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KPR	Study design and concept, obtaining funding, statistical analysis, data interpretation, drafting the manuscript

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Multisite ALLFTD study modelling progressive empathy loss from the earliest stages in behavioral variant frontotemporal dementia

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Abstract

INTRODUCTION: Empathy relies on fronto-cingular and temporal networks that are selectively vulnerable in behavioral variant frontotemporal dementia (bvFTD). This study modeled when in the disease process empathy changes begin, and how they progress.

METHODS: 431 individuals with asymptomatic genetic FTD (n=114), genetic and sporadic bvFTD (n=317), and 163 asymptomatic non-carrier controls were enrolled. In subsamples, we investigated empathy measured by the informant-based Interpersonal Reactivity Index (IRI) at each disease stage and over time (n=91), and its correspondence to underlying atrophy (n=51).

RESULTS: Empathic concern (estimate=4.38, 95%CI=[2.79, 5.97], $p<0.001$) and perspective taking (estimate=5.64, 95%CI=[3.81, 7.48], $p<0.001$) scores declined between the asymptomatic and very mild symptomatic stages regardless of pathogenic variant status. More rapid loss of empathy corresponded with subcortical atrophy.

DISCUSSION: Loss of empathy is an early and progressive symptom of bvFTD that is measurable by IRI informant-ratings and can be used to monitor behavior in neuropsychiatry practice and treatment trials.

Keywords

Behavioral variant frontotemporal dementia; emotional empathy; cognitive empathy; Interpersonal Reactivity Index; volumetric MRI; clinical trials

BACKGROUND

Striking loss of empathy is a well-known key feature of behavioral variant frontotemporal dementia (bvFTD),[1,2] which manifests early in the course of illness in reduced interest in, and emotional response to, other people's feelings. While bvFTD patients often show poor self-awareness of their socioemotional deficits,[3] caregivers of patients with loss of empathy show heightened levels of burden, loneliness, and depression.[4] Loss of empathy also has a negative impact on relationship status, including frequency of relationship dissolution and infidelity.[5] While numerous smaller, cross-sectional studies have examined various aspects of empathy in bvFTD,[2,6,7] until recently large longitudinal patient cohorts have not been available with which to model more precise empathy estimates or show the rate of empathy change over the whole course of the disease, including at the very earliest prodromal stages. The focus of this study is to perform this modeling by using for the first time the very comprehensive empathy dataset from the cohort of bvFTD patients in the large longitudinal multisite ALLFTD study.

Empathy involves a complex set of emotional and cognitive processes: an affective response that may include affect sharing, perspective taking, assignment of agency, suppression of one's viewpoint, and a prosocial motivation or the desire to help.[8,9] Emotional empathy engages mainly regions of two brain networks that are affected in early bvFTD: the salience network (SN) underlying homeostatically-guided attention,[10] and the semantic-appraisal network (SAN) that links stored social concepts with their hedonic valence, including reward value.[11] When empathy involves greater levels of cognitive perspective taking, regions of the default-mode network (DMN) that are involved in higher-order executive aspects of social cognition such as predicting outcomes and imagining others' intentions are recruited.[12,13]

We used the Interpersonal Reactivity Index (IRI)[14] to examine the trajectory of loss of empathy in bvFTD. Specifically, we investigated whether empathy changes as a function of disease stage from asymptomatic to very mild and more advanced bvFTD, both in carriers of pathogenic variants in the main FTD genes (*C9orf72* that is technically a hexanucleotide expansion and we will refer to simply as a gene; *GRN*; *MAPT*) and in non-carriers. In a true longitudinal subsample, we examined whether empathy declines with progression, and whether rate of change in empathy corresponds to rate of atrophy in the SN, SAN, and DMN. Based on cross-sectional evidence showing that emotional and cognitive empathy is affected in bvFTD,[1,2,15] we expected that both aspects of empathy would deteriorate over time. In addition, we hypothesized that rate of decline in emotional empathy would

correspond to rate of atrophy in the SN and SAN, whereas rate of decline in cognitive empathy would additionally be associated with rate of atrophy in the DMN.

METHODS

Participants

We enrolled 594 participants from the UCSF FTD PPG and the multisite ALLFTD (previously ARTFL and LEFFTDS consortia) studies between 1999 and 2018. The sample consisted of 307 patients with clinical bvFTD[16] (88 carried a pathogenic variant in one of the three autosomal dominant FTD genes *C9orf72, MAPT, GRN*), 10 pathogenic variant carriers with behavioral Mild Cognitive Impairment (MCI), and 277 asymptomatic pathogenic variant positive (n=114) and negative (n=163) individuals. Patients with behavioral MCI had one or two of the key features as required for possible bvFTD:[17] disinhibition, apathy or inertia, loss of sympathy/empathy, ritualistic/compulsive behavior, or hyperorality and appetite changes, and no cognitive domain impaired other than behavior. The asymptomatic pathogenic variant negative individuals were noncarrier family members who served as controls for the asymptomatic pathogenic variant positive group because of their similar demographics, background, and environment. Participants' diagnoses were based on thorough neurological, neuropsychological, neuroimaging, and genetic examination. Each participant was required to have a spouse/partner, first-degree family member or friend who had known the participant for five or more years, and to have at least one timepoint of informant ratings on the Empathic Concern (EC) and Perspective Taking (PT) subscales of the IRI[14] available. For our first set of analyses examining the EC and PT subscale scores at each level of disease severity, we included all 594 participants and all timepoints. For our second (true longitudinal) set of behavioral analyses in which we examined change in IRI subscale scores in bvFTD over time, we included only the 91 patients (212 observations) from the above sample (40 sporadic bvFTD, 37 genetic bvFTD, 7 genetic MCI, 6 asymptomatic pathogenic variant positive, 1 asymptomatic pathogenic variant negative) who had at least two timepoints of valid IRI data. The subsample with both longitudinal behavioral and structural imaging data available consisted of 51 participants (124 observations). The average time interval between IRI data collection and MRI scanning was 2.7±8.4 (M±SD) days. To compare patients' longitudinal pattern on the IRI to a healthy control group who had at least two timepoints of IRI data available, we included 130 neurologically and cognitively healthy older adults (age: 68.8±7.6; sex [M/F]: 56/74) from the Hillblom Network Program. The parent studies (PPG, ALLFTD, Hillblom) were conducted in accordance with IRB approval from each study institution, and all participants and their informants gave their consent to participate and to share data.

Clinical measures

To measure emotional and cognitive empathy, we used informant-ratings on the EC and PT subscales of the IRI informant questionnaire[14] because they show the best psychometric characteristics among the four IRI subscales[18,19] and are the most widely used informant-based measures of empathy in dementia.[2,20,21] The 7-item EC subscale assesses people's tendency to generate an other-centered prosocial response resulting from correctly inferring another's emotional state and resulting psychological needs (emotional empathy). By

contrast, the 7-item PT subscale measures people's tendency to spontaneously imagine the thought processes and perspective of another person (cognitive empathy). Each participant had an informant who described the subject's current level of empathy using a 5-point Likert scale, ranging from "does not describe well" to "describes very well". Each subscale score ranged between 7 and 35, with higher scores showing higher levels of empathy. The informants were carefully identified based on the relationship and closeness to the participant, frequency of contact, and cognitive status of the informant. The majority of informants were spouses (62%), followed by adult children, siblings or other relatives (26%), friends (7%), and others (5%).

We used another informant-based measure, the CDR® Dementia Staging Instrument plus Behavior and Language domains from the NACC FTLD Module (CDR® plus NACC FTLD) as a proxy of disease severity. The measure is an extension of the standard CDR, and includes two additional domains that are predominantly affected in FTD: behavior and language.[22] Each patient's CDR® plus NACC FTLD global score was calculated based on the scoring rules by Miyagawa et al. (2020)[20] (0=normal, 0.5=very mildly impaired/MCI stage, 1=mildly impaired, 2=moderately impaired, 3=severely impaired).

The Zarit Burden Interview[24] is a 22-item self-report measure of stress and burden experienced by caregivers. The questionnaire was used to assess burden in different domains, including behavioral symptoms and functional status of the patient, interpersonal relationships, finances, physical health, and social life.

Neuroimaging

Acquisition and preprocessing of structural images was performed as described in the supplementary materials. We used the Desikan brain atlas[25] and defined regions of interest (ROIs) in each network. The bilateral anterior insula (AI), dorsal anterior cingulate cortex (ACC), thalamus, and amygdala ROIs comprise the SN[10] (Supplementary Fig. 1). The SAN ROIs included the bilateral caudate, nucleus accumbens, temporal pole (medial part), lateral orbitofrontal cortex (OFC), and the subgenual ACC.[11] The ROIs of the DMN were defined in the bilateral dorsomedial prefrontal cortex, posterior cingulate cortex, hippocampus, parahippocampal gyrus, retrosplenial cortex, inferior parietal lobule, medial orbitofrontal cortex, temporal pole (lateral part), middle temporal gyrus, and supramarginal gyrus.[12]

Statistical analyses

Linear mixed effects (LME) models were performed in SAS Version 9.4 (Proc mixed) to examine in the full sample (n=594, 666 observations) whether the IRI scores are a significant predictor of the CDR® plus NACC FTLD score, controlling for age at first evaluation and sex. To investigate whether pathogenic variant carriers and non-carriers showed a different pattern of change in empathy over time, we added pathogenic variant status and the interaction pathogenic variant status by CDR® plus NACC FTLD to the model. To examine cross-sectional differences in empathy between asymptomatic FTD pathogenic variant carriers (*C9orf72*, *GRN*, *MAPT*) and asymptomatic non-carriers, we performed linear modelling (Proc GLM) and included each subscale as outcome variable, covarying for diagnostic group, age at first evaluation, and sex. In a subsample of

asymptomatic individuals, as well as patients with behavioral MCI and bvFTD (n=449) who had valid cross-sectional data of both Zarit Burden Interview and IRI available, linear modelling was performed to examine whether each subscale score predicted Zarit Burden score, controlling for age at first evaluation and sex.

In the subsample of patients with two or more timepoints of IRI data available (n=91, 212 observations), we used LME models with random intercepts and slopes to examine whether the IRI scores declined over time and whether the slope of decline differed (1) between pathogenic variant carriers and non-carriers, and (2) between patients with different disease severities at baseline. To investigate whether rate of change in empathy was similar in patients with different disease severities according to the CDR® plus NACC FTLD score, we divided the patient sample into three groups: patients with very mild (CDR®=0.5; n=20), mild (CDR®=1.0; n=43), and moderate/severe (CDR®=2/3; n=26) disease stage at baseline. The models were comprised of disease duration, age at symptom onset, and sex. In the first interaction model, the variable pathogenic variant status and the interaction of disease duration by pathogenic variant status were included. The second interaction model was comprised of the variables CDR® plus NACC FTLD at baseline and the interaction with disease duration.

We also investigated whether rate of decline on the EC and PT subscales was associated with rate of atrophy progression in predefined ROIs in the SN, SAN, and DMN. In the subsample of 51 patients (124 observations) who had at least two timepoints of valid IRI and structural imaging scans of sufficient quality collected on the same 3T scanner MRI data available, separate LME models with random intercepts and slopes were fitted for each subscale as outcome, and ROI, disease duration, age at symptom onset, sex, and TIV were included as predictors in the models. Because the gray matter volumes in the three networks were highly correlated (r SN/SAN: 0.94; r SN/DMN: 0.92; r SAN/DMN: 0.89), we also included the mean gray matter volume in the two networks of no interest as covariates.

RESULTS

Demographic and clinical features

The demographic and clinical features of the full sample are described in Table 1. The longitudinal subsample consisted of symptomatic pathogenic variant carriers (n=50) and symptomatic non-carriers (n=41) with different disease stages of bvFTD. Age at symptom onset was statistically significantly (p=0.020) younger in pathogenic variant carriers (M±SD: 51.0±11.7) than in non-carriers (M±SD: 57.7±8.4). Carriers and non-carriers did not statistically significantly differ with regard to disease duration, proportion of males and females, or education, thus we did not use these variables as potential confounds in subsequent analyses.

Cross-sectional behavioral modelling

Empathy by disease severity in the full sample: CDR® plus NACC FTLD was a statistically significant predictor of both the EC (p<0.001) and PT (p<0.001) score (Fig. 1A/B). The results showed that the EC score significantly declined at each stage

from asymptomatic to very mild (estimate=4.38, 95%CI=[2.79, 5.97], $p<0.001$), very mild to mild (estimate=−3.52, 95%CI=[−5.19, −1.84], $p<0.001$), and mild to moderate/severe (estimate=2.93, 95%CI=[1.71, 4.14], $p<0.001$) disease (Table 2). Similarly, the PT score showed a statistically significant drop between asymptomatic and very mild stages (estimate=5.64, 95%CI=[3.81, 7.48], $p<0.001$), very mild and mild stages (estimate=−3.24, 95%CI=[−4.82, −1.13], $p=0.002$), as well as mild and moderate/severe (estimate=1.49, 95%CI=[0.18, 2.79], $p=0.023$) stages. Because the interaction of CDR® plus NACC FTLD by pathogenic variant status did not reach statistical significance in either EC or PT models in our sample, further analyses of this relationship were not performed.

Relationship between empathy and caregiver burden: Lower EC (estimate=−0.03, 95%CI=[−0.06, −0.00], $p=0.033$) and PT (estimate=−0.04, 95%CI=[−0.09, −0.00], $p=0.043$) scores in patients were significant predictors of higher Zarit Burden score in caregivers, showing that caregivers of patients with lower levels of empathy reported more burden in their day-to-day life.

Empathy in asymptomatic pathogenic variant positive and negative individuals: Diagnostic group (*C9orf72*, *GRN*, *MAPT*, non-carriers) was a significant predictor of the EC score ($p=0.036$) in an omnibus analysis, though in post-hoc Dunnett-Hsu tests none of the individual asymptomatic pathogenic variant carrier groups showed a significant group difference from the asymptomatic non-carriers. The largest quantitative difference was between asymptomatic *C9orf72* carriers (M±SD: 27.0±0.8) and asymptomatic non-carriers (28.95±0.40) was small enough to not be clinically significant and the effect size was small (Eta-square: 0.03; 95%CI=[0.00, 0.07], $p=0.067$). Similarly, asymptomatic *GRN* and asymptomatic *MAPT* carriers did not show a statistically significant difference from non-carriers. In contrast to the EC subscale, diagnostic group did not reach statistical significance for predicting the PT score.

Longitudinal behavioral modelling

Empathy over time in the longitudinal subsample: Disease duration was a significant predictor of both EC (estimate=−0.58, 95%CI=[−0.88, −0.28], $p<0.001$) and PT (estimate=−0.29, 95%CI=[−0.50, −0.08], $p=0.010$) scores (Fig. 1 C/D). Disease duration also remained a significant predictor of EC (estimate=−0.65, 95%CI=[−1.02, −0.28], $p=0.001$) and PT (estimate=−0.36, 95%CI=[−0.63, −0.10], $p=0.015$) scores when pathogenic variant status and the interaction of disease duration by pathogenic variant status were added to the model, though the interaction of disease duration by pathogenic variant status did not reach statistical significance for predicting the EC or PT scores. To check whether the EC and PT scores showed a non-linear progression over time, we added the quadratic time (disease duration) term to the model. Our results showed that the quadratic term did not reach statistical significance in both the EC and PT model and therefore we proceeded with the simpler model for parsimony and interpretability reasons

Trajectory of empathy in different disease stages: When disease severity at baseline measured by the CDR® plus NACC FTLD and its interaction with disease duration were added to the model, disease duration was a significant predictor of EC

score (estimate=−0.79, 95%CI=[−1.5, −0.11], p=0.003), though the interaction was not independently significant (Fig. 2 A). The predictors disease duration (estimate=−0.34, 95%CI=[−0.87, 0.19], p=0.050) and the interaction between disease severity at baseline and disease duration did not reach statistical significance in the PT model (Fig. 2 B). As for the EC model, the quadratic time term (disease duration) was not significant, thus a linear progression of both the EC and PT scores over time was used for further analyses; however, our analysis may have been underpowered for detecting a quadratic effect. For comparison, the mean annual slope of change in EC (0.11±0.06) and PT (0.04±0.40) score in the normal control group was stable.

Longitudinal brain-behavior modelling

Relationship between change in empathy over time and progressive atrophy: Faster gray matter loss in the left thalamus (estimate=0.01, 95%CI=[0.00, 0.01], p<0.001) of the SN and the left caudate (estimate=0.01, 95%CI=[0.00, 0.01], p=0.049) of the SAN was significantly associated with more rapid worsening on the EC subscale. For PT score, greater volume loss in the left inferior parietal lobule (estimate=0.00, 95%CI=[0.00, 0.01], p=0.023) and right temporal pole (estimate=−0.01, 95%CI=[−0.01, −0.00], p=0.036) of the DMN were statistically significant predictors.

DISCUSSION

This study confirms in a large sample of patients from the multi-site ALLFTD study that loss of empathy is a very early feature of bvFTD, observed in the earliest symptomatic, and in some cases even in the presymptomatic, stage of the disease, and that the changes are burdensome for caregivers. We also found evidence that empathy continues decreasing once the full phenotype is established, with lower scores in FTLD-CDR stages 2/3 than in stage 1. One of our key findings is that level of empathy is lower in very mild bvFTD than in asymptomatic individuals. In addition, the analysis we performed in the asymptomatic subgroup of carriers and non-carriers of pathogenic variants shows that individuals carrying a pathogenic *C9orf72* variant have lower empathy score than either of the other two variants (*GRN*, *MAPT*) and non-carriers. Our longitudinal analyses revealed that the ability to empathize declines over time in bvFTD, and that the rate of loss of empathy corresponds to rate of volume loss in structures of the SN, SAN, and DMN. While two decades of clinical observations and smaller studies have suggested that empathy loss occurs early in bvFTD, this study is the first to provide comprehensive evidence to document this phenomenon in a well-powered sample at the very earliest disease stages.

One obstacle for early diagnosis and treatment of patients with bvFTD is that psychiatric conditions such as bipolar disorders or schizophrenia can mimic characteristic bvFTD social symptoms.[26] Our findings provide novel evidence that the psychometrically validated IRI informant-based questionnaire can pick up loss of empathy in persons who are in the pre-dementia stage. The lower empathy scores in asymptomatic *C9orf72* carriers compared to the other asymptomatic carrier and non-carrier groups are in line with previous studies showing that in *C9orf72* carriers' changes in behavior and in underlying key networks for social behavior predate the fully symptomatic phase of the disease, even by years.[27,28] In

addition, and in line with previous work,[4] our study shows that loss of empathy has a negative impact on informants' well-being, providing additional rationale for suggesting that caregivers should be incorporated early into the care planning process.

Our analyses investigating the temporal trajectory of empathy show that loss of empathy occurs at each stage in the disease progression and over time regardless of pathogenic variant status and disease severity at baseline. Consistent with cross-sectional evidence from individuals with neurodegenerative diseases,[15] our longitudinal brain-behavior analyses show that loss of emotional empathy over time corresponds to progressive atrophy in subcortical regions of the SN (thalamus) and SAN (caudate) underlying basic autonomic responsiveness, emotional resonance, and awareness.[29,30] In addition, we found that progressive changes in cognitive empathy are associated with loss of brain volume in lateral temporal regions of the DMN (temporal pole, inferior parietal lobule) that are involved in thinking about the emotional state of other people as well as in self-other distinction processes.[31,32] The importance of both cortical and subcortical regions of these social networks for empathy is in line with previous studies from patients with neurodegenerative diseases[2] and stroke[33], as well as with studies on empathy for pain in healthy participants.[34] Overall, our findings suggest that dementia health care providers can use the IRI to detect and monitor loss of empathy, and thus clinical and neuroanatomical progression, over the course of sporadic and genetic bvFTD. Thus, the IRI may be used as an outcome measure in ongoing clinical trials[35] for patients who are in both early and more advanced stages of bvFTD.

LIMITATIONS AND CONCLUSIONS

The focus of this study was to model loss of empathy across asymptomatic and symptomatic stages of bvFTD, and we did not investigate the temporal trajectory of empathy in other neurodegenerative disease syndromes. Though previous cross-sectional studies showed the usefulness of the IRI for differential diagnosis of neurodegenerative syndromes,[2,20] this work cannot answer whether the measure is able to differentiate neurodegenerative diseases as well as neurodegenerative from psychiatric conditions based on their longitudinal patterns of empathy. In our sample, pathogenic variant carriers showed earlier symptom onset than non-carriers. Though many participants did not know their own genetic status and we used informant ratings of empathy, it remains an open question whether awareness of pathogenic variant status is associated with an earlier recognition of symptoms. In addition, even though it is well known that bvFTD is a clinically, neuroanatomically, and pathologically heterogeneous syndrome, we did not examine the longitudinal patterns of empathy in different bvFTD subtypes. [36] These subtypes are associated with divergent patterns of volume loss in subcortical regions of the SN, SAN, and DMN, thus may also show different patterns of loss of empathy over time, which ought to be investigated in future research. Moreover, we were not able to investigate the relationship between empathy and other processes of social functioning (e.g., theory of mind) across different disease stages and over time because currently this data is not available for this large multisite dataset. Though previous evidence suggests that psychotropic drugs (e.g., selective serotonin inhibitors, antipsychotics) may be used for the management of behavioral symptoms in FTD,[37,38] the degree to which such medications improve symptoms of empathy still needs to

be investigated in future studies. Finally, future research should examine the degree to which loss of empathy in bvFTD is related to generalized loss of interest (i.e., apathy) versus direct damage to socioemotional systems including the SN, SAN, and DMN.

In conclusion, our study adds to the current literature on empathy in patients with neurodegenerative diseases by showing that the questionnaire can be broadly used for early diagnosis and to monitor clinical symptoms in patients with sporadic and genetic variants of bvFTD who are in asymptomatic and very mild symptomatic disease stages. Our findings also reiterate the need for both pharmacologic and non-pharmacologic therapeutic interventions that will target early behavioral symptoms like loss of empathy in patients with bvFTD, to mitigate the burden not only for affected patients but also for their caregivers and families.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Research in Context

Systematic Review:

The authors reviewed studies on the neuronal correlates of empathy, and loss of empathy in behavioral variant frontotemporal dementia (bvFTD) using PubMed. Numerous studies show that empathy is a multidimensional construct that relies on regions of the salience, semantic-appraisal, and default-mode networks. While many smaller studies demonstrate that empathy is affected in bvFTD, no previous study has comprehensively investigated empathy across asymptomatic and symptomatic disease stages.

Interpretation:

Our findings show that loss of empathy occurs in very early stages of bvFTD, and further declines with disease progression. This knowledge may help clinicians identify patients with bvFTD earlier and monitor their symptom progression over time.

Future directions:

To determine the value of IRI informant-ratings for differential diagnosis of neurodegenerative diseases and distinction of bvFTD subtypes, future studies need to investigate the temporal trajectories of empathy in other neurodegenerative syndromes and within the clinically and neuroanatomically heterogeneous bvFTD syndrome.

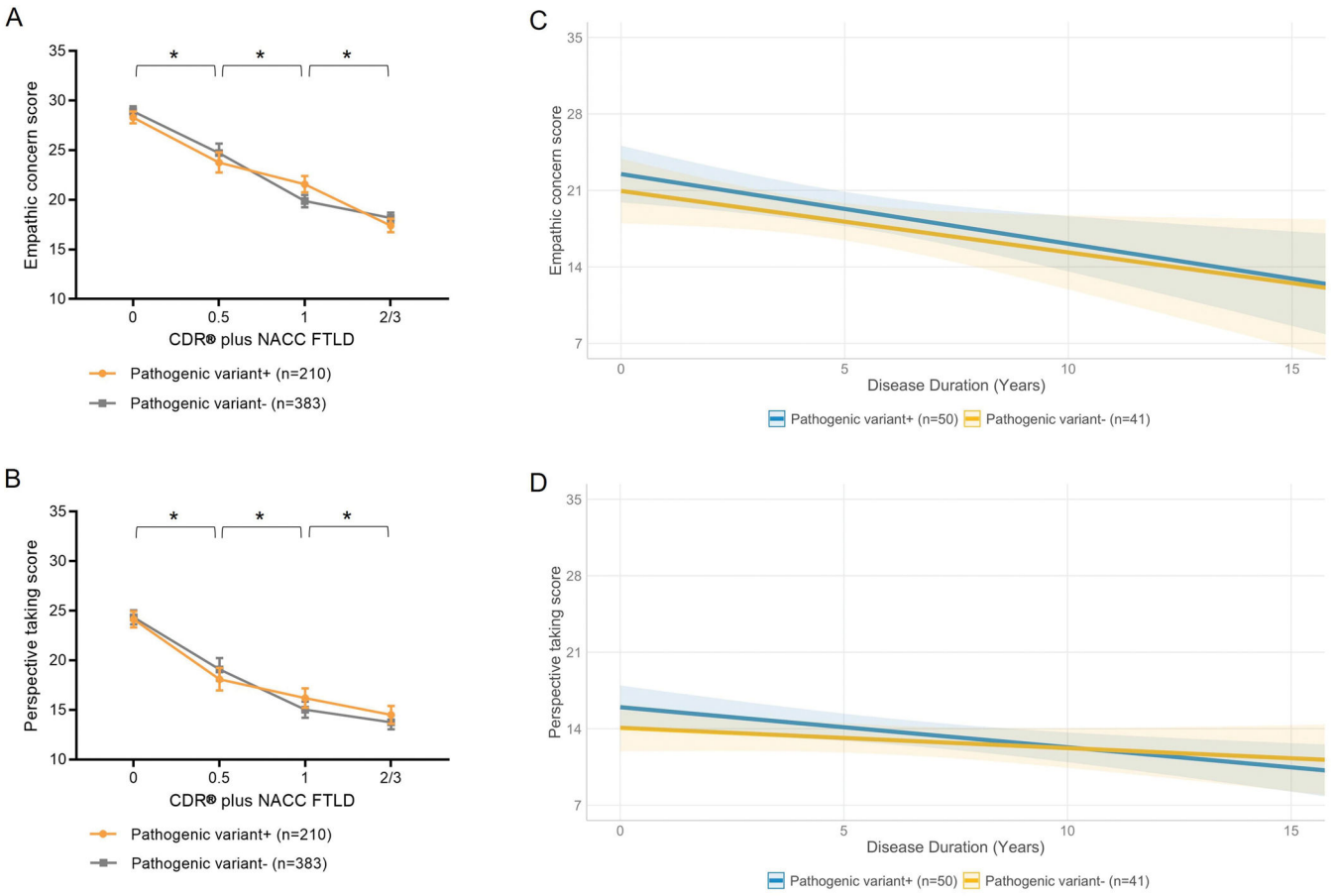

Fig. 1.

EC and PT scores reflect disease severity measured by the global CDR® plus NACC FTLD score regardless of pathogenic variant status, and worsen at a similar rate over time in pathogenic variant carriers and non-carriers.

(A) LME model analysis in the full sample (n=594) revealed a significant main effect of CDR® plus NACC FTLD (p<0.001) with regard to the EC score, showing that the score changes as a function of disease stage from asymptomatic to very mild (estimate=4.38, 95%CI=[2.79, 5.97], p<0.001), very mild to mild (estimate=−3.52, 95%CI=[−5.19, −1.84], p<0.001), and mild to moderate/severe (estimate=2.93, 95%CI=[1.71, 4.14], p<0.001) disease. The interaction between CDR® plus NACC FTLD and pathogenic variant status did not reach statistical significance. (B) Similar to the EC subscale, CDR® plus NACC FTLD significantly predicted the PT score (p<0.001), showing that the score significantly worsened between asymptomatic and very mild (estimate=5.64, 95%CI=[3.81, 7.48], p<0.001), very mild and mild (estimate=−3.24, 95%CI=[−4.82, −1.13], p=0.002), as well as between mild and moderate/severe (estimate=1.49, 95%CI=[0.18, 2.79], p=0.023) disease stage. The interaction CDR® plus NACC FTLD by disease stage at baseline did not reach statistical significance for predicting the PT score. (C) In the fully longitudinal sample (n=91), disease duration significantly predicted (estimate=−0.29, 95%CI=[−0.59, −0.00], p=0.049) the EC score, demonstrating that patients with longer disease duration had lower EC score compared to patients with shorter disease duration. However, the interaction disease

duration by pathogenic variant status was not statistically significant. (D) The PT score was significantly predicted by disease duration (estimate=−0.49, 95%CI=[−0.90, −0.09], p=0.019), showing that the score significantly decreased over time with longer disease duration. The interaction between disease duration and pathogenic variant status did not reach statistical significance for predicting the PT score. Age at symptom onset and sex were included as covariates of no interest in each analysis. CDR® plus NACC FTLD=CDR® Dementia Staging Instrument plus Behavior and Language domains from the NACC FTLD Module.

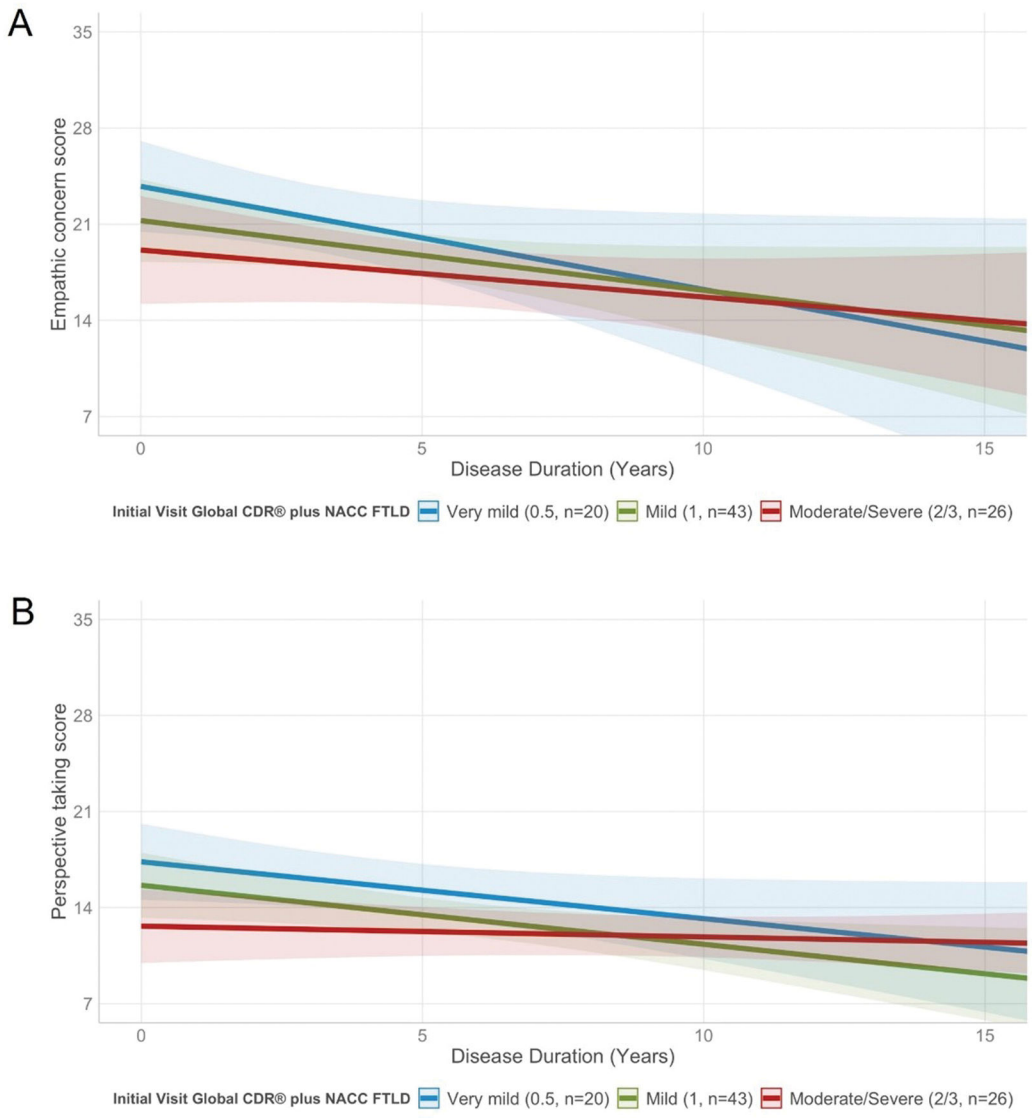

Fig. 2.

EC and PT scores of patients with early and more advanced disease stages at baseline significantly decline at a similar rate over time.

(A) The EC score was significantly predicted by disease duration (estimate=−0.42, 95%CI=[−0.98, 0.13], p=0.061), but the interaction disease duration by disease severity at baseline (very mild/mild versus moderate/severe) was not significant. This shows that patients who are in both early and more advanced disease stages show similar rates of decline on the EC subscale. (B) Disease duration significantly predicted the PT score in the main effect model (estimate=−0.21, 95%CI=[−0.57, 0.15], p=0.074). However, the interaction between disease duration and disease severity at baseline (very mild/mild versus moderate/advanced) did not reach statistical significance, demonstrating that rate of decline on the PT subscale is independent from disease severity at baseline. Age at symptom onset and sex were added to each model as covariates of no interest. CDR® plus NACC

FTLD=CDR® Dementia Staging Instrument plus Behavior and Language domains from the NACC FTLD Module.

Author	Contribution
GT	Study design and concept, statistical analysis, data interpretation, drafting the manuscript
YC	Statistical analysis, substantial contribution to the manuscript
PC	Statistical analysis, substantial contribution to the manuscript
BSA	Data acquisition, data interpretation, substantial contribution to the manuscript
DB	Data management, substantial contribution to the manuscript
KDR	Data interpretation, substantial contribution to the manuscript
LKF	Data interpretation, substantial contribution to the manuscript
NG	Data acquisition, data interpretation, substantial contribution to the manuscript
JGR	Data interpretation, substantial contribution to the manuscript
NRGR	Patient recruitment, substantial contribution to the manuscript
MG	Data interpretation, substantial contribution to the manuscript
HWH	Data acquisition, obtaining funding, substantial contribution to the manuscript
JK	Statistical analysis, substantial contribution to the manuscript
WK	Statistical analysis, substantial contribution to the manuscript
MIL	Data interpretation, substantial contribution to the manuscript
GL	Data interpretation, substantial contribution to the manuscript
IL	Data interpretation, substantial contribution to the manuscript
IRM	Data interpretation, substantial contribution to the manuscript
BP	Data interpretation, substantial contribution to the manuscript
EMR	Data interpretation, substantial contribution to the manuscript
KR	Data interpretation, substantial contribution to the manuscript
JCR	Data acquisition, substantial contribution to the manuscript
AMS	Statistical analysis, substantial contribution to the manuscript
MCT	Data interpretation, substantial contribution to the manuscript
AT	Data interpretation, substantial contribution to the manuscript
SW	Data management, substantial contribution to the manuscript
ZKW	Data interpretation, substantial contribution to the manuscript
BFB	Obtaining funding, data interpretation, substantial contribution to the manuscript
ALB	Obtaining funding, data interpretation, substantial contribution to the manuscript
HJR	Obtaining funding, data interpretation, substantial contribution to the manuscript
KPR	Study design and concept, obtaining funding, statistical analysis, data interpretation, drafting the manuscript

Table 1:

Demographic and clinical characteristics of patient sample.

	Asymptomatic pathogenic variant−	Asymptomatic pathogenic variant+	bvFTD pathogenic variant−	bvFTD pathogenic variant+	Behavioral MCI pathogenic variant+	*p*-value
n	163	114	219	88	10	--
Age at first evaluation	47.9 (13.6)	43.5 (14.5)	62.7 (8.7)	58.4 (8.5)	53.8 (12.5)	<0.0001
Pathogenic variant, *C9orf72, GRN, MAPT*	---	46, 30, 38	---	45, 13, 30	4, 3, 3	---
Sex, M/F	59/103	50/63	138/80	44/43	6/4	<0.0001
Education	15.5 (2.5)	15.6 (2.6)	15.7 (2.9)	15.3 (2.8)	14.8 (2.0)	=0.512
Global CDR® plus NACC FTLD	0	0	1.6 (0.7)	1.6 (0.7)	0.6 (0.2)	<0.001

bvFTD=behavioral variant frontotemporal dementia; MCI=Mild Cognitive Impairment; *C9orf72*=Chromosome 9 open reading frame 72; *GRN*=Progranulin; *MAPT*=Microtubule-associated protein tau; M=Male, F=Female; CDR® plus NACC FTLD= CDR® Dementia Staging Instrument plus Behavior and Language domains from the NACC FTLD Module

Longitudinal behavior subsample: Number of patients with 2 timepoints: 34; Number of patients with 3 timepoints: 13; Number of patients with 4+ timepoints: 4; Number of healthy controls with 2 timepoints: 55; Number of healthy controls with 3 timepoints: 30; Number of healthy controls with 4+ timepoints: 45.

Table 2:

Summary of significant results showing the relationship among empathy, disease stage, disease duration, and neuroanatomy.

Sample	Modeled variables	*b* coefficient	95% CI	p-value
Full (n=594, 666 obs.)	*Empathic Concern (EC)*			
	-Asymptomatic (0) vs. very mild (0.5)	4.38	2.79, 5.97	<0.001
	-Very mild (0.5) vs. mild (1)	−3.52	−5.19, −1.84	<0.001
	-Mild (1) vs. moderate/severe (2/3)	2.93	1.71, 4.14	<0.001
	Perspective Taking (PT)			
	-Asymptomatic (0) vs. very mild (0.5)	5.64	3.81, 7.48	<0.001
	-Very mild (0.5) vs. mild (1)	−3.24	−4.82, −1.13	=0.002
	-Mild (1) vs. moderate/severe (2/3)	1.49	0.18, 2.79	=0.023
Asymptomatic (n=277, 277 obs.)	*Empathic Concern (EC)*			
	-Asymptomatic (0) *C9orf72* vs. asymptomatic (0) pathogenic variant negative	η^2=0.03	0.00, 0.07	=0.067
Longitudinal (n=91, 212 obs.)	*Disease duration*			
	-Empathic Concern (EC)	−0.58	−0.88, −0.28	<0.001
	-Perspective Taking (PT)	−0.29	−0.50, −0.08	=0.010
	-CDR® plus NACC FTLD/EC	−0.79	−1.5, −0.11	=0.003
	-CDR® plus NACC FTLD/PT	−0.34	−0.87, 0.19	=0.050
	Anatomic correlations			
	-Left thalamus/EC	0.01	0.00, 0.01	<0.001
	-Left caudate/EC	0.01	0.00, 0.01	=0.049
	-Left inferior parietal/PT	0.00	0.00, 0.01	=0.023
	-Right temporal pole/PT	−0.01	−0.01, −0.00	=0.036

obs=observations, CDR® plus NACC FTLD= CDR® Dementia Staging Instrument plus Behavior and Language domains from the NACC FTLD Module