Detailed structural analysis of the hypothalamus in behavioural variant frontotemporal dementia

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Background

Abnormal eating behaviours such as hyperphagia and craving for sweet foods are frequently reported in behavioural variant frontotemporal dementia (bvFTD). The hypothalamus is the regulatory centre for feeding and satiety but its role in bvFTD has not been fully clarified, partly due to its difficult identification on magnetic resonance images (MRIs).

Methods

We investigated hypothalamic volume and shape in a sample of 18 bvFTD patients (including 9 *MAPT* mutation carriers and 6 *C9orf72* expansion carriers) with abnormal eating behaviour compared with 18 cognitively-normal controls. All participants were scanned on a 3T Siemens Trio, and the presence of abnormal eating behaviour was assessed with the revised version of the Cambridge Behavioural Inventory (CBI-R). A novel optimized multimodal manual segmentation protocol of the whole hypothalamus was developed using 3D T1 and T2-weighted MRIs (intrarater intraclass correlation coefficients ≥0.93). The whole hypothalamus was subsequently segmented manually into five different subunits (**Figure 1**). Shape differences were investigated using the using spherical harmonic-point distribution model (SPHARM-PDM toolbox).

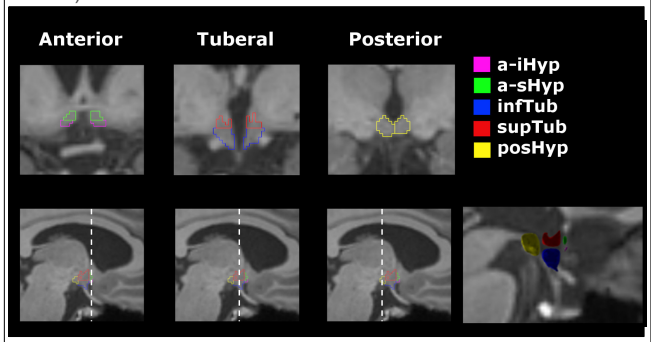

Figure 1. Segmentation of the hypothalamic subunits mapped on a 3T T1-weighted MR image of a control subject and their 3D reconstruction on a sagittal view.
a-iHyp=anterior inferior hypothalamus, a-sHyp=anterior superior hypothalamus, infTub=inferior tuberal hypothalamus, supTub=superior tuberal hypothalamus, posHyp=posterior hypothalamus.
Definitions from Makris et al., Neuroimage 2013;69:1-10.

Results

	Controls (n=18)	bvFTD (n=18)	bvFTD- *MAPT* (n=9)	bvFTD - *C9orf72* (n=6)
Gender, male	9 (50%)	15 (83%)	7 (78%)	5 (83%)
Age at scan	56 (14)	63 (9)	60 (9)	65 (7)
Disease duration	--	9 (6)	8 (6)	11 (4)
Age at onset	--	54 (9)	51 (6)	54 (10)
Education	14 (3)	14 (4)	14 (5)	13 (4)
MMSE	29.2 (1.2)	25.0 (4)*	25.8 (5.0)*	24.0 (4.0)*
CBI-R Total	--	76.5 (31.8)	76.4 (36.9)	78.7 (33.4)
CBI-R Eating disturbance	--	7.7 (3.9)	7.9 (4.2)	8.3 (3.2)

Table 1. Demographic, clinical and behavioural variables for the bvFTD patients and controls. *Values denote mean (standard deviation) or n (%). *p<0.05 disease group versus controls (Mann-Whitney U test).*

	Controls	bvFTD	difference	p-value
Hypothalamus R	477 (38)	398 (62)	-17%	**<0.0005**
Hypothalamus L	467 (39)	385 (53)	-18%	**<0.0005**
a-iHyp	18 (8)	30 (18)	-40%	0.064
a-sHyp	27 (13)	46 (18)	-41%	**0.001**
infTub	314 (37)	317 (38)	-1%	0.673
supTub	225 (38)	289 (54)	-22%	**0.001**
posHyp	199 (59)	263 (49)	-24%	**0.001**

Table 2. Volumetry of hypothalamus and its subunits in 18 bvFTD and 18 control subjects. *Volumes are corrected for total intracranial volume. Values denote mean (standard deviation) volumes in mm^3. P-values denote significance on Mann-Whitney U test.*

Results

Subjects' characteristics are summarized in **Table 1. Table 2** reported the volumetric results, corrected for total intracranial volume. *MAPT* mutation carriers showed a trend for lower volumes on both sides compared with *C9orf72* (12% difference).

Specifically, in both shape and volumetric analyses, we found a strong evidence for the involvement of the dorsal tuberal hypothalamus in bvFTD patients, compared with controls (**Figure 2**).

In the total bvFTD group, patients who scored in the severe to very severe range of the CBI-R eating disturbance subscale had a trend to a lower total hypothalamic volume than those in the mild to moderate range. This trend for a lower volume in those scoring in the severe to very severe range was also seen in the superior tuberal region.

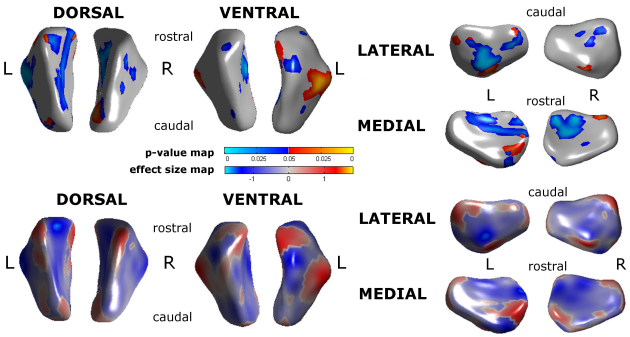

Figure 2. Maps of shape difference displayed on the mean left and right hypothalamus. *Inward deformations in the hypothalamus in bvFTD patients compared with healthy controls are shown in cool colours (turquoise to blue), while outward deformations are shown in warm colours (red to yellow). First row shows the p-value maps (FDR corrected). The bottom row shows the effect size maps (in mm). Analyses were adjusted for age, gender and total intracranial volume.*

Conclusions

In summary, bvFTD patients showed lower hypothalamic volumes compared with controls: this reduction is localized to the subnuclei that regulate food intake, reward and perception of satiety. Different genetic mutations may have a differential impact on the hypothalamus.

Acknowledgements: The Dementia Research Centre is supported by Alzheimer's Research UK, Brain Research Trust, and The Wolfson Foundation. This work was supported by funding from the UK Medical Research Council, Wellcome Trust and NIHR Queen Square Biomedical Research Unit. JDR is supported by an NIHR Rare Disease TRC Fellowship. EG is supported by an Alzheimer's Society PhD Studentship. JB and EM are funded by Alzheimer's Research UK.