Presymptomatic abnormal perception of pain in C9orf72 expansion carriers: early autonomic changes in the GENFI cohort

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INTRODUCTION

Frontotemporal dementia (FTD) is typically associated with changes in behaviour and/or language. However, studies have shown that patients with FTD can also present with autonomic symptoms: cardiac, urinary, gastrointestinal, and thermoregulatory dysfunction, as well as altered pain perception1 have been reported in patients with FTD. Central autonomic structures, including the thalamus and the insula, have also been shown to undergo early anatomical and pathological changes1. Despite this, the relationship between autonomic symptoms and anatomical changes in FTD has not been widely explored.

METHODS

Participants

We investigated autonomic symptoms in 281 FTD mutation carriers (104 C9orf72, 128 GRN, 49 MAPT) from the Genetic FTD Initiative (GENFI) cohort and 181 mutation-negative controls. Patients were grouped by mutation type, and into early presymptomatic, late presymptomatic (<5 years to estimated onset), and symptomatic stages. Patient demographics are reported in Table 1.

Analysis

Autonomic symptoms were assessed via a questionnaire. Participants reported changes in blood pressure (BP), gastrointestinal symptoms (gastro), thermoregulation (thermo), urinary symptoms, and pain perception. A score of 0 (absent), 0.5 (questionable/very mild), 1 (mild), 2 (moderate) and 3 (severe) was given for each symptom. A Kruskal-Wallis test was used to detect differences in symptoms between genetic groups and controls, followed by a Mann-Whitney U test for pairwise comparisons. Using SPM12, T1-weighted images were segmented into grey matter (GM) maps that were registered to multiple regression models, incorporating mutation-carriers only, for each genetic group and for each autonomic symptom. Age, gender, TIV, and scanner type were included in the regression as nuisance variables. A significance threshold was set at p<0.001, uncorrected.

RESULTS

Autonomic symptoms were frequently reported in symptomatic individuals with FTD (Table 2) with C9orf72 carriers being significantly more affected than controls by all symptoms (p<0.001) except for blood pressure changes. From the presymptomatic groups, only the late presymptomatic C9orf72 carrier group showed a significant difference from controls, in altered pain perception (p=0.007).

Pain symptoms in C9orf72 were associated with atrophy in the posterior thalamus and ventral striatum bilaterally, as well as the anterior insula, orbitofrontal cortex (OFC), and right cerebellum (Figure 1). Autonomic symptoms across all mutations were generally associated with a pattern of atrophy involving the OFC, ventral striatum, temporal lobe, and the cerebellum.

DISCUSSION

Here we show that symptomatic individuals with FTD display significant autonomic problems, especially individuals with C9orf72 mutations. C9orf72 carriers displayed presymptomatic altered pain perception, associated with bilateral atrophy in the posterior thalami. Afferents conveying pain information relay via postero-lateral thalamic nuclei to the somatosensory cortex, indicating an early disruption of central somatosensory and homeostatic signal processing in C9orf72. Given the diverse presentation of C9orf72-associated disease, we have shown that autonomic problems are prominent and early, and may be underpinned by the disruption of a cortico-thalamic network.

Autonomic problems were also frequently reported in people with GRN and MAPT mutations and associated with a network of cortical and subcortical regions. The findings suggest that the presence of autonomic problems is an important issue in FTD, with wider implications for the clinical management of symptoms.

REFERENCES