDR plus NACC FTLD sum of boxes (SB). N equals the number of participants.

	CDR plus NACC FTLD - global	N	% Male	Age		Education		MMSE		CDR plus NACC FTLD-SB	
Controls	0	216	40	45.7	13.0	14.3	3.3	29.3	1.1	0	0
C9orf72	0	94	41	43.9	11.6	14.3	3.0	29.1	1.2	0	0
	0.5	33	45	49.9	11.3	13.9	2.7	28.4	2.2	1.1	0.7
	1+	65	66	62.9	9.5	13.0	3.6	23.2	6.8	11.1	5.6
GRN	0	121	33	45.9	12.1	14.7	3.4	29.5	0.8	0	0
	0.5	25	44	51.4	13.6	14.0	4.2	28.6	2.3	1.0	0.8
	1+	47	47	63.0	7.4	11.7	3.4	20.1	7.7	9.8	6.2
MAPT	0	41	39	38.6	11.2	14.5	3.3	29.5	0.8	0	0
	0.5	13	31	46.4	12.8	13.6	2.5	28.1	2.3	1.1	0.8
	1+	21	57	58.9	9.4	13.6	4.0	21.9	8.1	10.3	6.0

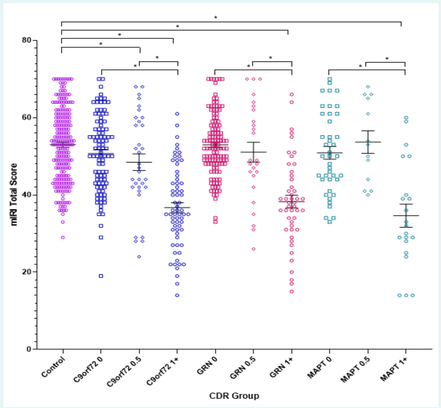

Figure 1: Modified Interpersonal Reactivity Index (mIRI) Total scores in each genetic group stratified by CDR plus NACC FTLD (0 = asymptomatic, 0.5 = mildly symptomatic/prodromal, 1+ = fully symptomatic). Means and standard errors are shown. Significant differences from controls and within groups are starred.

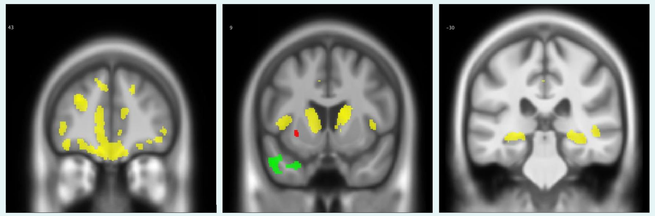

Figure 2: Neural correlates of the modified Interpersonal Reactivity Index (mIRI) Total score. Results for all three genetic groups are displayed at p < 0.05, corrected for Family Wise Error. A study-specific T1-weighted MRI template in MNI space was used to show results. Red: C9orf72 carriers, yellow: GRN carriers, green: MAPT carriers.

Results

All symptomatic groups (CDR 1+) scored significantly lower on the mIRI Total and both subscores when compared to controls and their asymptomatic and mildly symptomatic counterparts (all $p < 0.001$) (Figure 1). Notably, the mildly symptomatic *C9orf72* expansion carriers mIRI Total score was also significantly lower than controls ($p = 0.046$) (Figure 1). No other significant differences were observed across or within genetic groups.

All three phenotype groups (bvFTD, PPA and FTD-ALS) scored significantly worse than controls (all $p \leq 0.007$). Symptomatic carriers with a bvFTD and FTD-ALS phenotype scored lower on the mIRI Total than the PPA group ($p < 0.001$, $p = 0.012$ respectively). A moderate negative correlation was found for each genetic group between the mIRI Total score and disease severity (rho -0.46 to -0.51, all $p < 0.001$).

Neural correlates of empathy varied between groups: the left frontal cortex and basal ganglia for *C9orf72* expansion carriers, the anterior cingulate, frontal, and temporal cortices bilaterally, as well as the right insula and subcortical regions for *GRN* mutation carriers, and the anteromedial temporal lobe and right insula for *MAPT* mutation carriers.

Conclusions

Empathy deficits are a prominent feature in genetic FTD, with significant impairments presenting in symptomatic patients within each genetic mutation group, particularly for individuals with a bvFTD phenotype. The neuroanatomical data suggests that the OFC, insula, putamen, hippocampus and temporal poles serves as the neural substrates of empathy.

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