











## SHORT REPORT

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

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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 (SD 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.<sup>1–5</sup>

Descriptions of reduced response to pain in FTD have been intermittently reported over many years, although with variable frequency, for example, only 3% in one report,<sup>4</sup> but up to 45% in papers from another research group.<sup>1,2</sup> 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.<sup>1</sup> A more recent study 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 non-fluent aphasia (PNFA), with decreased responsiveness more typical in bvFTD, and increased responsiveness in the language variants, SD and PNFA.<sup>5</sup> For the first time, this study found a particular association with mutations in the *C9orf72* gene, although only six patients were studied.<sup>5</sup> 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 GENFI study,<sup>6</sup> 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

**Table 1** Participant demographics

	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
<i>C9orf72</i>	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
<i>GRN</i>	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
<i>MAPT</i>	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

Age, FTLD-CDR sum of boxes and the abnormal pain perception score are shown as means (SD). CDR, Clinical Dementia Rating.

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. Participant demographics are reported in [table 1](#).

**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.<sup>6</sup> Voxel-based morphometry was performed using Statistical Parametric Mapping V.12 software (<https://www.fil.ion.ucl.ac.uk/spm/>) in MATLAB. The T1-weighted images were first normalised and segmented into grey matter (GM), white matter and cerebrospinal fluid probability maps using DARTEL.<sup>7</sup> 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.<sup>8</sup> Total intracranial volume (TIV) was calculated by summing the three tissue class volumes.<sup>9</sup> Preprocessed 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 (SD 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 nine people scoring abnormally in the *C9orf72* group, seven had bvFTD, one had FTD with amyotrophic lateral sclerosis and one 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](#), online supplementary table 1).

No differences were found in any of the presymptomatic groups compared with controls ([table 1](#), online 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](#), online supplementary table 2).

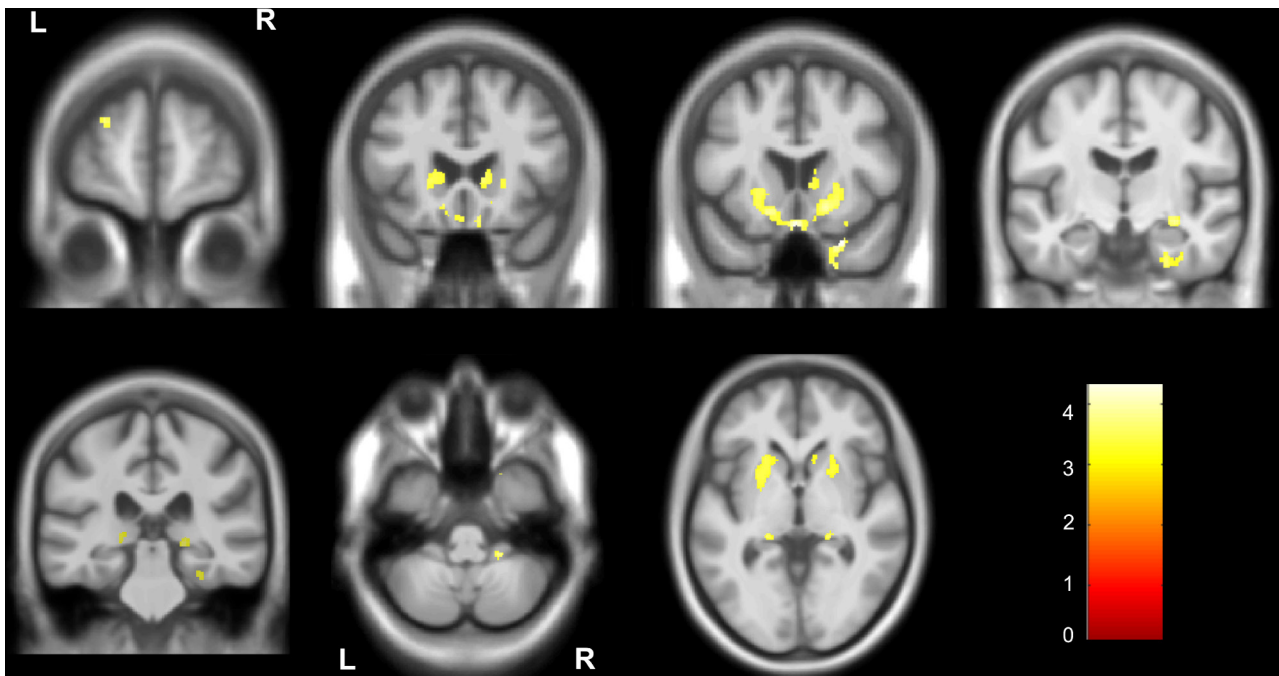
**DISCUSSION**

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*, 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,<sup>5</sup> 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,<sup>10 11</sup> with afferents conveying pain information via posterolateral thalamic nuclei to the somatosensory cortex and insula.<sup>12 13</sup> 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.<sup>14</sup>

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.<sup>15</sup> The right temporal lobe has been previously implicated in non-verbal sensory semantic (including pain) processing,<sup>5</sup> and the orbitofrontal cortex is thought to affect pain perception through its role in the processing of reward.<sup>16</sup> In *C9orf72* expansion carriers, it is therefore likely that a complex combination of altered



**Figure 1** Neural correlates of abnormal pain perception in *C9orf72* mutation 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.

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.

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**Contributors** RC, MB and JR contributed to the study design, acquisition, analysis and interpretation of the data as well as drafting and revising the manuscript. All other authors (CVG, KM, DMc, JCVS, FM, RS-V, BB, RJrL, MM, MCT, CG, DG, JBR, EF, MS, RV, AdeM, FT, IS, SD, CRB, AG, JL, AD, MO, JW) contributed to the acquisition of data and study coordination as well as helping to critically review and revise the manuscript.

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