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Basal parasympathetic deficits in *C9orf72* hexanucleotide repeat expansion carriers relate to smaller frontoinsula and thalamus volume and lower empathy

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ABSTRACT

Diminished basal parasympathetic nervous system activity is a feature of frontotemporal dementia that relates to left frontoinsula dysfunction and empathy impairment. Individuals with a pathogenic expansion of the hexanucleotide repeat in chromosome 9 open reading frame 72 (*C9orf72*), the most common genetic cause of frontotemporal dementia and amyotrophic lateral sclerosis, provide a unique opportunity to examine whether parasympathetic activity is disrupted in genetic forms of frontotemporal dementia and to investigate when parasympathetic deficits manifest in the pathophysiological cascade. We measured baseline respiratory sinus arrhythmia, a parasympathetic measure of heart rate variability, over two minutes in a sample of 102 participants that included 19 asymptomatic expansion carriers ($C9^+$ asymp), 14 expansion carriers with mild cognitive impairment ($C9^+$ MCI), 16 symptomatic expansion carriers with frontotemporal dementia ($C9^+$ FTD), and 53 expansion-negative healthy controls ($C9^-$ HC) who also underwent structural magnetic resonance imaging. In follow-up analyses, we compared baseline respiratory sinus arrhythmia in the $C9^+$ FTD group with an independent age-, sex-, and clinical severity-matched group of 26 people with sporadic behavioral variant frontotemporal dementia. The Frontotemporal Lobar Degeneration-modified Clinical Dementia Rating-Sum of Boxes score was used to quantify behavioral symptom severity, and informant ratings on the Interpersonal Reactivity Index provided measures of participants' current emotional (empathic concern) and cognitive (perspective-taking) empathy. Results indicated that the $C9^+$ FTD group had lower baseline respiratory sinus arrhythmia than the $C9^+$ MCI, $C9^+$ asymp, and $C9^-$ HC groups, a deficit that was comparable to that of sporadic behavioral variant frontotemporal dementia. Linear regression analyses indicated that lower baseline respiratory sinus arrhythmia was associated with worse behavioral symptom severity and lower empathic concern and perspective-taking across the *C9orf72* expansion carrier clinical spectrum. Whole-brain voxel-based morphometry analyses in participants with *C9orf72* pathogenic expansions found that lower baseline respiratory sinus arrhythmia correlated with smaller gray matter volume in the left frontoinsula and bilateral thalamus, key structures that support parasympathetic function, and in the bilateral parietal lobes, occipital lobes, and cerebellum, regions that are also vulnerable in individuals with *C9orf72* expansions. This study provides novel evidence that basal parasympathetic functioning is diminished in FTD due to *C9orf72* expansions and suggests that baseline respiratory sinus arrhythmia may be a potential non-invasive biomarker that is sensitive to behavioral symptoms in the early stages of disease.

Abbreviations: UCSF, University of California, San Francisco; CDR, Clinical Dementia Rating Scale; VBM, voxel-based morphometry; RSA, Respiratory Sinus Arrhythmia, *C9orf72*, Chromosome 9 open reading frame 72.

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1. Introduction

Genetic forms of frontotemporal dementia (FTD) provide a critical window into the disease's earliest manifestations. Approximately 15–30 % of FTD cases are familial and caused by autosomal dominant mutations. (Greaves and Rohrer, 2019) The hexanucleotide repeat expansion in chromosome 9 open reading frame 72 (*C9orf72* or *C9*) is the most common genetic cause of FTD and amyotrophic lateral sclerosis (ALS). (DeJesus-Hernandez et al., 2011; Gijselinck et al., 2012; Ling et al., 2013) While in FTD there is predominant atrophy in the frontal and temporal lobes, in ALS there is progressive dysfunction in upper and lower motor neuron systems. Both FTD and ALS due to *C9orf72* expansions are associated with frontotemporal lobar degeneration with TAR DNA-binding protein 43 pathology (FTLD-TDP) and form two ends of a clinicoanatomical spectrum. People in families with *C9orf72* expansions, therefore, can present with either syndrome or exhibit mixed features of both. (Rohrer et al., 2015; Boeve et al., 2012) In some cases, dipeptide repeat protein inclusions and RNA foci may precede FTLD-TDP aggregation in *C9orf72* expansion carriers and create a preclinical window in which people lack overt symptoms but exhibit early signs of a disease process. (Lehmer et al., 2017; Gendron et al., 2017; Vatsavayai et al., 2019).

People with the pathogenic *C9orf72* expansion carry the genetic mutation from birth but typically do not develop symptoms until mid- to late-life. (Majounie et al., 2012; Gijselinck et al., 2016; Moore et al., 2019) Although changes in language do not often arise in the clinical phase, alterations in emotions and social behavior are common. (Convery et al., 2019) Many *C9orf72* pathogenic expansion carriers develop the behavioral variant of FTD (bvFTD), (Sha et al., 2012; Solje et al., 2015) the most common clinical subtype of FTD, (Bang et al., 2015) which is characterized by loss of empathy, apathy, disinhibition, compulsivity, hyperorality, and executive dysfunction. (Rascovsky et al., 2011; Barker et al., March 10, 2022) The symptoms that emerge in *C9orf72* pathogenic expansion carriers with bvFTD resemble those of sporadic disease but more often include delusions and hallucinations. (Sha et al., 2012; Mahoney et al., 2012a; Devenney et al., 2014; Snowden et al., 2012; Kertesz et al., 2013) Anatomically, prominent atrophy and dysfunction in the frontoinsula (i.e., ventral anterior insula) and anterior cingulate cortex (Zhou et al., 2010; Pan et al., 2012; Rosen et al., 2002)—key hubs in the salience network (Seeley et al., 2007)—and in the frontal and temporal lobes more broadly are hallmark characteristics of bvFTD. (Rosen et al., 2002; Kril et al., 2005; Seeley et al., 2008) The neuroimaging features of bvFTD due to a *C9orf72* pathogenic expansion resemble those of sporadic cases but also often include atrophy in the medial pulvinar nucleus of the thalamus, parietal lobes, and cerebellum. (Rohrer et al., 2015; Sha et al., 2012; Mahoney et al., 2012a, b; Whitwell et al., 2012; Yokoyama and Rosen, 2012; Bonham et al., 2022; Bertrand et al., 2018; Lee et al., 2017; Bocchetta et al., 2020).

In bvFTD, salience network dysfunction relates to alterations in autonomic nervous system outflow. The salience network is a distributed neural system that guides behavior by triggering phasic bursts of autonomic and motor reactivity during emotions and by maintaining tonic physiological rhythms at rest. (Seeley et al., 2007; Sturm et al., 2018a; Guo et al., 2016b; Beissner et al., 2013) Laboratory-based studies have shown that people with bvFTD have diminished autonomic reactivity to stimuli that typically elicit negative emotions including disgust, embarrassment, and sadness, and these emotional reactivity deficits are associated with atrophy in salience network structures. (Sturm et al., 2013b; Sturm et al., 2006; Sturm et al., 2008; Scherling et al., 2017; Hua et al., 2019; Eckart et al., 2012; Verstaen et al., 2016; Muhtadie et al., 2019; Joshi et al., 2014; Marshall et al., 2019) Basal physiology (i.e., autonomic nervous system activity measured in task-free settings) is also impaired in bvFTD. Compared to healthy controls, people with bvFTD have lower baseline skin conductance levels, a sympathetic measure of eccrine sweat gland activity, and lower baseline respiratory sinus arrhythmia (RSA), a parasympathetic measure of vagally-mediated heart rate variability. (Sturm et al., 2018a; Guo et al., 2016b; Joshi et al., 2014; Berntson et al., 1997; Sturm et al., 2018b) Lower baseline RSA in bvFTD relates to atrophy and lower functional connectivity in left-lateralized structures, including the left frontoinsula and anterior cingulate cortex, (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b) structures that make important contributions to the dynamic control of the vagus nerve on the heart across the respiratory cycle. (Craig, 2005; Berntson et al., 1993).

Our previous studies have shown that diminished parasympathetic activity underlies some of the core socioemotional symptoms, such as loss of empathy, in bvFTD. (Sturm et al., 2018b) Empathy can come in several forms. Whereas emotional empathy (e.g., empathic concern) produces feeling states that are shared between people, cognitive empathy (e.g., perspective-taking) allows people to identify the thoughts and feelings of others. (Stellar et al., 2015; Beauchaine et al., 2013; Di Bello et al., 2020; Kogan et al., 2015; Miller et al., 2016; Porges, 2003; Porges, 2009; Oveis et al., 2009; Batson et al., 1995; Goetz et al., 2010) The parasympathetic nervous system encourages empathy and prosocial behaviors, such as helping and consoling, by orienting attention outward onto others and by reducing feelings of personal distress. (Smith, 2006; Singer and Klimecki, 2014) We have found diminished baseline RSA in bvFTD relates to reduced informant-reported agreeableness and lower prosocial behavior during laboratory-based tasks, deficits that both correlate with tissue loss in the left frontoinsula. (Sturm et al., 2018b; Sturm et al., 2017) Smaller gray matter volume in the bilateral medial pulvinar nucleus of the thalamus, a vulnerable region in *C9orf72* pathogenic expansion carriers, was also associated with diminished baseline RSA, prosocial behavior, and generosity in bvFTD. (Guo et al., 2016b; Sturm et al., 2018b).

In the present study, we examined basal parasympathetic activity and its relation to gray matter volume, behavioral symptom severity, and empathy in *C9orf72* pathogenic expansion carriers across the clinical continuum. We hypothesized that, like in sporadic bvFTD, baseline RSA would be impaired in people with FTD due to *C9orf72* pathogenic expansions but that lower baseline RSA levels might also be evident earlier in the disease course. Even decades prior to symptom onset, asymptomatic *C9orf72* pathogenic expansion carriers have weaker salience network connectivity (Lee et al., 2014) and lower informant-reported empathy than healthy family members who do not carry the mutation. (Foster et al., 2022; Gossink et al., 2022) To gain insights into when parasympathetic deficits manifest, we also assessed asymptomatic and mildly symptomatic *C9orf72* pathogenic expansion carriers with the expectation that baseline RSA impairments would be more pronounced in those with greater symptom severity. We next investigated where lower gray matter volume in the brain related to diminished baseline RSA across the *C9orf72* clinical spectrum. While some of the neural correlates of RSA deficits in *C9orf72*-mediated FTD may differ from those in sporadic cases, we expected much overlap with our prior studies. (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b) We hypothesized that in *C9orf72* pathogenic expansion carriers, lower baseline RSA would relate to smaller gray matter volume in the frontoinsula and medial pulvinar nucleus of the thalamus, early sites of dysfunction in *C9orf72* pathogenic expansion carriers, and to lower empathy.

2. Materials and methods

2.1. Participants

We enrolled 102 participants from the ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) project, a study that follows families with known or suspected familial FTD. All participants were evaluated at the University of California, San Francisco (UCSF) Memory and Aging Center. This study was approved by the Human Research Protection Program at the University of California, San Francisco, and all participants, or their surrogates, gave their informed

consent before participating.

Participants underwent an extensive multidisciplinary assessment that included a clinical interview, neurological exam, functional assessment, neuropsychological testing, and neuroimaging. The neuropsychological battery included tests of memory, language, executive functioning, visuospatial processing, and mood. (Kramer et al., 2003) The Frontotemporal Lobar Degeneration-Specific Clinical Dementia Rating scale (FTLD-CDR), which is based on a semi-structured interview with an informant, was used to assess behavioral symptom severity. (Knopman et al., 2008) Scores on the FTLD-CDR range from 0 (no symptoms) to 0.5 (very mild symptoms), 1 (mild symptoms), 2 (moderate symptoms), and 3 (severe symptoms).

Genetic testing confirmed that 49 participants in our sample had a *C9orf72* pathogenic repeat expansion ($C9^+$). We used participants' clinical diagnoses and FTLD-CDR scores to determine their disease stage at the time of testing and to assign them to a clinical group. The $C9^+$ group included healthy individuals without symptoms ($C9^+$ asymp, $n = 19$); those with mild cognitive impairment (MCI) or mild behavioral changes that did not interfere with functioning ($C9^+$ MCI, $n = 14$); and symptomatic individuals who met criteria for FTD ($C9^+$ FTD, $n = 16$). (Rascovsky et al., 2011) In the symptomatic group, nine met criteria for bvFTD, five had FTD and motor neuron disease (FTD-MND), one had semantic variant primary progressive aphasia, and one met no published research criteria yet exhibited executive deficits and disinhibition. The remaining 53 participants came from families with a known FTD-causing mutation but did not carry a pathogenic variant in the *C9orf72*, granulin precursor protein (*GRN*), or microtubule-associated protein tau (*MAPT*) genes. As the participants in this group did not carry the *C9orf72* pathogenic repeat expansion ($C9^-$), and they were functionally intact (FTLD-CDR score of 0) and free of neurological and untreated psychiatric disorders, they served as the $C9^-$ healthy control (HC) group (henceforth, "$C9^-$ HC").

To investigate our results in more detail, we included two additional comparison groups in subsequent analyses. Twenty-six participants with sporadic bvFTD (Rascovsky et al., 2011) (all were negative on genetic testing for *C9*; *MAPT*, and *GRN* mutations) and 25 older healthy controls (older HC) who were community-dwelling volunteers recruited from the Hillblom Healthy Aging Network, a longitudinal study of healthy aging at UCSF. These older HC, who were closer in age to the $C9^+$ FTD group, completed the same clinical assessment as the other participants in the study. In addition to being cognitively normal and free of psychiatric and neurological disorders, all older HC had FTLD-CDR scores of zero. By including these additional groups in follow-up analyses, we were able to: (1) compare baseline RSA levels in $C9^+$ FTD and sporadic FTD to assess whether there were comparable deficits were in both groups, and (2) confirm that baseline RSA deficits in $C9^+$ FTD were still evident when compared to older HC instead of the younger $C9^-$ HC group.

2.2. Procedure

Autonomic nervous system testing was conducted at the UCSF Center for Psychophysiology and Behavior. Prior to testing, height, and weight were recorded. and later used to compute measures of body mass index (BMI), which can influence RSA. (Masi et al., 2007; Maver et al., 2004; Arone et al., 1995) Participants also reported on their caffeine and tobacco use in the 24 h prior to the laboratory assessment. Their prescribed psychotropic medications psychotropic medications (i.e., benzodiazepine, dopamine agonist, serotonin antagonist and reuptake inhibitors, selective serotonin reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, and tricyclic antidepressants) were also recorded. Assessment of baseline autonomic activity, our focus here, was the first task in a larger battery of emotion-relevant tests that participants completed. These tasks and measures are not relevant to the present study.

2.3. Resting baseline task

Participants were seated in a comfortable chair in a well-lit experiment room and sat 4.25 feet away from a 21.4-inch computer monitor. Participants were asked to clear their minds and to look at a black "X" on a white background for two minutes.

2.4. Physiological recordings

Sensors were applied to participants to obtain continuous measures of physiological activity. Biopac MP150 bioamplifiers and a computer equipped with data acquisition software were used for all physiological data collection. Electrodes were placed in a bipolar configuration on opposite sides of the participant's chest to collect inter-beat interval (IBI) data. Inter-cycle interval (ICI) data was collected with pneumatic bellows or a respiration transducer that was stretched around the thoracic region. RSA was calculated as the difference in milliseconds between the shortest inter-beat interval during inspiration and the longest inter-beat interval during expiration. This "peak-valley" approach to RSA calculation provides an index of vagally-mediated parasympathetic activity. (Berntson et al., 1997; Grossman and Kollai, 1993).

Physiological data were processed using a custom pipeline, (Sturm et al., 2018b) scripted in AcqKnowledge software (v4.4, https://www.biopac.com). Four $C9^+$ participants were tested but excluded from this study due to invalid physiological data (one participant had a sensor fail during testing, and three participants had cardiac arrhythmias for more than 10 percent of the baseline period).

2.5. Structural neuroimaging

Participants ($n = 99$) underwent research-quality structural magnetic resonance imaging (MRI). Ninety-five percent of scans were collected within one week of the autonomic testing; in the remaining five percent, two $C9^+$ participants had scans collected within three months of the autonomic testing, and three $C9^-$ HC had scans collected within 12 months. Scans were completed on a 3 Tesla Siemens TIM Trio scanner equipped with a 12-channel head coil or a 3 Tesla Siemens Prisma scanner quipped with a 64-channel head coil both located at the UCSF Neuroscience Imaging Center. Whole brain structural images were acquired using volumetric 3D T1-weighted sagittal Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (160 sagittal slices; slice thickness = 1.0 mm; field-of-view [FOV] = 256 x 240 mm^2; matrix 256 x 240; voxel size 1.0 x 1.0 x 1.0 mm^3; repetition time [TR] = 2300 msec; TE=2.98 msec; flip angle = 9 degrees).

All structural MRI images were visually inspected for movement artifacts prior to being preprocessed in Statistical Parametric Mapping 12 (SPM12). (Penny et al., 2011) Structural images were segmented into gray matter using the segment program in SPM12 where images were modulated and warped to the Montreal Neurological Institute template. All other SPM12 default parameters were used. Segmented images were visually inspected for adequate segmentation and then smoothed with an 8 mm full-width at half-maximum Gaussian kernel.

2.6. Informant-Reported empathy

Informants rated the $C9^+$ participants current empathy levels on a short-from version of the Interpersonal Reactivity Index (IRI), a multidimensional measure of empathy (Davis, 1983) that is psychometrically valid in clinical and dementia populations. (Foster et al., 2022; Rankin et al., 2006) The Empathic Concern subscale measures the degree to which one helps and cares for others in need, a type of emotional empathy; the Perspective-Taking subscale measures the degree to which one can identify others' emotions and perspectives, a type of cognitive empathy. Each IRI subscale consists of seven items that are rated on 5-point Likert scales from 1 (*does not describe well*) to 5 (*describes well*).

Items were summed to calculate total subscale scores. Scores ranged from 7 to 35 with lower scores indicating lower empathy. IRI data were included if collected within six months of the autonomic assessment (95 % of participants had IRI measures completed by informants within a week of their autonomic testing). Seven $C9^+$ participants did not have available IRI data.

2.7. Statistical analysis

The statistical analyses were conducted in R Project (R Core Team, 2021) using RStudio. (RStudio Team, 2020) Analysis of variance (ANOVA) and chi-squared tests, where appropriate, were used to examine differences among the groups on the demographic, clinical, and neuropsychological measures.

We examined the distribution of baseline RSA and assessed the homogeneity of variance across the groups using Levene's test for equality of variances. As the baseline RSA data were skewed, and the groups had unequal variances, F=3.86, p = 0.012, we conducted a natural log transformation of RSA, which improved the proximity to a normal distribution and resolved the issue with homogeneity of variance, F=1.82, p = 0.149. An analysis of covariance (ANCOVA), controlling for age and sex, was used to test for group differences in baseline RSA. We also conducted several follow-up analyses in order to evaluate the robustness of our findings across the $C9^+$ spectrum with regard to age, medication use, and BMI. To compare baseline RSA in $C9^+$ FTD with that of sporadic bvFTD and older HC, we ran an additional ANCOVA (controlling for age and sex) in the $C9^-$ HC, older HC, $C9^+$ FTD, and sporadic bvFTD groups. Tukey-corrected *post hoc* tests were performed on all significant group effects to determine pairwise differences. In linear regression analyses, we examined whether lower baseline RSA predicted higher scores on the FTLD CDR Sum of Boxes and lower IRI empathy scores in the $C9^+$ participants when controlling for age and sex. Although we also investigated whether lower baseline RSA predicted lower scores on the Mini-Mental State Examination (MMSE), we did not expect an association given that MMSE is less sensitive to clinical severity in FTD. In all analyses, two-tailed tests were used with an alpha level of 0.05 to determine significance.

We conducted voxel-based morphometry (VBM) analyses with the voxel-based lesion-symptom mapping (VLSM) (Bates et al., 2003) toolbox in MATLAB. All analyses were masked to gray matter and included age, sex, total intracranial volume (to account for individual differences in head size), and scanner type as nuisance covariates. Whole-brain VBM analyses were performed to compare gray matter volume among the groups and to identify areas in which gray matter volume correlated with baseline RSA in the $C9^+$ participants (n = 47). We also ran follow-up analyses of baseline RSA (same covariates as above) in the sporadic bvFTD group (n = 26). To reduce Type 1 error resulting from multiple comparisons, permutation analyses were performed in VLSM. Statistical maps were calculated for 1,000 random assignments of the dependent variable, and the fifth percentile of the maximum cluster size was applied as a threshold to the raw $p < 0.001$ map. This combined peak and extent threshold permutation-based method has been used in prior imaging studies using similar methods in related clinical groups. (Wilson et al., 2010; Sturm et al., 2013a; Shdo et al., 2022).

3. Results

3.1. Demographics and Neuropsychological Performance.

The groups did not differ in sex, $X^2(3, N{=}102) = 3.44$, $p = 0.328$, or education, $F(3, 96) = 0.94$, $p = 0.426$. Although the racial compositions of the groups were similar, $X^2(15, N{=}94) = 9.60$, $p = 0.844$, the sample was predominantly White, which is consistent with the higher prevalence of *C9orf72* pathogenic expansions in Europe and North America (Renton et al., 2011). As expected, there were group differences in age, $F(3, 98) = 6.56$, $p < 0.001$, such that the $C9^+$ FTD group was older than the $C9^-$ HC and $C9^+$ asymp groups. There were no differences in BMI, $F(3, 90) = 1.02$, $p = 0.389$. The groups did not differ in their reported use of caffeine, $X^2(3, N{=}101) = 3.67$, $p = 0.300$, or tobacco, $X^2(3, N{=}102) = 5.64$, $p = 0.131$, in the 24 h prior to testing. They also did not differ in their prescribed medications, $X^2(3, N{=}102) = 3.60$, $p = 0.308$.

On neuropsychological testing, the $C9^+$ FTD group had lower scores than the other groups on tests of visuospatial processing, semantic knowledge, and verbal episodic memory. The $C9^+$ MCI group had lower scores than both the $C9^-$ HC and $C9^+$ asymp groups on select tests of executive functioning and visual episodic memory. On a test of nonverbal generation, the $C9^+$ MCI group had lower scores than the $C9^-$ HC group but not the $C9^+$ asymp group. The $C9^+$ asymp group performed well on cognitive testing in general and did not differ from the $C9^-$ HC group on any cognitive measure. There were no group differences on the Geriatric Depression Scale, and scores were in the range of minimal depressive symptoms for all groups. See Table 1.

3.2. Baseline RSA is diminished in $C9^+$ FTD

An ANCOVA (controlling for age and sex) revealed a main effect of group on baseline RSA, $F(3, 96) = 4.28$, $p = 0.007$. Tukey-corrected *post hoc* tests indicated that baseline RSA was lower in the $C9^+$ FTD group than in the $C9^-$ HC, t = -2.87, $p = 0.025$; $C9^+$ asymp, t = -3.33, $p = 0.006$; and $C9^+$ MCI, t = -2.83, p = 0.028, groups. No other pairwise comparisons were significant (see Fig. 1a). The five individuals in the $C9^+$ FTD group with FTD-MND were not outliers in baseline RSA (their RSA levels fell within 2 standard deviations of the group mean). See Supplementary Fig. 1.

3.3. Follow-Up analyses

We conducted several follow-up analyses to test the robustness of our findings in people along the $C9^+$ clinical spectrum.

Medications. Twenty-six participants (11 $C9^-$ HC, 6 $C9^+$ asymp, 6 $C9^+$ MCI, and 3 $C9^+$ FTD) were prescribed beta blockers or psychotropic medications. First, we coded whether people were prescribed these medications (0 = no, 1 = yes) and added this variable as an additional covariate in our original analyses in the full sample. Controlling for medication use had little effect on our results: the main effect of group on baseline RSA persisted, $F(3, 95) = 4.08$, $p = 0.009$, and the significant pairwise comparisons from the Tukey-corrected *post hoc* tests also remained unchanged. Next, we removed participants who were prescribed beta blockers or psychotropic medications from our full sample analysis, and our initial results endured. An ANCOVA revealed baseline RSA differences among the groups, $F(3, 70) = 5.33$, $p = 0.002$, and the Tukey-corrected *post hoc* tests indicated the same significant pairwise differences.

BMI. In 94 participants with available data, we examined whether BMI related to our results. Consistent with prior studies, (Masi et al., 2007; Maver et al., 2004; Arone et al., 1995) higher BMI correlated with lower baseline RSA, r = -0.24, t = -2.41, p = 0.018, across the sample. When we added BMI as an additional covariate in our original analyses in the full sample, our main effect of group held, $F(3, 87) = 3.60$, p = 0.017. While *post hoc* pairwise comparisons between the $C9^+$ FTD and $C9^-$ HC groups and the $C9^+$ FTD and $C9^+$ asymp groups remained significant, the comparison between $C9^+$ FTD and $C9^+$ MCI fell to trend level (p = 0.051).

Age. Even in healthy populations, RSA is often lower in older adults than in younger adults, and heart rate variability can exhibit normal age-related decline. (De Meersman, 1993a; Lipsitz, 2002; Mulcahy et al., 2019; Uchino et al., 2010) Given that FTD symptoms become more likely with advancing age, we conducted additional tests to confirm that the baseline RSA deficits we detected in people with $C9^+$ FTD were not due to the older mean age of this group. To create an age-matched sample (n = 82), we removed the youngest individuals from the $C9^-$ HC and $C9^+$

Table 1
Demographics and descriptive statistics.

	n	*C9*⁻ HC	*C9*⁺ asymp	*C9*⁺ MCI	*C9*⁺ FTD	Test Statistic	*p*
		n = 53	n = 19	n = 14	n = 16		
Age	102	46.5 (12.5)[d]	43.9 (13.1)[d]	53.9 (13.0)	59.3 (7.7)[ab]	F=6.56	0<.001
Sex	102					χ^2 = 3.44	0.328
F		31 (58.5 %)	10 (52.6 %)	6 (42.9 %)	12 (75 %)		
M		22 (41.5 %)	9 (47.4 %)	8 (57.1 %)	4 (25 %)		
Race	94					χ^2 = 9.60	0.844
Asian Indian		1 (1.9 %)	0 (0 %)	0 (0 %)	0 (0 %)		
Chinese		0 (0 %)	0 (0 %)	0 (0 %)	1 (6.2 %)		
Filipino		1 (1.9 %)	0 (0 %)	0 (0 %)	0 (0 %)		
Multiracial (White + Native American)		1 (1.9 %)	0 (0 %)	0 (0 %)	0 (0 %)		
Multiracial (White + not specified)		1 (1.9 %)	0 (0 %)	0 (0 %)	0 (0 %)		
White		42 (79.2 %)	19 (100 %)	14 (100 %)	14 (87.5 %)		
Did not specify		7 (13.2 %)	0 (0 %)	0 (0 %)	1 (6.2 %)		
Education	100	15.8 (2.5)	16.3 (1.7)	14.9 (2.1)	15.8 (2.6)	F=0.94	0.426
Medications	102					χ^2 = 3.60	0.308
Yes		11 (20.8 %)	6 (31.6 %)	6 (42.9 %)	3 (18.8 %)		
No		42 (79.2 %)	13 (68.4 %)	8 (57.1 %)	13 (81.2 %)		
Body Mass Index	94	28.0 (6.3)	25.1 (4.8)	27.9 (5.3)	27.6 (7.3)	F=1.02	0.389
Caffeine Consumption	101					χ^2 = 3.67	0.300
Yes		48 (90.6 %)	15 (78.9 %)	11 (78.6 %)	11 (73.3 %)		
No		5 (9.4 %)	4 (21.1 %)	3 (21.4 %)	4 (26.7 %)		
Tobacco Use	101					χ^2 = 5.64	0.131
Yes		8 (15.1 %)	0 (0 %)	2 (14.3 %)	0 (0 %)		
No		45 (84.9 %)	19 (100 %)	12 (85.7 %)	15 (100 %)		
Mini-Mental State Examination	93	28.7 (1.2)[cd]	28.5 (1.2)[d]	26.1 (2.6)[ad]	23.0 (6.2)[abc]	F=7.28	0.001
Modified Trails Errors	93	0.2 (0.4)	0.0 (0.0)	1.2 (0.9)	2.9 (3.4)	F=n/a	n/a
Modified Trails (# correct in 60 s)	93	42.7 (14.5)[cd]	46.2 (15.6)[cd]	22.4 (13.8)[ab]	18.2 (15.0)[ab]	F=16.6	0<.001
Design Fluency Correct (# correct in 60 s)	93	12.7 (3.6)[cd]	11.2 (2.7)[d]	8.5 (2.8)[a]	6.8 (3.0)[ab]	F=14.74	0<.001
Design Fluency Repetitions	93	1.8 (2.4)	0.8 (1.3)	0.8 (0.9)	2.5 (2.3)	F=2.38	0.074
Benson Figure Copy (/17)	94	15.7 (0.6)[d]	15.8 (0.5)[d]	15.7 (0.7)[d]	14.4 (1.2)[abc]	F=6.17	0.002
Calculation	94	4.6 (0.6)[d]	4.7 (0.5)[d]	4.2 (0.7)	3.5 (1.2)[ab]	F=5.62	0.004
Digits Backwards	94	5.5 (1.4)[cd]	5.3 (1.0)[cd]	4.0 (1.1)[ab]	3.1 (1.5)[ab]	F=15.37	0<.001
Peabody Picture Vocabulary Test (/16)	94	15.5 (0.9)[d]	15.7 (0.5)[d]	15.0 (1.0)[d]	13.3 (2.6)[abc]	F=5.88	0.003
Phonemic Fluency (# correct in 60 s)	94	16.4 (5.1)[d]	15.2 (4.1)[d]	12.6 (5.5)	7.8 (6.0)[ab]	F=11.03	0<.001
Semantic Fluency (# correct in 60 s)	94	22.9 (5.6)[cd]	23.1 (4.6)[cd]	16.9 (3.1)[ab]	13.2 (6.9)[ab]	F=14.74	0<.001
Benson Figure Copy 10-Minute Recall (/17)	94	13.4 (2.3)[cd]	12.6 (2.1)[cd]	9.4 (3.3)[ab]	7.9 (5.0)[ab]	F=9.6	0<.001
Boston Naming Test Spontaneous Correct (/15)	93	14.1 (1.2)[d]	13.9 (0.9)[d]	13.1 (1.9)	11.3 (3.7)[ab]	F=3.49	0.029
CVLT-MS: 10-Minute Delay Correct (/9)	89	7.8 (1.3)[d]	7.1 (1.9)[d]	6.3 (1.9)[d]	3.7 (3.1)[abc]	F=9.15	0<.001
Geriatric Depression Scale (/30)	86	5.2 (4.3)	4.5 (6.0)	5.7 (4.9)	9.4 (6.8)	F=2.26	0.087

ANOVAs or chi-square tests, where appropriate, were used to compare the groups. Means (and standard deviations) are presented for the continuous variables; counts and within-group percentages are presented for the categorical variables. n/a = not applicable. Tukey-corrected *post hoc* tests were applied to significant ANOVAs: a = different from *C9*⁻ HC, b = different from *C9*⁺ asymp, c = different from *C9*⁺ MCI, and d = different from *C9*⁺ FTD at $p < 0.05$.

asymp groups (14 *C9*⁻ HC group and 6 *C9*⁺ asymp) until these groups no longer differed in age from the *C9*⁺ FTD group (see Supplementary Table 1). Consistent with the results in the full sample, an ANCOVA (controlling for age and sex) in the age-matched sample yielded a main effect of group on baseline RSA, $F(3, 76) = 4.23$, $p = 0.008$. Tukey-corrected *post hoc* tests revealed the same significant pairwise comparisons as in the full sample (see Fig. 1b).

Additional Group Comparisons. To confirm that the baseline RSA deficits in the sporadic bvFTD and the *C9*⁺ FTD groups were similar and that they persisted when RSA in these groups was contrasted with the older HC as well as the younger *C9*⁻ HC, we conducted an ANCOVA (controlling for age and sex) that compared baseline RSA among the *C9*⁻ HC, older HC, *C9*⁺ FTD, and sporadic bvFTD groups. The groups were similar in sex, education, and race, and they had similar cognitive profiles on neuropsychological testing. Although the older HC group was older than the *C9*⁻ HC and *C9*⁺ FTD groups, their mean age did not differ from the sporadic bvFTD group. Likewise, the *C9*⁺ FTD and sporadic bvFTD groups were both older than the *C9*⁻ HC group but did not differ from each other. See Supplementary Table 2.

The ANCOVA revealed a main effect of group on baseline RSA, $F(3, 114) = 8.93$, $p < 0.001$. Tukey-corrected *post hoc* tests indicated that both the *C9*⁺ FTD group, $t = -3.05$, $p = 0.015$, and the sporadic bvFTD group, $t = -2.64$, $p = 0.045$, had lower baseline RSA than the *C9*⁻ HC group. The *C9*⁺ FTD group, $t = -4.00$, $p < 0.001$, and the sporadic bvFTD group, $t = -3.89$, $p < 0.001$, also had lower baseline RSA than the older HC group. As expected, the *C9*⁺ FTD and sporadic bvFTD groups did not differ from each other, $t = 0.62$, $p = 0.925$. Baseline RSA in the *C9*⁻ HC and older HC groups also did not differ, $t = 1.22$, $p = 0.613$. See Supplementary Fig. 2.

3.4. Lower baseline RSA predicts greater behavioral symptom severity and lower empathy in *C9*⁺ participants

A linear regression analysis in the *C9*⁺ group found that lower baseline RSA predicted higher FTLD CDR Sum of Boxes scores, $\beta = -0.43$, $t(45) = -2.65$, $p = 0.011$, but not lower MMSE, $\beta = 0.30$, $t(41) = 1.61$, $p = 0.116$ (see Fig. 2). In the *C9*⁺ participants, lower baseline RSA also predicted lower scores on both empathic concern, $\beta = 0.63$, $t(38) = 3.16$, $p = 0.003$, and perspective taking, $\beta = 0.46$, $t(38) = 2.25$, $p = 0.032$, subscales of the IRI (Fig. 3). The individuals in the *C9*⁺ FTD group with FTD-MND were not outliers in empathic concern or perspective taking (their levels fell within 2 standard deviations of the group mean) and did not drive the associations found across the *C9*⁺ clinical spectrum. See Supplementary Fig. 3.

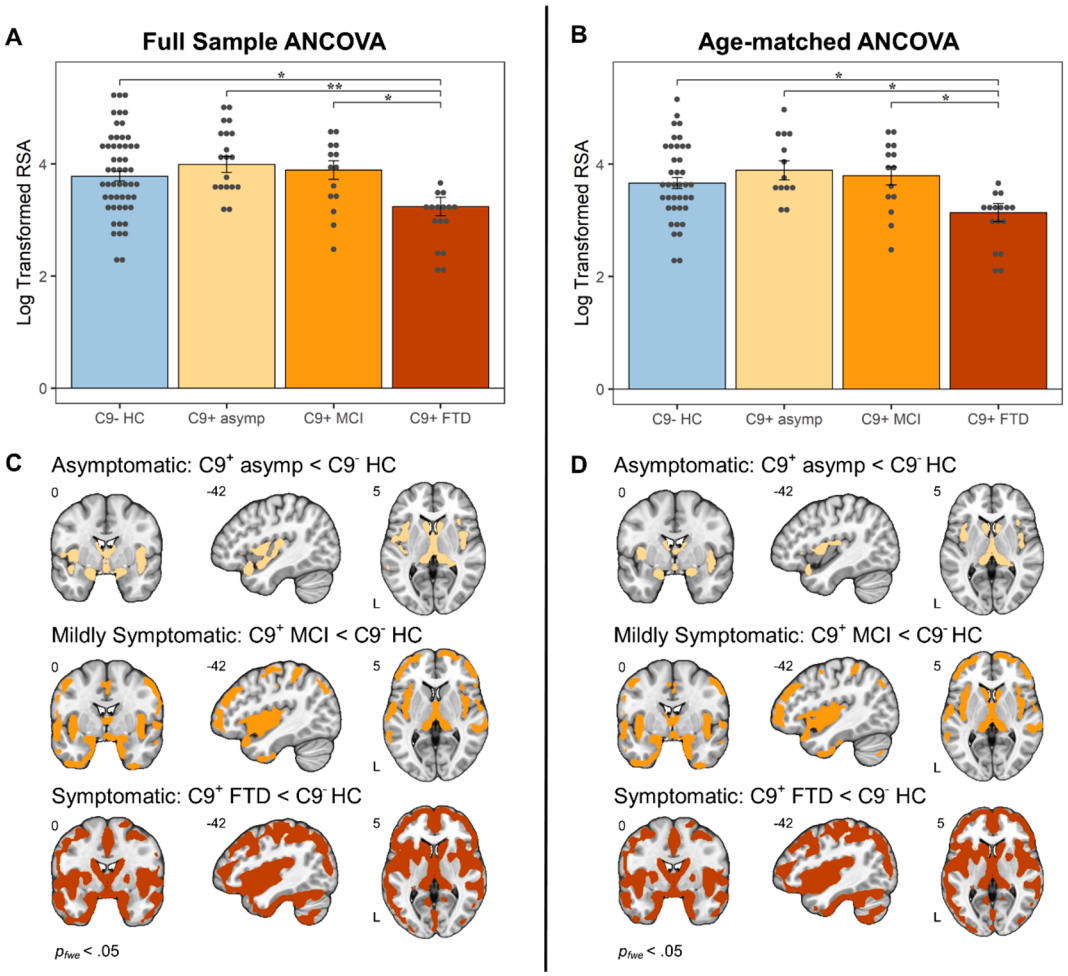

Fig. 1. Baseline respiratory sinus arrhythmia levels and gray matter maps in the *C9orf72* pathogenic expansion carriers.

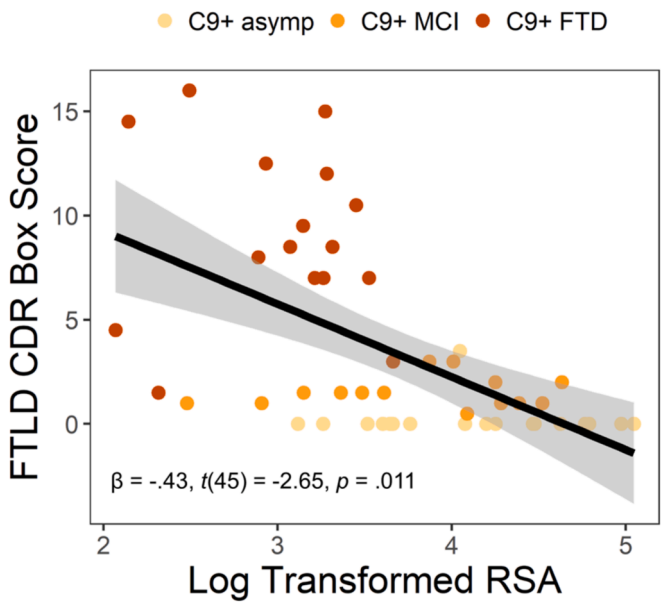

Fig. 2. Greater disease severity related to lower baseline respiratory sinus arrhythmia in *C9orf72* pathogenic expansion carriers.

3.5. Smaller gray matter volume in C9+ participants at each stage of behavioral symptom severity

Consistent with prior studies, (Sha et al., 2012; Mahoney et al., 2012a; Whitwell et al., 2012; Yokoyama and Rosen, 2012; Heuer et al., 2020) whole-brain neuroimaging analyses found smaller gray matter volume in the frontal and temporal lobes as well as in the insula, thalamus, parietal lobes, cingulate cortex, operculum, basal ganglia, and cerebellum in the *C9+* FTD group than in the *C9-* HC (see Supplementary Table 3). Compared to the other *C9+* groups, the atrophy in the *C9+* FTD group was the most severe and distributed. While the *C9+* MCI and *C9+* asymp participants also had smaller gray matter volume in the insula, thalamus, operculum, and basal ganglia than the *C9-* HC, only in the *C9+* MCI participants did these differences extend to the frontal lobes, parietal lobes, cingulate cortex, temporal lobes, and cerebellum, which is consistent with previous studies (Lee et al., 2017; Cash et al., 2018). See Fig. 1c and Supplementary Table 3. In the age-matched sample, the gray matter topographies of each group were consistent with those seen in the full sample (see Fig. 1d).

3.6. Lower baseline RSA correlates with smaller left frontoinsula and bilateral thalamus volume across the C9+ clinical spectrum

Whole-brain neuroimaging analyses in the *C9+* participants revealed that lower baseline RSA correlated with smaller gray matter volume in the left frontoinsula, bilateral thalamus (including bilateral medial pulvinar nuclei), cerebellum (including the cerebellum VI and vermis VI), and occipital lobe, $p_{FWE} < 0.05$ (see Table 2 and Fig. 4A). There were

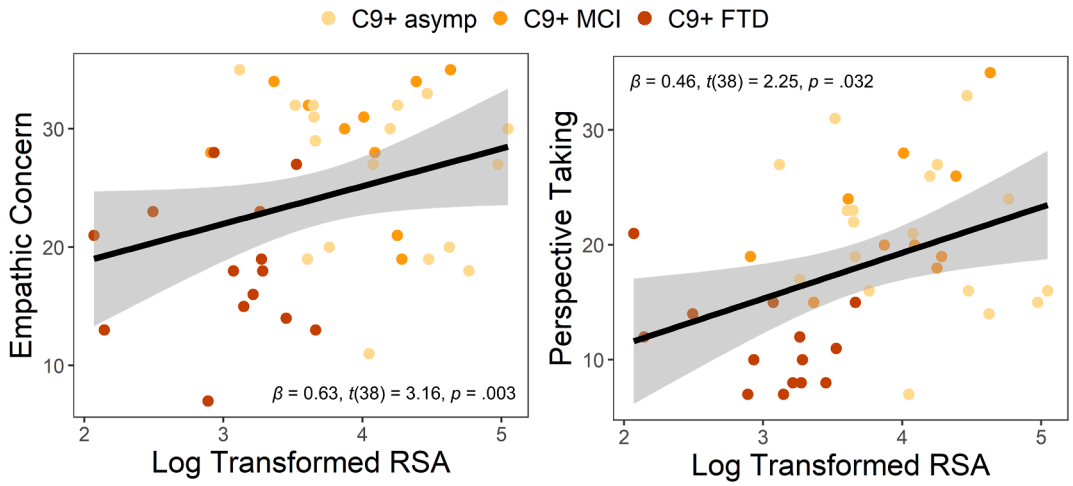

Fig. 3. Lower baseline RSA predicted lower empathy in the *C9orf72* pathogenic expansion carriers.

Table 2
Regions in which smaller gray matter volume related to lower baseline RSA in the $C9^+$ group.

Anatomical Region	Cluster Extent (mm^3)	Peak MNI Coordinates x	y	z	Maximum *T*
Occipital Middle, L	29,736	−32	−87	32	6.31
Thalamus, Bilateral	—	—	—	—	—
Cerebellum, Bilateral	—	—	—	—	—
Rectus, L	1912	−3	29	−27	4.33
Frontal Medial Orbital, L	—	—	—	—	—
Rectus, R	—	—	—	—	—
Frontal Inferior Orbital 2, L	1547	−53	23	−11	4.41
Frontoinsula, L	—	—	—	—	—
Frontal Middle 2, R	726	50	21	36	5.07

All clusters presented survived 1000 permutations at a cut off cluster size with an α = 0.05. Regions were labeled using the AAL2 atlas. x, y, and z = Montreal Neurological Institute (MNI) coordinates in the left–right, anterior-posterior, and inferior-superior dimensions, respectively. All contrasts are positive (smaller gray matter volume related to lower RSA).

no regions at this threshold in which lower baseline RSA related to larger gray matter volume. To ensure that the VBM correlations were not accounted for by extreme values in any of the clinical groups, we extracted the gray matter volume in the two clusters with the strongest associations with baseline RSA. Scatterplots confirmed baseline RSA had a linear association with volume in the left frontoinsula cluster (see Fig. 4B) and the occipitoparietal – thalamus cluster (Supplementary Fig. 4) across the $C9^+$ clinical spectrum. The same neuroimaging analyses in the sporadic bvFTD group revealed no significant clusters at this statistical threshold.

4. Discussion

The findings of the present study indicate that, like in sporadic bvFTD, baseline parasympathetic activity is impaired in FTD due to *C9orf72* pathogenic expansions. (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b) In $C9^+$ participants, baseline RSA deficits were more notable in those with FTD than in those who were asymptomatic or with very mild symptoms and were comparable to deficits found in sporadic bvFTD. These results were robust and held when accounting for various potential confounding factors including age, sex, beta-blocker and psychotropic medication prescription, and BMI. RSA deficits were also substantially lower when compared to the older HC sample, further supporting the disease-specific effects on parasympathetic decline. Although the asymptomatic $C9^+$ participants did not differ from the mildly symptomatic $C9^+$ participants or the $C9^-$ healthy controls in the pairwise comparisons, the means fell in a pattern suggestive of gradual decline. Linear regressions across the $C9^+$ clinical spectrum found additional evidence for more pronounced baseline RSA impairment with disease progression as participants with lower baseline RSA had greater behavioral symptom severity (as measured by the FTLD CDR Sum of Boxes) and lower empathy. Lower baseline RSA was not associated with greater cognitive impairment (as measured by the MMSE), however,

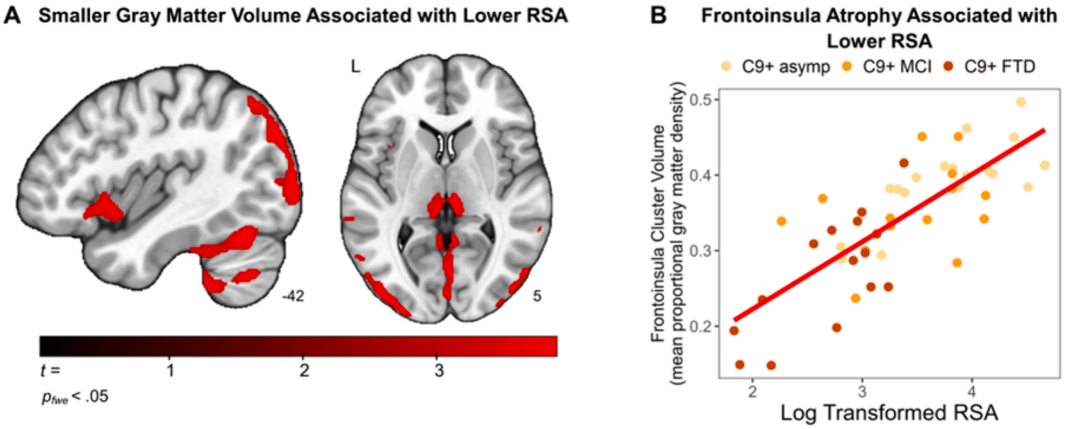

Fig. 4. Smaller gray matter volume related to lower baseline respiratory sinus arrhythmia in *C9orf72* pathogenic expansion carriers.

which suggests RSA deficits may have a stronger association with behavioral decline. Whole-brain structural neuroimaging analyses across the *C9*$^{+}$ clinical spectrum revealed lower baseline RSA related to smaller gray matter volume in the left frontoinsula and bilateral thalamus, parietal lobe, occipital lobe, and cerebellum, regions that are important for parasympathetic function and vulnerable in *C9orf72* pathogenic expansion carriers.

Our previous research has uncovered baseline RSA impairments in bvFTD that relate to degeneration and dysfunction in brain regions that support parasympathetic control. (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b) While our prior studies examined samples that included sporadic and genetic cases of bvFTD, here we clarify that basal parasympathetic activity is diminished in both sporadic bvFTD and in FTD due to *C9orf72* pathogenic expansions. The neural correlates of baseline RSA deficits in *C9*$^{+}$ participants resemble those found in bvFTD and highlight the central role of the left frontoinsula in parasympathetic control. Considered a final waystation in central parasympathetic networks, the left frontoinsula receives afferent information from the viscera that first passes through the brainstem, (Sturm et al., 2018a; Seeley et al., 2012) thalamus, posterior insula, and mid-insula. (Sturm et al., 2018a; Guo et al., 2016b; Sturm et al., 2018b; Beauchaine, 2001; Porges, 2001; Thayer and Lane, 2000; Decety, 2015; Decety, 2011; Craig, 2002; Critchley and Harrison, 2013) In *C9*$^{+}$ participants, smaller gray matter volume in the bilateral thalamus (including the medial pulvinar nucleus), parietal cortex, occipital cortex, and cerebellum was also related to lower baseline RSA. Although occipital and parietal cortices are not typically associated with RSA, the cerebellum plays a role in parasympathetic activity (Beissner et al., 2013; Gianaros et al., 2004; Muhtadie et al., 2014) and empathy (Adamaszek et al., 2017; Singer et al., 2004) through its connections with the frontoinsula and anterior cingulate cortex. (Guo et al., 2016a) Disruption of these pathways in *C9orf72* pathogenic expansions may impede transmission of internal signals that are critical for parasympathetic functioning and associated socioemotional processes.

The parasympathetic nervous system promotes empathy and prosocial behavior by fostering shared feeling states and emotional understanding. (Porges, 2001) In our prior research, we found lower baseline RSA in bvFTD predicted diminished prosocial behavior during a laboratory-based task in which participants witnessed an experimenter struggling to find a lost key. (Sturm et al., 2018b) The results of the present study suggest that waning parasympathetic activity may also underlie the lower empathy levels that characterize the asymptomatic and symptomatic phases of *C9orf72*-mediated disease. (Lee et al., 2014; Foster et al., 2022) Years before functional impairment, asymptomatic *C9orf72* pathogenic expansion carriers have reduced empathy (Foster et al., 2022) in addition to lower functional connectivity (Lee et al., 2017; Lee et al., 2014; Foster et al., 2022) and smaller gray matter volume (Yokoyama and Rosen, 2012; Agosta et al., 2017; Sha et al., 2012; Lee et al., 2017; Lee et al., 2014; Cash et al., 2018; Whitwell et al., 2007) in the medial pulvinar nucleus of the thalamus, an area in which atrophy relates to diminished prosocial behavior in FTD. (Sturm et al., 2018b; Sturm et al., 2017) Although it remains to be determined when the parasympathetic nervous system begins to falter in *C9orf72* pathogenic expansion carriers, we found some evidence for baseline RSA disruption early in the clinical course when symptoms are very mild. We speculate that parasympathetic decline may contribute to the emergence and progression of behavioral symptoms in *C9orf72* pathogenic expansion carriers by reducing their access to physiological cues that typically shape emotional experience and encourage empathy. (Miller et al., 2016; Sassenrath et al., 2021; Hastings and Miller, 2014; Palser et al., 2021).

Recent years have brought rapid advances in FTD biomarker development, and baseline RSA may be useful for monitoring in the early stages of the disease. Although fluid biomarkers (e.g., poly-GP and neurofilament light chain levels) measured from cerebrospinal fluid show promise for tracking symptom imminence and disease progression in *C9orf72* pathogenic expansions and other forms of FTD, (Meeter et al., 2018; Cajanus et al., 2020; Wilke et al., 2022) noninvasive biomarkers in FTD are still lacking. Given the central role that the parasympathetic system plays in social behavior and empathy, RSA may be a potential new biomarker that is sensitive to behavioral symptom progression in FTD. Consistent with this possibility, we found a strong linear association between baseline RSA and FTLD CDR Sum of Boxes scores, but not MMSE, in *C9*$^{+}$ participants across the clinical spectrum. While our results suggest there may be a gradual decline in baseline RSA over time, it is also possible that RSA remains relatively stable until symptoms emerge. As disease onset can be difficult to determine in *C9orf72* pathogenic expansion carriers (Sha et al., 2012; Mahoney et al., 2012a; Devenney et al., 2014; Snowden et al., 2012; Kertesz et al., 2013)—with some people exhibiting psychiatric symptoms in the initial stages of the illness, (Takada and Sha, 2012) and others showing a slow clinical progression (Khan et al., 2012)—additional research is necessary to determine the temporal trajectory of RSA decline throughout the disease course and to elucidate how parasympathetic deficits relate to other biomarkers and pathological changes such as aggregation of FTLD-TDP, dipeptide repeat protein inclusions, and RNA foci. (Meeter et al., 2018; Vatsavayai et al., 2016) A better understanding of the pathophysiological cascade and its relation to parasympathetic dysfunction may not only be relevant to FTD due to *C9orf72* pathogenic expansions but may also shed light on the biological mechanisms underlying sporadic disease.

There are limitations to this research to consider. First, this study was cross-sectional, and we did not have longitudinal autonomic and neuroimaging data available in our sample. As the asymptomatic and very mildly symptomatic *C9*$^{+}$ participants varied in age and proximity to symptom onset, (Rohrer et al., 2015; Gijselinck et al., 2016; Glasmacher et al., 2020) baseline RSA may have varied widely even within each clinical group. Studies that measure baseline RSA over time in *C9orf72* pathogenic expansion carriers will be needed to determine how parasympathetic changes relate to within-subject clinical progression. Second, we focused on the structural neuroanatomical correlates of baseline RSA deficits in *C9*$^{+}$ participants, but functional connectivity neuroimaging studies would also help to shed light on how neural network dysfunction relates to parasympathetic impairment. In *C9orf72* pathogenic expansion carriers, deficits in functional connectivity may precede atrophy and, thus, may be more sensitive to early disruption. (Lee et al., 2017) Network-based analyses will be important for elucidating how salience network hypoconnectivity might underlie baseline RSA deficits in *C9orf72* pathogenic expansion carriers. Third, there are numerous other potential confounding variables that could influence RSA that we did not assess in the present study. For example, sleep plays a crucial role in the modulation of autonomic activity, and prior work has shown that sleep deprivation can influence autonomic regulation and health of the cardiovascular system. (Takase et al., 2004; Bourdillon et al., 2021; Krause et al., 2017) Exercise, in contrast, may increase vagal tone. (Stein et al., 1999; De Meersman, 1993b; Sandercock et al., 2005) Although BMI did not significantly impact our findings, we did not directly assess physical activity or level of fitness in the participants. We also did not assess recent recreational drug use, which could have affected baseline RSA levels. Fourth, our study focused on *C9*$^{+}$ participants, which may limit the generalizability of our findings to sporadic FTD or to FTD due to other genetic causes. Whether parasympathetic deficits are also present in other familial forms of FTD will be an important topic for future research.

This study provides novel evidence that basal parasympathetic activity is diminished in FTD due to a *C9orf72* pathogenic expansion, much like it is impaired in sporadic bvFTD. Baseline RSA deficits were more pronounced in individuals with more severe behavioral symptoms and related to smaller gray matter volume in brain regions that support parasympathetic function and to lower empathy. Overall, our findings suggest autonomic measures offer a new avenue for biomarker development in genetic forms of FTD where the prediction of symptom onset

is critical as disease-modifying therapies are on the horizon.

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CRediT authorship contribution statement

Ashlin R. K. Roy: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fate Noohi:** Writing – review & editing. **Nathaniel A. Morris:** Writing – review & editing, Resources, Investigation. **Peter Ljubenkov:** Resources. **Hilary Heuer:** Resources, Data curation. **Jamie Fong:** Resources, Data curation. **Matthew Hall:** Resources, Data curation. **Argentina Lario Lago:** Resources, Data curation. **Katherine P. Rankin:** Writing – review & editing, Resources. **Bruce L. Miller:** Writing – review & editing, Funding acquisition. **Adam L. Boxer:** Resources. **Howard J. Rosen:** Resources, Funding acquisition. **William W. Seeley:** Writing – review & editing, Supervision. **David C. Perry:** Writing – review & editing, Supervision. **Jennifer S. Yokoyama:** Writing – review & editing, Supervision. **Suzee E. Lee:** Writing – review & editing, Supervision, Funding acquisition. **Virginia E. Sturm:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2024.103649.

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