SHORT REPORT

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

Rhian S Convery ,[1] Martina Bocchetta ,[1] Caroline V Greaves ,[1] Katrina M Moore ,[1] David M Cash,[1,2] John Van Swieten ,[3] Fermin Moreno,[4] Raquel Sánchez-Valle,[5] Barbara Borroni ,[6] Robert Laforce Jr,[7] Mario Masellis,[8] Maria Carmela Tartaglia,[9] Caroline Graff,[10] Daniela Galimberti,[11,12] James B Rowe ,[13] Elizabeth Finger ,[14] Matthis Synofzik,[15,16] Rik Vandenberghe,[17,18] Alexandre de Mendonca,[19] Fabrizio Tagliavini,[20] Isabel Santana,[21,22] Simon Ducharme,[23,24] Christopher Butler,[25] Alex Gerhard,[26,27] Johannes Levin,[28,29] Adrian Danek,[29] Markus Otto ,[30] Jason D Warren,[1] Jonathan D Rohrer ,[1] on behalf of the Genetic FTD Initiative (GENFI)

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For numbered affiliations see end of article.

Correspondence to
Dr Jonathan D Rohrer, Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London WC1N 3BG, UK; j.rohrer@ucl.ac.uk

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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.[1–5]

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,[4] but up to 45% in papers from another research group.[1 2] 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.[1] 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.[5] For the first time, this study found a particular association with mutations in the *C9orf72* gene, although only six patients were studied.[5] 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,[6] 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
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

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.[6] 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.[7] GM segments were transformed in MNI space, modulated and smoothed using a Gaussian kernel with 6 mm full-width at half maximum before analysis. Finally, a GM mask was applied.[8] Total intracranial volume (TIV) was calculated by summing the three tissue class volumes.[9] 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,[5] 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,[10 11] with afferents conveying pain information via posterolateral thalamic nuclei to the somatosensory cortex and insula.[12 13] 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.[14]

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

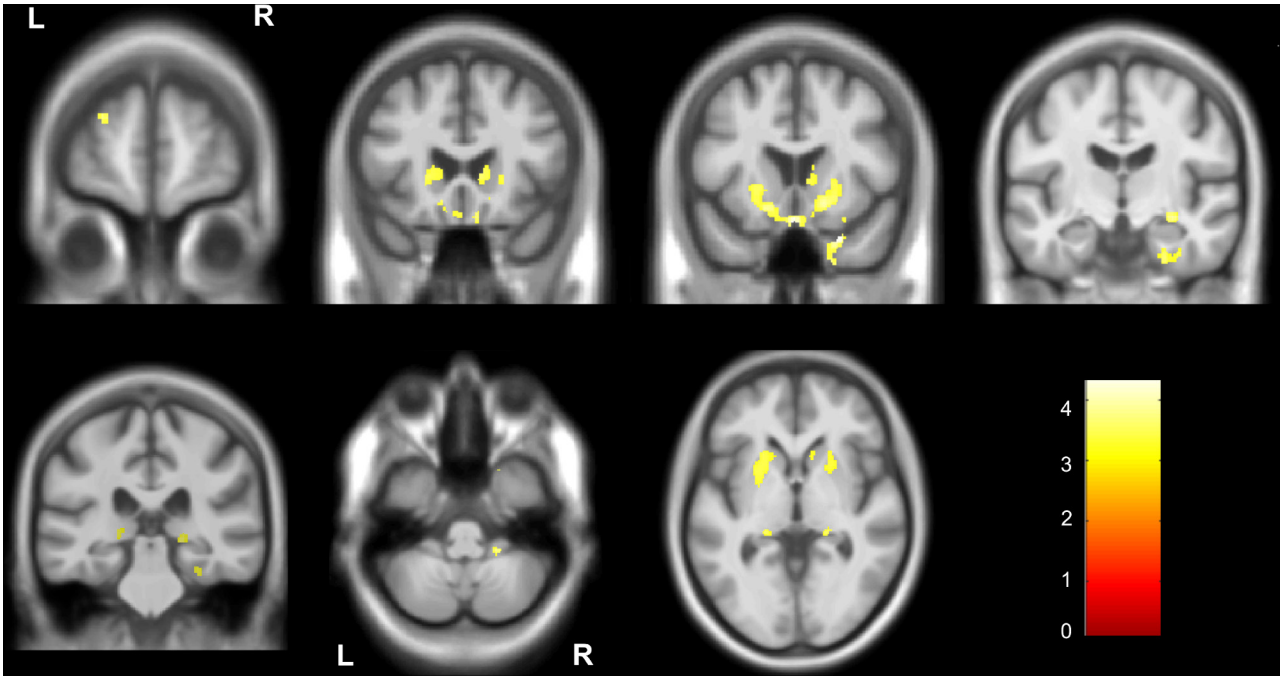

Figure 1 Neural correlates of abnormal pain perception in *C9orf72* mutation carriers. Statistical parametric maps are thresholded at p<0.001 uncorrected. Results are rendered on a study-specific T1-weighted MRI template in MNI space. The colour bar indicates the T-score.

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.

Author affiliations
[1]Dementia Research Centre, Department of Neurodegenerative Disease, UCL Queen Square Institute of Neurology, University College London, London, UK
[2]Centre for Medical Image Computing, Department of Medical Physics and Biomedical Engineering, University College London, London, UK
[3]Department of Neurology, Erasmus Medical Center, Rotterdam, The Netherlands
[4]Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital Gipuzkoa Building, San Sebastian, Spain
[5]Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clínic, Institut d'Investigacións Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain
[6]Centre for Ageing Brain and Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
[7]Clinique Interdisciplinaire de Mémoire (CIME), Département des Sciences Neurologiques du CHU de Québec, Laval University, Quebec, Quebec City, Canada
[8]Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Ontario, Canada
[9]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Ontario, Canada
[10]Department of Geriatric Medicine, Karolinska University Hospital-Huddinge, Stockholm, Sweden
[11]La Fondazione IRCCS Ospedale Maggiore Policlinico, Milano, Italy
[12]Centro Dino Ferrari, University of Milan, Milano, Italy
[13]Department of Clinical Neurosciences, University of Cambridge, Cambridge, UK
[14]Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario, Canada
[15]Hertie-Institute for Clinical Brain Research and Center of Neurology, Department of Neurodegenerative Diseases, University of Tübingen, Tübingen, Germany
[16]German Centre for Neurodegenerative Diseases, Tübingen, Germany
[17]Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium
[18]Leuven Brain Institute, KU Leuven, Leuven, Belgium
[19]Laboratory of Neurosciences, Institute of Molecular Medicine, Faculty of Medicine, University of Lisbon, Lisboa, Portugal
[20]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologico Carlo Besta, Milano, Italy
[21]Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[22]Centre of Neurosciences and Cell Biology, University of Coimbra, Coimbra, Portugal
[23]Department of Psychiatry, McGill University Health Centre, McGill University, Montreal, Quebec, Canada
[24]McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada
[25]Nuffield Department of Clinical Neurosciences, Medical Sciences Division, University of Oxford, Oxford, UK
[26]Division of Neuroscience and Experimental Psychology, Wolfson Molecular Imaging Centre, The University of Manchester, Manchester, UK
[27]Departments of Geriatric Medicine and Nuclear Medicine, University of Duisburg-Essen, Duisburg, Germany
[28]German Centre for Neurodegenerative Diseases Site Munich, Munchen, Germany
[29]Neurologische Klinik, Ludwig-Maximilians-Universitat Munchen, Munchen, Germany
[30]Department of Neurology, University of Ulm, Ulm, Germany

Twitter Simon Ducharme @sducharme66

Collaborators Martin N. Rossor, Nick C. Fox, Ione O.C. Woollacott, Rachelle Shafei, Carolin Heller, Georgia Peakman, Imogen J. Swift, Emily Todd, Rita Guerreiro, Jose Bras, David L. Thomas, Jennifer Nicholas, Simon Mead, Lize Jiskoot Lieke Meeter, Jessica Panman, Janne Papma, Rick van Minkelen, Yolande Pijnenburg, Myriam Barandiaran, Begoña Indakoetxea, Alazne Gabilondo, Mikel Tainta, Maria de Arriba, Ana Gorostidi, Miren Zulaica, Jorge Villanua, Zigor Diaz, Sergi Borrego-Ecija, Jaume Olives, Albert Lladó, Mircea Balasa, Anna Antonell, Nuria Bargallo, Enrico Premi, Maura Cosseddu, Stefano Gazzina, Alessandro Padovani, Roberto Gasparotti, Silvana Archetti, Sandra Black, Sara Mitchell, Ekaterina Rogaeva, Morris Freedman, Ron Keren, David Tang-Wai, Linn Öijerstedt, Christin Andersson, Vesna Jelic, Hakan Thonberg, Andrea Arighi, Chiara Fenoglio, Elio Scarpini, Giorgio Fumagalli, Thomas Cope, Carolyn Timberlake, Timothy Rittman, Christen Shoesmith, Robart Bartha, Rosa Rademakers, Carlo Wilke, Hans-Otto Karnarth, Benjamin Bender, Rose Bruffaerts, Philip Vandamme, Mathieu Vandenbulcke, Catarina B. Ferreira, Gabriel Miltenberger, Carolina Maruta, Ana Verdelho, Sónia Afonso, Ricardo Taipa, Paola Caroppo, Giuseppe Di Fede, Giorgio Giaccone, Sara Prioni, Veronica Redaelli, Giacomina Rossi, Pietro Tiraboschi, Diana Duro, Maria Rosario Almeida, Miguel Castelo-Branco, Maria João Leitão, Miguel Tabuas-Pereira, Beatriz Santiago, Serge Gauthier, Pedro Rosa-Neto, Michele Veldsman, Toby Flanagan, Catharina Prix, Tobias Hoegen, Elisabeth Wlasich, Sandra Loosli, Sonja Schonecker, Elisa Semler, Sarah Anderl-Straub.

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ORCID iDs
Rhian S Convery http://orcid.org/0000-0002-9477-1812
Martina Bocchetta http://orcid.org/0000-0003-1814-5024
Caroline V Greaves http://orcid.org/0000-0002-6446-1960
Katrina M Moore http://orcid.org/0000-0002-4458-8390
John Van Swieten http://orcid.org/0000-0001-6278-6844
Barbara Borroni http://orcid.org/0000-0001-9340-9814
James B Rowe http://orcid.org/0000-0001-7216-8679
Elizabeth Finger http://orcid.org/0000-0003-4461-7427
Markus Otto http://orcid.org/0000-0002-6647-5944
Jonathan D Rohrer http://orcid.org/0000-0002-6155-8417

REFERENCES

1 Snowden JS, Bathgate D, Varma A, *et al*. Distinct behavioural profiles in frontotemporal dementia and semantic dementia. *J Neurol Neurosurg Psychiatry* 2001;70:323–32.
2 Bathgate D, Snowden JS, Varma A, *et al*. Behaviour in frontotemporal dementia, Alzheimer's disease and vascular dementia. *Acta Neurol Scand* 2001;103:367–78.
3 Carlino E, Benedetti F, Rainero I, *et al*. Pain perception and tolerance in patients with frontotemporal dementia. *Pain* 2010;151:783–9.
4 Landqvist Waldö M, Santillo AF, Gustafson L, *et al*. Somatic complaints in frontotemporal dementia. *Am J Neurodegener Dis* 2014;3:84–92.
5 Fletcher PD, Downey LE, Golden HL, *et al*. Pain and temperature processing in dementia: a clinical and neuroanatomical analysis. *Brain* 2015;138:3360–72.
6 Rohrer JD, Nicholas JM, Cash DM, *et al*. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the genetic frontotemporal dementia initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol* 2015;14:253–62.
7 Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage* 2007;38:95–113.
8 Ridgway GR, Omar R, Ourselin S, *et al*. Issues with threshold masking in voxel-based morphometry of atrophied brains. *Neuroimage* 2009;44:99–111.
9 Malone IB, Leung KK, Clegg S, *et al*. Accurate automatic estimation of total intracranial volume: a nuisance variable with less Nuisance. *Neuroimage* 2015;104:366–72.
10 Bushnell MC, Duncan GH. Sensory and affective aspects of pain perception: is medial thalamus restricted to emotional issues? *Exp Brain Res* 1989;78:415–8.
11 Tracey I. Nociceptive processing in the human brain. *Curr Opin Neurobiol* 2005;15:478–87.
12 Craig AD, Bushnell MC, Zhang ET, *et al*. A thalamic nucleus specific for pain and temperature sensation. *Nature* 1994;372:770–3.
13 Craig AD. How do you feel? Interoception: the sense of the physiological condition of the body. *Nat Rev Neurosci* 2002;3:655–66.
14 Bocchetta M, Iglesias JE, Neason M, *et al*. Thalamic nuclei in frontotemporal dementia: Mediodorsal nucleus involvement is universal but pulvinar atrophy is unique to C9orf72. *Hum Brain Mapp* 2020;41:1006–16.
15 Borsook D, Upadhyay J, Chudler EH, *et al*. A key role of the basal ganglia in pain and analgesia--insights gained through human functional imaging. *Mol Pain* 2010;6:27.
16 Ong W-Y, Stohler CS, Herr DR. Role of the prefrontal cortex in pain processing. *Mol Neurobiol* 2019;56:1137–66.