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Apathy is not Associated with Basal Ganglia Atrophy in Frontotemporal Dementia

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Abstract

Objective—To determine whether basal ganglia atrophy known to be associated with apathy in non-dementia populations was associated with presence of apathy in patients with frontotemporal dementia (FTD).

Methods—A cross-sectional case study was conducted at two tertiary dementia care clinics in Toronto, Ontario. Striatal and thalamic grey matter volumes and apathy measures were collected from 21 subjects with FTD; 6 of whom did not show apathy on the Neuropsychiatric Inventory (NPI).

Results—No significant differences in grey matter volumes were found between apathetic and non-aphathetic groups for the striatum or for the thalamus.

Conclusions—Our findings imply that the etiology of apathy seen in FTD patients differs from that of patients with apathy after acquired injuries to the basal ganglia. Further study is needed to determine whether posterior thalamic atrophy correlates with apathy in FTD, or functional imaging techniques might successfully find a relationship between basal ganglia dysfunction and apathy.

Keywords

frontotemporal dementia; basal ganglia; apathy; atrophy

Objective

Apathy is commonly accepted as one of the prevalent features of frontotemporal dementia (FTD), manifesting in 60–90% of cases.¹ Apathy, defined as an impairment in voluntary and goal-directed behaviours² has been linked by several studies to atrophy in various cortical regions: dorsolateral and medial prefrontal,² and orbitofrontal cortex (right and lateral).³

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Beyond cortical atrophy correlates, the relationship between lesions to subcortical components of frontosubcortical circuits and changes in motivation has also been well-documented. Levy and Dubois reviewed articles that correlated basal ganglia (BG) dysfunction with apathy.² Those studies examined various BG lesions of varying extents and their co-occurrence with apathy. These regions of interest included the caudate nuclei, caudate combined with putamen as striatum, globus pallidus, and the thalamus. The etiologies for the lesions in Levy and Dubois' review were not related to dementia. We investigated whether there is a similar subcortical atrophy association with apathy in FTD.

Methods

This study and methods of obtaining consent were approved by Research Ethics Boards at Sunnybrook Health Sciences Centre and Baycrest. In a previous study, we assessed a sample of 21 FTD subjects and 21 age- and gender-matched healthy comparison subjects for striatal and thalamic atrophy and found that FTD subjects, especially those more impaired in activities of daily living, had atrophy in the left anterior thalamus and bilaterally in the striatum.⁴

Our sample consisted of 21 subjects diagnosed with FTD at the Memory Disorders Clinics of the Sunnybrook Health Sciences Centre and Baycrest, Toronto, Canada between 1995 and 2004. Demographics for this FTD population are detailed in Table 1. No significant differences were found between apathetic and non-aphathetic groups on any of the demographic factors.

Each of the subjects underwent MR imaging (most within 3 months of FTD diagnosis) in a 1.5-tesla Signa scanner (GE Medical Systems, software v. 8.4M4, with CV 40 mT/m gradients). High-resolution T1-weighted (an axial 3-dimensional SPGR with 5 ms TE, 35 ms TR, 1 NEX, 35° flip angle, 22×16.5 cm FOV, 0.859×0.859 mm in-plane resolution, and 1.2–1.4 mm slice thickness depending on the head size) and interleaved proton density/T2-weighted (an interleaved axial spin echo with TEs of 30 and 80 ms, 3 s TR, 0.5 NEX, 20×20 cm FOV, 0.781×0.781 mm in-plane resolution, and 3 mm slice thickness) were acquired for each subject.

Regional volumetric information was acquired by two MR operators through brain extraction, tissue segmentation and parcellation processes. These steps were followed by semi-automated tri-feature brain extraction to segment the T1-images into grey matter, white matter and cerebrospinal fluid tissue compartments. Semi-automatic brain region extraction (SABRE) methods (as described by Dade, et. al.) were used to obtain regional parcellations.⁵ 8 major landmarks (central sulcus, sylvian fissure, parieto-occipital sulcus, anterior and posterior commissure) were identified in each T1-weighted image using ANALYZE software (Biomedical Imaging Resource Mayo Clinic, Rochester, Minn., USA). A 3-dimensional surface-rendered MR image was also created to guide the automated delineation of frontal regions, divided into left and right sides. Left and right SABRE parcellations was also used to generate grey matter component volumes of interest (VOI) for striatum bilaterally, as well as anterior and posterior thalamus bilaterally.

To process the six subcortical volumes we calculated the ratio of VOI to total supratentorial intracranial volume for each individual, and then multiplied by the mean total supratentorial intracranial volume of a comparison sample (1, 219.27 ml, n=30), yielding a normalized volume for each brain region.

Presence or absence of apathy was determined by caregiver responses to the Neuropsychiatric Inventory (NPI),⁶ typically administered within two months of the MRI scan.

A series of six independent t-tests were conducted to determine whether apathetic patients presented with greater atrophy in any of the six ROIs. Cohen's d was also calculated for each VOI using the following formula:

$$d = \frac{\mu_1 - \mu_2}{\sqrt{[(\sigma_1^2 + \sigma_2^2) / 2]}}$$

Where μ = mean and σ = standard deviation

Results

Of the 21 FTD subjects, 15 had apathy and 6 did not. Given the findings reported by Levy and Dubois, we suspected that the apathetic FTD subjects would have significantly more atrophy (smaller mean VOI) than those who did not demonstrate apathy by independent samples t-test.

There were no significant differences between VOI direct measures from apathetic vs non-apathetic groups. While both posterior thalamic mean VOIs of apathetic subjects were smaller than those in the non-apathetic group, VOIs were unexpectedly smaller or the same in the non-apathetic group for the other four VOIs (See Table 2).

Conclusions

We did not find differences in subcortical atrophy for FTD subjects with or without apathy. The lack of positive finding may be related to small sample size (N=21) and the resulting lack of power.

These results may suggest that the apathy exhibited in FTD patients differs in etiology from that of patients with apathy due to the acquired, non-neurodegenerative BG lesions, as reported by Levy and Dubois. The damage assessed in these articles was variable, including vascular insult causing infarction or haemorrhage, neoplasm, necrosis and lesions caused by anoxic or toxic encephalopathy.² Another possibility is that the apathy reviewed by Levy and Dubois confounded co-existent neuropathologic changes to the prefrontal cortex or other brain regions that can contribute to loss of motivation, though the authors recognize that these preliminary data are but a starting point from which this possibility might further be explored, especially with respect to the posterior thalamus.

Atrophy on structural neuroimaging may not be the best indicator of basal ganglia dysfunction. For example, evaluation of dopaminergic pathways with [18F]-dopa PET imaging might also lead to understanding how the basal ganglia contribute to apathy.

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Table 1

Characterization of the Sample

	Presence of Apathy (n=15)	No Apathy Present (n=6)
Sex (% male)	33.3%	50.0%
Age (mean and standard deviation)	65.07 $\pm$ 8.5	64.83 $\pm$ 10.8
Education (yrs, mean and standard deviation)	12.20 $\pm$ 3.9	16.00 $\pm$ 6.4
Duration (yrs, mean and standard deviation)	4.64 $\pm$ 3.1	2.91 $\pm$ 2.0
Handedness (% right)	73.3%	100%
MMSE (mean and standard deviation)	23.73 $\pm$ 6.3	20.83 $\pm$ 8.8
Total NPI Score (mean and standard deviation)	24.33 $\pm$ 19.1	10.17 $\pm$ 9.9

Table 2

Subcortical Volumes of Interest (VOI) *

Region of Interest	Apathetic (N=15) Mean VOI (ml) $\pm$ Standard Deviation	Non-Apathetic (N=6) Mean VOI (ml) $\pm$ Standard Deviation	P value	Cohen's d
Left Striatum	5.64 $\pm$ 1.43	5.56 $\pm$ 1.10	0.36	0.063
Right Striatum	6.56 $\pm$ 1.75	5.91 $\pm$ 1.20	0.47	0.433
Left Anterior Thalamus	1.14 $\pm$ 0.29	1.06 $\pm$ <u>0.30</u>	0.65	0.271
Right Anterior Thalamus	1.34 $\pm$ 0.32	1.33 $\pm$ 0.24	0.64	0.0354
Left Posterior Thalamus	2.51 $\pm$ 0.63	2.59 $\pm$ 0.35	0.10	0.157
Right Posterior Thalamus	2.75 $\pm$ 0.77	3.09 $\pm$ 0.25	0.06	0.594

*
t-tests, df= 19