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Patterns of regional cerebellar atrophy in genetic frontotemporal dementia

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ABSTRACT

Background: Frontotemporal dementia (FTD) is a heterogeneous neurodegenerative disorder with a strong genetic component. The cerebellum has not traditionally been felt to be involved in FTD but recent research has suggested a potential role.
Methods: We investigated the volumetry of the cerebellum and its subregions in a cohort of 44 patients with genetic FTD (20 *MAPT*, 7 *GRN*, and 17 *C9orf72* mutation carriers) compared with 18 cognitively normal controls. All groups were matched for age and gender. On volumetric T1-weighted magnetic resonance brain images we used an atlas propagation and label fusion strategy of the Diedrichsen cerebellar atlas to automatically extract subregions including the cerebellar lobules, the vermis and the deep nuclei.
Results: The global cerebellar volume was significantly smaller in *C9orf72* carriers (mean (SD): 99989 (8939) mm^3) compared with controls (108136 (7407) mm^3). However, no significant differences were seen in the *MAPT* and *GRN* carriers compared with controls (104191 (6491) mm^3 and 107883 (6205) mm^3 respectively). Investigating the individual subregions, *C9orf72* carriers had a significantly lower volume than controls in lobule VIIa-Crus I (15% smaller, $p < 0.0005$), whilst *MAPT* mutation carriers had a significantly lower vermal volume (10% smaller, $p = 0.001$) than controls. All cerebellar subregion volumes were preserved in *GRN* carriers compared with controls.
Conclusion: There appears to be a differential pattern of cerebellar atrophy in the major genetic forms of FTD, being relatively spared in *GRN*, localized to the lobule VIIa-Crus I in the superior-posterior region of the cerebellum in *C9orf72*, the area connected via the thalamus to the prefrontal cortex and involved in cognitive function, and localized to the vermis in *MAPT*, the 'limbic cerebellum' involved in emotional processing.

1. Introduction

Frontotemporal dementia (FTD) is a clinically, pathologically and genetically heterogeneous neurodegenerative disorder, commonly presenting with progressive impairment in behaviour (behavioural variant FTD, bvFTD) or language (primary progressive aphasia, PPA). Around a third of patients with FTD have an autosomal dominant mutation in one of three genes: microtubule-associated protein tau (*MAPT*), progranulin (*GRN*) and chromosome 9 open reading frame 72 (*C9orf72*) (Rohrer and Warren, 2011). Neuroimaging and pathological studies of FTD have emphasized the key roles of the frontal, temporal, insular and cingulate cortices as well as subcortical structures such as the striatum and thalamus, but minimal attention has been paid to the potential role of the cerebellum.

Although its function has traditionally been felt to be related solely to the co-ordination of movement, research over the past twenty years has highlighted a role for the cerebellum in cognitive and emotional processing (Schmahmann, 1991; D'Angelo and Casali, 2013; Middleton and Strick, 2000; Strick et al., 2009; Makris et al., 2003). It is extensively connected with different brain regions, including key areas involved in FTD, e.g. via the thalamus to the prefrontal cortex (Behrens et al., 2003; Palesi et al., 2015), and to the limbic system via a direct cerebello-limbic pathway (Arrigo et al., 2014).

Interest in the cerebellum in FTD has arisen from the association of *C9orf72* mutations with cerebellar pathology at *post-mortem* and a number of voxel-based morphometry MRI studies have now found involvement of the cerebellum in this group (Whitwell et al., 2012; Irwin et al., 2013; Mahoney et al., 2012; Rohrer et al., 2015). However detailed region of interest studies have not been performed, nor direct comparison

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across the different major genetic forms of FTD. Therefore, the aim of this study was to investigate the volume of the cerebellum and its subregions in a cohort of genetic FTD patients, and to determine whether specific cerebellar regions are associated with genetic mutations in *MAPT*, *GRN* and *C9orf72* genes.

2. Methods

We reviewed the UCL Dementia Research Centre FTD database to identify all patients who were symptomatic carriers of a mutation in the *MAPT*, *GRN* or *C9orf72* genes and who had also undergone a volumetric T1-weighted MRI. 44 patients were identified: 20 *MAPT* (19 with bvFTD and one with a corticobasal syndrome), 7 *GRN* (3 bvFTD and 4 PPA) and 17 *C9orf72* (13 bvFTD, 2 FTD with motor neurone disease and 2 PPA). No significant differences were seen in age at scan ($p = 0.071$, Kruskal–Wallis test) or gender ($p = 0.301$ Chisquare test) between the groups: 57.6 (7.1) years for *MAPT* (75% male), 63.0 (7.0) years for *GRN* (43% male) and 61.4 (6.7) years for *C9orf72* (65% male). Disease duration at time of scan was significantly different between the groups ($p = 0.026$, Kruskal–Wallis test): 7.0 (4.3) years for *MAPT*, 2.7 (1.9) for *GRN* and 6.0 (4.1) years for *C9orf72*. However, each genetic FTD cause is known to vary in its disease progression and so we examined whole brain volume (corrected for total intracranial volume, TIV) as a proxy of overall disease stage. No significant differences were seen between the groups ($p = 0.610$, Kruskal–Wallis test): 1108.8 (388.7) cm^3 for *MAPT*, 1118.9 (411.7) cm^3 for *GRN* and 1098.1 (661) cm^3 for *C9orf72*, suggesting that the groups were approximately matched for disease severity. Eighteen cognitively normal subjects, with a similar age and gender to the carriers, were identified as controls: 56.4 (14.3) years (50% male). The study was approved by the local ethics committee and written informed consent was obtained from all participants.

Raw MR images were pre-processed to correct for magnetic field bias (inhomogeneity) using a non-parametric non-uniform intensity normalization (N3) algorithm (Sled et al., 1998; Boyes et al., 2008). We then used an atlas propagation and label fusion strategy of the Diedrichsen cerebellar atlas to automatically extract subregions of the cerebellum: the cerebellar lobules (I-IV, V, VI, VIIa-Crus I, VIIa-Crus II, VIIb, VIIIa, VIIIb, IX and X), the vermis and the deep nuclei (dentate, interposed and fastigial) (Cardoso et al., 2015; Diedrichsen et al., 2009, 2011). No significant asymmetry was noted in the volumes and so right and left-sided results were combined for each subregion. All volumes were corrected for TIV, which was calculated using the Statistical Parametric Mapping (SPM) 12 software, version 6470 (www.fil.ion.ucl.ac.uk/spm), running under Matlab R2014b (Math Works, Natick, MA, USA) (Malone et al., 2015). Statistical analyses were performed in SPSS software (SPSS Inc., Chicago, IL, USA) version 22.0, with differences in volumes of the cerebellar lobules, vermis and deep nuclei between all groups tested using the Mann–Whitney U test.

3. Results

C9orf72 mutation carriers showed the lowest global cerebellar volume (mean (SD): 99989 (8939) mm^3), significantly smaller than controls (108136 (7407) mm^3, $p = 0.006$ on Mann–Whitney U test), and the *GRN* group (107883 (6205) mm^3, $p = 0.028$), but not from the *MAPT* group (104191 (6491) mm^3; $p = 0.080$). No significant differences were seen in the *GRN* or *MAPT* groups in comparison with each other or the control group ($p = 0.196$, *MAPT* versus controls; $p = 0.836$, *GRN* versus controls; $p = 0.370$, *GRN* versus *MAPT*).

For the 14 individual subregions of the cerebellum, a Bonferroni correction for multiple comparisons was made so that only a threshold of $p < 0.003$ was considered significant. The *C9orf72* group showed a significantly lower volume compared with controls of the lobule VIIa-Crus I only ($p < 0.0005$, 15.2% smaller than controls), whilst the *MAPT* group showed a significantly lower volume of the vermis only ($p =$

Table 1
Volumetry of cerebellar subregions in 18 healthy non-carrier controls and 44 genetic FTD patients. Values denote mean and standard deviation (SD) volumes in mm^3 or n (%). p-values denote significance on Mann–Whitney U test. Bold represents a significant difference between groups after correcting for multiple comparisons.

	Controls (18)		*C9orf72* (17)		*MAPT* (20)		*GRN* (7)		*C9orf72* vs Controls	*MAPT* vs Controls	*GRN* vs Controls	*C9orf72*	*MAPT*	*GRN*	*GRN* vs *C9orf72*	*GRN* vs *MAPT*	*C9orf72* vs *MAPT*
Structure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p-Value	p-Value	p-Value	% difference vs controls	% difference vs controls	% difference vs controls	p-Value	p-Value	p-Value
Lobule I–IV	6236	670	6363	861	6250	433	7053	674	0.660	0.534	0.012	−2.0	−0.2	−13.1	0.099	0.013	0.775
Lobule V	8911	897	8623	905	8922	742	9371	737	0.503	0.553	0.125	3.2	−0.1	−5.2	0.034	0.145	0.311
Lobule VI	15639	1452	14587	2000	15277	1390	16590	1930	0.067	0.534	0.244	6.7	2.3	−6.1	0.034	0.104	0.133
Lobule VIIa-Crus I	21091	2467	17885	1984	20360	3303	19298	2237	**<0.0005**	0.675	0.125	15.2	3.5	8.5	0.099	0.498	0.013
Lobule VIIa-Crus II	17610	2311	15807	2863	16015	1822	17666	752	0.067	0.033	0.534	10.2	9.1	−0.3	0.147	0.036	0.845
Lobule VIIb	7565	802	7330	976	7488	781	7460	611	0.483	0.515	0.534	3.1	1.0	1.4	0.951	0.850	0.729
Lobule VIIIa	7799	704	7724	927	7957	558	8033	756	0.909	0.361	0.495	1.0	−2.0	−3.0	0.534	0.766	0.517
Lobule VIIIb	7451	900	6926	894	7318	1077	7233	834	0.245	0.806	0.790	7.0	1.8	2.9	0.288	0.685	0.270
Lobule IX	6200	828	5563	799	5520	709	5659	864	0.013	0.010	0.158	10.3	11.0	8.7	0.318	0.533	0.988
Lobule X	860	88	850	108	909	124	882	146	0.883	0.228	1.000	1.1	−5.7	−2.6	0.757	0.607	0.149
Vermis	5034	375	4624	584	4554	412	4862	408	0.025	**0.001**	0.297	8.1	9.5	3.4	0.260	0.145	0.940
Dentate nuclei	3291	426	3303	406	3214	422	3325	524	1.000	0.361	0.836	−0.4	2.3	−1.0	0.951	0.766	0.341
Interposed nuclei	392	44	351	31	357	31	394	54	0.004	0.007	0.836	10.4	8.9	−0.4	0.099	0.104	0.821
Fastigial nuclei	57	10	51	6	51	6	56	10	0.062	0.033	0.836	10.5	11.1	0.9	0.147	0.104	0.988