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Thursday

Lower baseline parasympathetic activity in *C9orf72* hexanucleotide repeat expansion carriers relates to smaller left frontoinsula gray matter volume and lower empathy

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State of the art:
In FTD, deficits in baseline parasympathetic nervous system activity relate to left frontoinsula atrophy and lower empathic behavior. Whether parasympathetic deficits are also present in individuals with hexanucleotide repeat expansions in chromosome 9 open reading frame 72 (*C9*) and have similar anatomical and behavioral correlates is unknown.

Methodology:
We measured baseline respiratory sinus arrhythmia (RSA), a parasympathetic measure of heart rate variability, over two minutes in 19 asymptomatic expansion carriers (*C9*+asymp), 14 mildly symptomatic expansion carriers (*C9*+MCI), 16 symptomatic expansion carriers (*C9*+FTD), and 53 expansion-negative healthy controls (*C9*-HC). Disease severity was assessed with the FTLD Clinical Dementia Rating-Sum of Boxes score, and current empathy was evaluated with the Interpersonal Reactivity Index. Participants also completed a structural MRI scan.

Results:
An analysis of covariance (controlling for age and sex) revealed the C9+FTD group had lower baseline RSA than the other groups. Although the *C9*+MCI did not differ from the *C9*+asymp group, regression analyses indicated that lower baseline RSA was associated with worse disease severity and lower informant-reported empathy across the *C9*+ clinical spectrum. Voxel-based morphometry analyses in *C9*+ found that lower baseline RSA correlated with smaller gray matter volume in the left frontoinsula and bilateral thalamus.

Conclusions:
Baseline RSA is diminished in FTD due to *C9* expansions, and this deficit is related to smaller gray matter volume in brain structures with known roles in parasympathetic function. In *C9*, lower baseline RSA may be a non-invasive biomarker that is sensitive to early disease and symptom progression.

Conflicts of interest

N/A