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.

Authors

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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 el., 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).

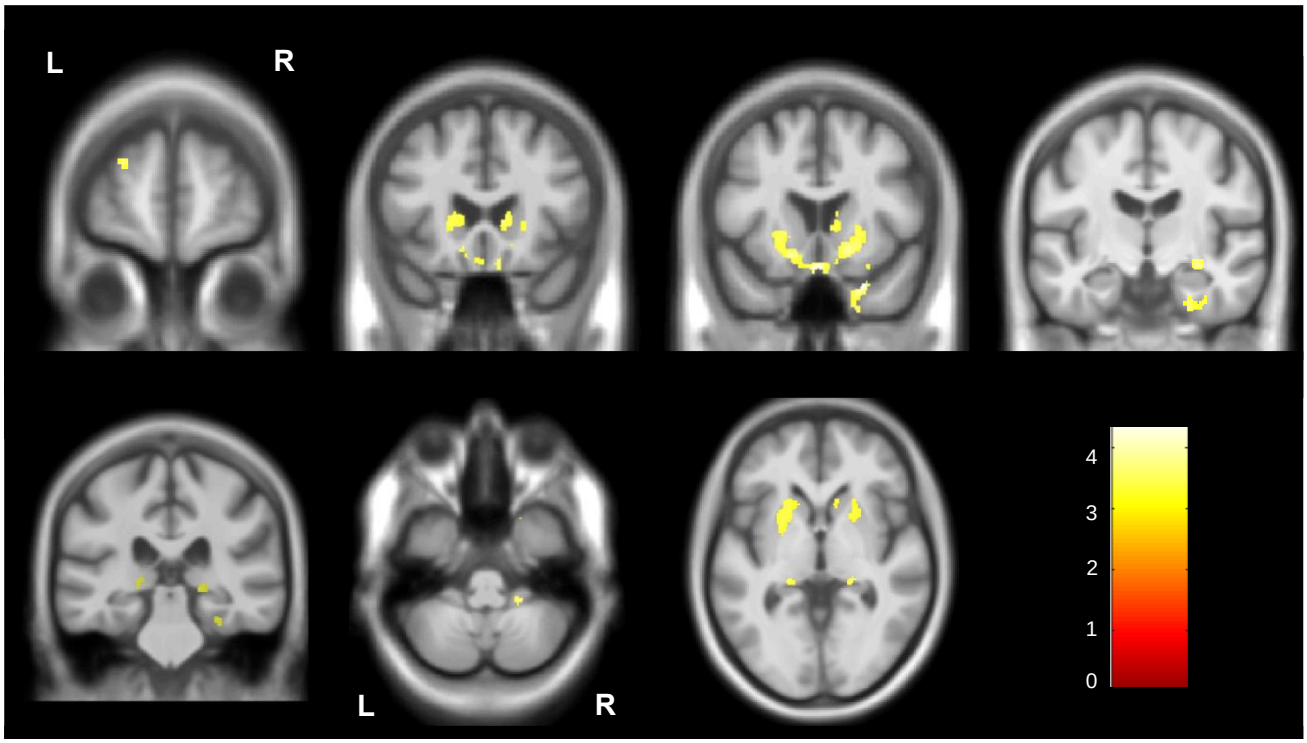

Figure 1. Neural correlates of abnormal pain perception in *C9orf72* expansion carriers. Statistical parametric maps are thresholded at *p*<0.001 uncorrected. Results are rendered on a study-specific T1-weighted MRI template in MNI space. The colour bar indicates the T-score

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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References

1. Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007; 38: 95–113.
2. Bathgate D, Snowden JS, Varma A, Blackshaw A, Neary D. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. Acta Neurol Scand. 2001 Jun;103(6):367-78.
3. Bocchetta M, Iglesias JE, Neason M, Cash DM, Warren JD, Rohrer JD. Thalamic nuclei in frontotemporal dementia: Mediodorsal nucleus involvement is universal but pulvinar atrophy is unique to C9orf72. Hum Brain Mapp. 2020 Mar;41(4):1006-1016.
4. Borsook D, Upadhyay J, Chudler EH, Becerra L. A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging. Mol Pain. 2010 May 13;6:27.
5. Bushnell MC, Duncan GH. Sensory and affective aspects of pain perception: is medial thalamus restricted to emotional issues? Exp. Brain Res. 1989; 78: 415–418.
6. Carlino E, Benedetti F, Rainero I, Asteggiano G, Cappa G, Tarenzi L, Vighetti S, Pollo A. Pain perception and tolerance in patients with frontotemporal dementia. Pain. 2010 Dec;151(3):783-9.
7. Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. Nat. Rev. Neurosci. 2002; 3: 655–666.
8. Craig AD, Bushnell MC, Zhang E-T, Blomqvist A. A thalamic nucleus specific for pain and temperature sensation. Nature 1994; 372: 770–773.
9. Fletcher PD, Downey LE, Golden HL, Clark CN, Slattery CF, Paterson RW, et al. Pain and temperature processing in dementia: A clinical and neuroanatomical analysis. Brain 2015; 138: 3360–3372.
10. Landqvist Waldö M, Santillo AF, Gustafson L, Englund E, Passant U. Somatic complaints in frontotemporal dementia. Am J Neurodegener Dis. 2014 Sep 6;3(2):84-92.
11. Malone IB, Leung KK, Clegg S, Barnes J, Whitwell JL, Ashburner J, et al. Accurate automatic estimation of total intracranial volume: A nuisance variable with less nuisance. Neuroimage 2015; 104: 366–372.
12. Ong WY, Stohler CS, Herr DR. Role of the Prefrontal Cortex in Pain Processing. Mol Neurobiol. 2019 Feb;56(2):1137-1166.
13. Ridgway GR, Omar R, Ourselin S, Hill DL, Warren JD, Fox NC (2009) Issues with threshold masking in

voxel-based morphometry of atrophied brains. Neuroimage 44, 99-111.

14. Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, van Minkelen R, Rombouts SA, Cardoso MJ, Clegg S, Espak M, Mead S, Thomas DL, De Vita E, Masellis M, Black SE, Freedman M, Keren R, MacIntosh BJ, Rogaeva E, Tang-Wai D, Tartaglia MC, Laforce R Jr, Tagliavini F, Tiraboschi P, Redaelli V, Prioni S, Grisoli M, Borroni B, Padovani A, Galimberti D, Scarpini E, Arighi A, Fumagalli G, Rowe JB, Coyle-Gilchrist I, Graff C, Fallström M, Jelic V, Ståhlbom AK, Andersson C, Thonberg H, Lilius L, Frisoni GB, Pievani M, Bocchetta M, Benussi L, Ghidoni R, Finger E, Sorbi S, Nacmias B, Lombardi G, Polito C, Warren JD, Ourselin S, Fox NC, Rossor MN, Binetti G. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (**GENFI**) study: a cross-sectional analysis. Lancet Neurol. 2015 Mar;14(3):253-62.
15. Snowden JS, Bathgate D, Varma A, Blackshaw A, Gibbons ZC, Neary D. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. J Neurol Neurosurg Psychiatry. 2001 Mar;70(3):323-32.
16. Tracey I. Nociceptive processing in the human brain. Curr. Opin. Neurobiol. 2005; 15: 478–487.