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

Convery R[1], Bocchetta M[1], Woollacott IOC[1], Shafei R[1], Moore K[1], Neason M[1], Cash D[1], Thomas D[1], Greaves C[1], van Swieten J[2], Borroni B[3], Galimberti D[4], Sanchez-Valle R[5], Laforce R[6], Moreno F[7], Synofzik M[8], Graff C[9], Masellis M[10], Tartaglia C[11], Rowe J[12], Vandenberghe R[13], Finger E[14], Tagliavini F[15], de Mendonça A[16], Santana I[17], Butler C[18], Ducharme S[19], Gerhard A[20], Danek A[21], Levin J[21], Otto M[22], Rohrer JD[1] on behalf of GENFI

[1]Dementia Research Centre, UCL Institute of Neurology, Queen Square, London, United Kingdom, [2]Department of Neurology, Erasmus Medical Centre, Rotterdam, Netherlands,[3]Cognitive Disorders Unit, Department of Neurology, Donostia University Hospital, San Sebastian, Gipuzkoa, Spain, [4]Alzheimer's disease and Other Cognitive Disorders Unit, Neurology Service, Hospital Clinic, Barcelona, Spain, [5]Centre for Neurodegenerative Disorders, Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy,[6]Clinique Interdisciplinaire de Mémoire Département des Sciences Neurologiques Université Laval Québec Quebec Canada, [7]Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, University of Toronto, Toronto, Canada, [8]Tanz Centre for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada, [9]Department of Geriatric Medicine, Karolinska University Hospital-Huddinge, Stockholm, Sweden, [10]University of Milan, Centro Dino Ferrari, Milan, Italy, [11]Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom, [12] Department of Clinical Neurological Sciences, University of Western Ontario, London, Ontario Canada, [13]Department of Neurodegenerative Diseases, Hertie-Institute for Clinical Brain Research and Center of Neurology, University of Tübingen, Tübingen, Germany, [14]Laboratory for Cognitive Neurology, Department of Neurosciences, KU Leuven, Leuven, Belgium , [15]Faculty of Medicine, University of Lisbon, Lisbon, Portugal, [16]Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Istituto Neurologica Carlo Besta, Milano, Italy, [17]Faculty of Medicine, University of Coimbra, Coimbra, Portugal, [18]Department of Neurology and Neurosurgery, McGill University, Montreal, Québec, Canada, [19]Department of Clinical Neurology, University of Oxford, Oxford, United Kingdom, [20]Faculty of Medical and Human Sciences, Institute of Brain, Behaviour and Mental Health, University of Manchester, Manchester, UK, [21]Neurologische Klinik, Ludwig-Maximilians-Universität München, Munich, Germany, [22]Department of Neurology, University of Ulm, Ulm

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[1,2] as well as altered pain perception[3] 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 changes[4]. 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 MNI space, modulated and smoothed. GM tissue maps were fitted to several 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.

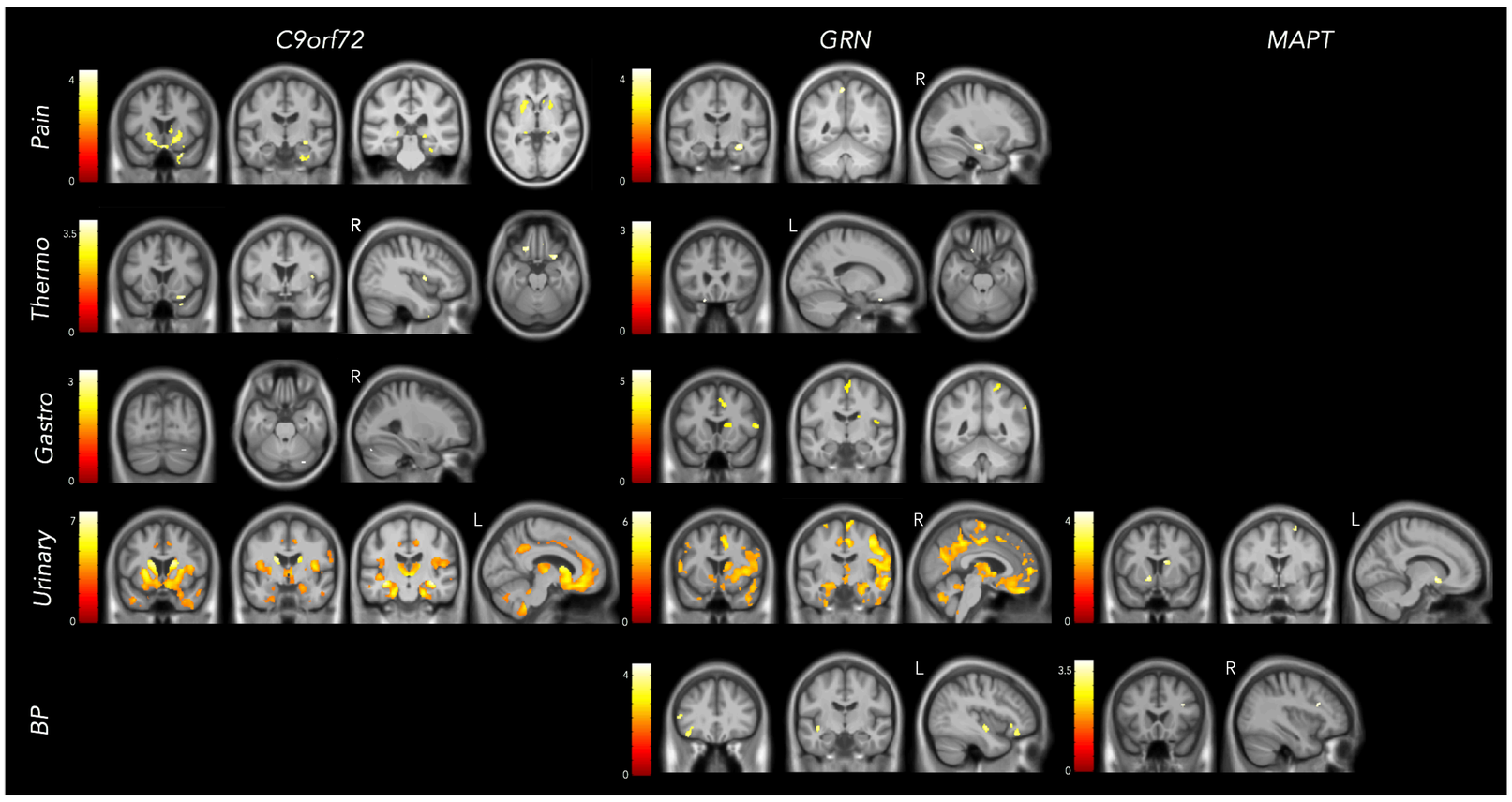

Figure 1. Association of GM atrophy with autonomic symptom score by mutation type. Statistical parametric maps are thresholded at $p<0.001$ uncorrected. Images are shown with the right hemisphere on the right of the image for the coronal and axial sections, for sagittal sections R=right sided, L=left sided. Blank boxes indicate symptoms that displayed no significant associations with GM atrophy.

	Disease stage	*N*	Age	Gender (%M)	FTLD-CDR	Disease duration, y
Control		181	45.9 (12.5)	44	0.19 (0.66)	N/A
C9orf72	Early	62	43.1 (10.6)	40	0.15 (0.48)	N/A
	Late	11	59.5 (7.2)	9	0.68 (1.23)	N/A
	Affected	31	62.5 (7.9)	65	8.89 (6.01)	5.5 (4.5)
GRN	Early	79	41.7 (9.0)	29	0.07 (0.19)	N/A
	Late	25	61.6 (6.7)	48	0.16 (0.51)	N/A
	Affected	24	61.7 (10.6)	42	8.60 (6.33)	1.7 (5.5)
MAPT	Early	29	37.4 (8.1)	35	0.29 (0.66)	N/A
	Late	10	52.1 (11.3)	50	0.05 (0.16)	N/A
	Affected	10	58.6 (6.8)	50	7.80 (5.64)	5.8 (6.2)

Table 1. Patient demographics. Early=Early Presymptomatic (>5 years to symptom onset), Late=Late Presymptomatic (<5 years to symptom onset), Affected=Symptomatic. Bracketed values represent standard deviations.

	Disease stage	BP		Gastro		Thermo		Urinary		Pain	
		Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value	Mean (SD)	p-value
Control		0.03 (0.14)		0.05 (0.24)		0.05 (0.26)		0.03 (0.16)		0.00 (0.04)	
C9orf72	Early	0.05 (0.20)	0.637	0.03 (0.15)	0.834	0.03 (0.18)	0.482	0.02 (0.13)	0.259	0.02 (0.13)	0.422
	Late	0.00 (0.00)	0.450	0.00 (0.00)	0.425	0.00 (0.00)	0.425	0.00 (0.00)	0.450	**0.20 (0.06)***	0.007
	Affected	0.16 (0.43)	0.076	**0.27 (0.56)***	<0.001	**0.48 (0.84)***	<0.001	**0.74 (0.99)***	<0.001	**0.40 (0.71)***	<0.001
GRN	Early	0.02 (0.10)	0.668	0.02 (0.10)	0.543	0.01 (0.08)	0.280	0.04 (0.24)	0.684	0.00 (0.00)	0.509
	Late	0.00 (0.00)	0.255	0.00 (0.00)	0.230	0.00 (0.00)	0.230	0.02 (0.10)	0.821	0.00 (0.00)	0.710
	Affected	0.04 (0.20)	0.891	0.12 (0.48)	0.164	**0.27 (0.68)***	0.035	**0.48 (0.71)***	<0.001	0.04 (0.20)	0.089
MAPT	Early	0.09 (0.27)	0.229	0.03 (0.19)	0.657	0.03 (0.19)	0.651	0.00 (0.00)	0.221	0.03 (0.19)	0.134
	Late	0.00 (0.00)	0.471	0.00 (0.00)	0.446	0.00 (0.00)	0.447	0.00 (0.00)	0.471	0.00 (0.00)	0.814
	Affected	0.05 (0.16)	0.498	0.05 (0.16)	0.570	0.15 (0.34)	0.069	**0.15 (0.34)***	0.045	**0.10 (0.32)***	0.004

Table 2. Mean autonomic symptom score of mutation groups in comparison to controls. BP=blood pressure, **p*-values <0.05.

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 right amygdala, right temporal pole, right 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 thalamus. Afferents conveying pain information relay via postero-lateral thalamic nuclei to the somatosensory cortex[5], 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: [1]Ahmed, R. *et al*. (2015) *Journal of Neurology, Neurosurgery and Psychiatry*, 86(9), pp.1048–1049. [2]Diehl-Schmid, J. *et al*., (2007) *Fortschritte der Neurologie-Psychiatrie*, *75*(12), pp.708-713. [3]Fletcher, P. D. *et al*. (2015) *Brain*, 138(11), pp. 3360–3372. [4]Seeley, W.W. (2010) *Brain Structure and Function*, *214*(5-6), pp.465-475. [5]Craig, A.D. (2002) *Nature reviews neuroscience*, *3*(8), p.655.

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