

SHORT REPORT

Main Title

Abnormal pain perception is associated with thalamo-cortico-striatal atrophy in *C9orf72* expansion carriers in the GENFI cohort

Running Title

Pain in FTD.

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Abstract

Objective

Frontotemporal dementia (FTD) is typically associated with changes in behaviour, language and movement. However, recent studies have shown that patients can also develop an abnormal response to pain, either heightened or diminished. We aimed to investigate this symptom in mutation carriers within the Genetic FTD Initiative (GENFI).

Methods

Abnormal responsiveness to pain was measured in 462 GENFI participants: 281 mutation carriers and 181 mutation-negative controls. Changes in responsiveness to pain were scored as absent (0), questionable or very mild (0.5), mild (1), moderate (2) or severe (3). Mutation carriers were classified into *C9orf72* (104), *GRN* (128) and *MAPT* (49) groups, and into presymptomatic and symptomatic stages. An ordinal logistic regression model was used to compare groups, adjusting for age and sex. Voxel-based morphometry was performed to identify neuroanatomical correlates of abnormal pain perception.

Results

Altered responsiveness to pain was present to a significantly greater extent in symptomatic *C9orf72* expansion carriers than in controls: mean score 0.40 (standard deviation 0.71) vs. 0.00 (0.04), reported in 29% vs 1%. No significant differences were seen between the other symptomatic groups and controls, or any of the presymptomatic mutation carriers and controls. Neural correlates of altered pain perception in *C9orf72* expansion carriers were the bilateral thalamus and striatum as well as a predominantly right-sided network of regions involving the orbitofrontal cortex, inferomedial temporal lobe and cerebellum.

Conclusion

Changes in pain perception are a feature of *C9orf72* expansion carriers, likely representing a disruption in somatosensory, homeostatic and semantic processing, underpinned by atrophy in a thalamo-cortico-striatal network.

Introduction

Frontotemporal dementia (FTD) is a complex neurodegenerative disease that encompasses a spectrum of symptoms. Whilst a combination of behavioural abnormalities, language dysfunction, cognitive deficits, and motor impairments form the classical phenotype of FTD, a number of other symptoms have been reported that are often overlooked, including altered perception of pain (Snowden et al., 2001; Bathgate et al., 2001; Carlino et al., 2010; Landqvist Waldö et al., 2014; Fletcher et al., 2015).

Descriptions of reduced response to pain in FTD have been intermittently reported over many years, although with variable frequency e.g. only 3% in one report (Landqvist Waldö et al., 2014), but up to 45% in papers from another research group (Snowden et al., 2001; Bathgate et al., 2001). An exaggerated reaction to pain has also been reported, with one series finding its presence in up to 55% of people with FTD, particularly in those with the temporal variant (Snowden et al., 2001). A more recent study (Fletcher et al., 2015) described altered responsiveness to pain in 8/15 (67%) people with behavioural variant FTD (bvFTD), 8/11 (72%) with semantic dementia (SD), and 2/5 (40%) with progressive nonfluent aphasia (PNFA), with decreased responsiveness more typical in bvFTD, and increased responsiveness in the language variants, SD and PNFA. For the first time this study found a particular association with mutations in the *C9orf72* gene, although only six patients were studied (Fletcher et al., 2015). We therefore set out to explore the presence of this symptom in a larger cohort of patients with genetic FTD, through the Genetic FTD Initiative (GENFI), investigating the frequency of altered responsiveness to pain in both the symptomatic and presymptomatic period, and its neural correlates.

Methods

Participants were recruited from the third data freeze of the Genetic FTD Initiative (GENFI) study (Rohrer et al., 2015) which incorporated 533 participants from 22 centres. Of these participants, 462 had data on abnormal pain perception from the GENFI core clinical assessment: 281 mutation carriers (104 *C9orf72*, 128 *GRN*, 49 *MAPT*), classified as either presymptomatic or symptomatic, and 181 mutation-negative controls. Of note, the symptomatic *C9orf72*, *GRN* and *MAPT* groups did not differ in severity as measured by the FTLD-CDR sum of

boxes score. Altered responsiveness to pain (either diminished or heightened response) was assessed via a clinical questionnaire, performed as a semi-structured interview with the patient and an informant, modelled on the Clinical Dementia Rating (CDR) scale with severity scored from 0 to 3: 0 = absent, 0.5 = questionable or very mild change in responsiveness to pain, 1 = mild change with no limitation on daily activities, 2 = moderate change with some limitation on daily activities (<50%), 3 = severe with limitation on most daily activities. The study was approved by the local ethics committees and all participants gave their consent to take part. Participant demographics are reported in Table 1.

| | Disease stage | Number of participants | Age | Sex (%male) | FTLD-CDR sum of boxes | Abnormal pain perception score | Abnormal pain perception – % with score of 0/0.5/1/2/3 |
|-----------------|----------------|------------------------|-------------|-------------|-----------------------|--------------------------------|--|
| Controls | | 181 | 45.9 (12.5) | 44 | 0.2 (0.7) | 0.00 (0.04) | 99/1/0/0/0 |
| C9orf72 | Presymptomatic | 73 | 45.6 (11.8) | 36 | 0.2 (0.7) | 0.04 (0.26) | 97/0/1/1/0 |
| | Symptomatic | 31 | 62.5 (7.9) | 65 | 8.9 (6.0) | 0.40 (0.71) | 71/3/13/13/0 |
| GRN | Presymptomatic | 104 | 46.5 (12.0) | 34 | 0.1 (0.3) | 0.00 (0.00) | 100/0/0/0/0 |
| | Symptomatic | 24 | 61.7 (10.6) | 42 | 8.6 (6.3) | 0.04 (0.20) | 96/0/4/0/0 |
| MAPT | Presymptomatic | 39 | 41.1 (11.0) | 38 | 0.2 (0.6) | 0.03 (0.16) | 100/0/0/0/0 |
| | Symptomatic | 10 | 58.6 (6.8) | 50 | 7.8 (5.6) | 0.10 (0.32) | 90/0/10/0/0 |

Table 1. Participant demographics. Age, FTLD-CDR sum of boxes, and the abnormal pain perception score are shown as means (standard deviation).

Statistical analysis

Abnormal pain perception scores were compared between the groups using an ordinal logistic regression model, adjusting for age and sex.

Imaging analysis

Participants underwent volumetric T1 MR imaging on a 3T scanner in accordance with the GENFI imaging protocol (Rohrer et al., 2015). Voxel-based morphometry (VBM) was performed using Statistical Parametric Mapping (SPM) version 12 software (<https://www.fil.ion.ucl.ac.uk/spm/>) in MATLAB. The T1-weighted images were first normalized and segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) probability maps using DARTEL (Ashburner, 2007). GM segments were transformed in MNI space, modulated and smoothed using a Gaussian kernel with 6mm full-width at half maximum before analysis. Finally, a GM mask was applied (Ridgway et al., 2009). Total intracranial volume (TIV) was calculated by summing the 3 tissue class volumes (Malone et al., 2015). Pre-processed GM tissue maps were fitted to a multiple regression model to identify correlations between GM density and abnormal pain perception. Age, sex, TIV, and scanner type were included in the regression as nuisance variables. Statistics threshold was set at an uncorrected p-value of 0.001, with a minimum cluster size of 20 voxels.

Results

Abnormal pain perception was significantly greater in the symptomatic *C9orf72* expansion carriers compared with controls ($p=0.001$): mean score of 0.40 (standard deviation 0.71) in the *C9orf72* group with 9/31 (29%) scoring >0 , 0.00 (0.04) in healthy controls with 1/181 (1%) scoring >0 . Of the 9 people scoring abnormally in the *C9orf72* group, 7 had bvFTD, 1 had FTD with amyotrophic lateral sclerosis, and 1 had PNFA. No significant difference was found between either the symptomatic *GRN* (only 1/24 = 4% scoring >0) or *MAPT* (only 1/10 = 10% scoring >0) groups and controls (Table 1, Supplementary Table 1). No differences were found in any of the presymptomatic groups compared with controls (Table 1, Supplementary Table 1).

Altered pain perception in *C9orf72* was associated with bilateral atrophy in the posterior part of the thalamus (pulvinar), the striatum (caudate, putamen and nucleus accumbens) and the orbitofrontal cortices, as well as atrophy of the right inferomedial temporal lobe (temporal pole, fusiform gyrus and amygdala), and cerebellum

(Figure 1, Supplementary Table 2).

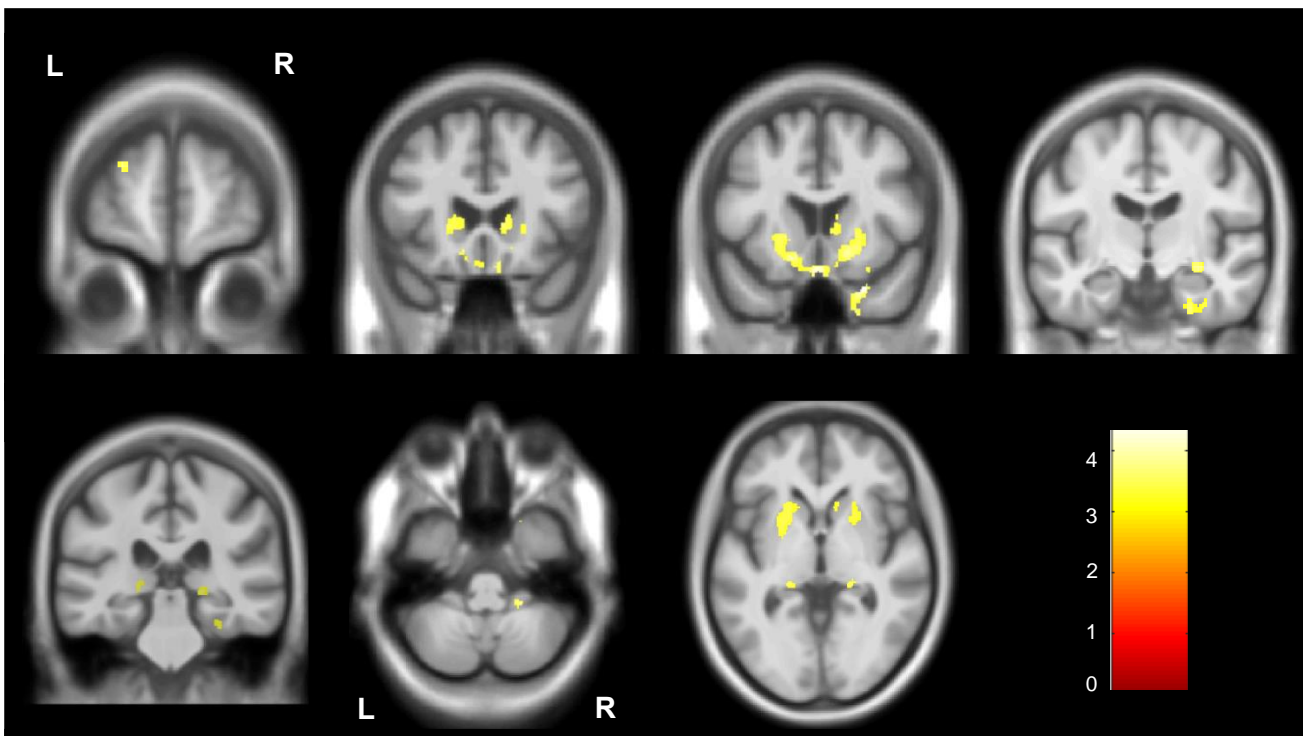


Figure 1. Neural correlates of abnormal pain perception in *C9orf72* expansion carriers. Statistical parametric maps are thresholded at $p < 0.001$ uncorrected. Results are rendered on a study-specific T1-weighted MRI template in MNI space. The colour bar indicates the T-score

Discussion

We show that changes in pain perception are a feature of *C9orf72* expansion carriers within the GENFI cohort, developing after phenoconversion to the symptomatic period. Such changes were no different to controls in those with *GRN* and *MAPT* mutations, and were not seen during the presymptomatic period. Neural correlates of altered pain perception in *C9orf72* mutation carriers were regions in the posterior thalamus (pulvinar), striatum, and cerebellum as well as both frontal and temporal cortical regions.

The study confirms the previous report in six symptomatic *C9orf72* mutation carriers by Fletcher et al., 2015, showing that the symptom is present in around one third of symptomatic carriers within the GENFI cohort, but

is not present to a greater extent than a control population in a large group of presymptomatic carriers. Greater awareness of the specific genetic association of this symptom will improve its recognition in clinical practice: we recommend asking about it in all those with a *C9orf72* expansion as its presence is not always volunteered.

The association with bilateral thalamic atrophy has been previously reported (Fletcher et al., 2015), although in that study a combination of altered pain and temperature processing was studied. The thalamus is an established pain region involved in affective and sensory signal processing (Bushnell et al., 1989; Tracey, 2005) with afferents conveying pain information via postero-lateral thalamic nuclei to the somatosensory cortex and insula (Craig et al., 1994; Craig, 2002). In the current study, the association is seen particularly with the pulvinar nucleus, a posterior region of the thalamus affected particularly in those with *C9orf72* expansions in comparison with other forms of FTD (Bocchetta et al., 2020).

We also found an association of altered pain perception with other brain regions. The striatum has connections to the thalamus and cortex, and is thought to potentially integrate motor, cognitive, autonomic and emotional responses to pain through this thalamo-cortico-striatal network (Borsook et al., 2010), whilst the insula is highly involved in interoception, the ability to receive and appraise internal body signals including pain (Craig, 2002). The right temporal lobe has been previously implicated in non-verbal sensory semantic (including pain) processing (Fletcher et al., 2015), and the orbitofrontal cortex is thought to affect pain perception through its role in the processing of reward (Ong et al., 2019). In *C9orf72* expansion carriers, it is therefore likely that a complex combination of altered somatosensory, homeostatic, semantic and reward processing underlies the altered perception of pain.

We did not separate out decreased and increased responsiveness in this study, but further studies of genetic FTD should do this, and attempt to understand whether there are specific correlates of these two features. Furthermore, future longitudinal studies that include those that convert from presymptomatic to symptomatic status will allow a clearer timeline of when altered pain perception starts in the disease process of *C9orf72*-

associated FTD.

Supplementary material

Supplementary Table 1. Results of ordinal logistic regression model comparing between groups with coefficients, 95% confidence intervals, and p-values (and significant differences shown in bold).

| | | C9orf72 | | GRN | | MAPT | |
|----------------|-----------------------|------------------------------|--|--------------------------------------|---|-------------------------------------|-------------------------------------|
| | | Presymptomatic | Symptomatic | Presymptomatic | Symptomatic | Presymptomatic | Symptomatic |
| Control | | 1.68 -0.75, 4.11 0.174 | 3.73 1.49, 5.97 0.001 | -14.18 -3094.10, 3065.74 0.993 | 1.30 -1.61, 4.22 0.381 | 1.85 -0.98, 4.68 0.200 | 2.53 -0.36, 5.41 0.086 |
| C9orf72 | Presymptomatic | | 2.05 0.21, 3.89 0.029 | -15.86 -3095.78, 3064.06 0.992 | -0.38 -2.00, 2.24 0.776 | 0.17 -2.30, 2.63 0.894 | 0.84 -1.73, 3.42 0.520 |
| | Symptomatic | | | -17.91 -3097.83, 3062.01 0.991 | -2.43 -4.62, -0.24 0.030 | -1.88 -4.28, 0.51 0.123 | -1.21 -3.44, 1.03 0.290 |
| GRN | Presymptomatic | | | | 15.48 -3064.44, 3095.40 0.992 | 16.03 -3063.89, 3095.95 0.992 | 16.71 -3063.21, 3096.63 0.992 |
| | Symptomatic | | | | | 0.55 -2.50, 3.60 0.725 | 1.22 -1.69, 4.14 0.410 |
| MAPT | Presymptomatic | | | | | | 0.68 -2.30, 3.66 0.656 |
| | Symptomatic | | | | | | |

Supplementary Table 2. Neural correlates of abnormal pain perception in *C9orf72* expansion carriers.

| Region | Cluster | T | Co-ordinates (mm) | | |
|--|---------|------|-------------------|-----|-----|
| | | | x | y | z |
| Right temporal pole | 155 | 4.45 | 26 | 18 | -33 |
| | | 3.63 | 21 | 14 | -44 |
| Left/right orbitofrontal cortex Left/right putamen, caudate and accumbens Right basal forebrain Left/right subcallosal area | 2043 | 4.17 | -2 | 14 | -21 |
| | | 4.01 | -15 | 16 | -12 |
| | | 3.83 | 10 | 9 | -18 |
| Right amygdala | 71 | 3.91 | 30 | -12 | -12 |
| Left superior/middle frontal gyrus | 21 | 3.81 | -24 | 60 | 21 |
| Right thalamus (pulvinar) | 31 | 3.70 | 21 | -30 | -3 |
| Right inferior cerebellum | 35 | 3.67 | 21 | -42 | -45 |
| Right fusiform gyrus | 33 | 3.67 | 42 | -42 | -28 |
| Right parahippocampal gyrus | 114 | 3.66 | 26 | -12 | -36 |
| | | 3.56 | 34 | -10 | -33 |
| Left thalamus (pulvinar) | 34 | 3.52 | -20 | -32 | -2 |
| Right orbitofrontal cortex | 26 | 3.47 | 27 | 12 | -20 |
| Left fusiform gyrus | 42 | 3.44 | -32 | -27 | -30 |
| Right fusiform gyrus | 40 | 3.43 | 30 | -30 | -24 |

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