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Magnetic Resonance Imaging in Frontotemporal Dementia Shows Subcortical Atrophy

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Key Words
Basal ganglia · Frontotemporal dementia · Frontotemporal lobar degeneration · Thalamus

Abstract
Background/Aims: The clinical syndrome of the frontotemporal dementias (FTD) overlaps with frontal-subcortical circuit syndromes. We explored the extent to which subcortical atrophy on structural magnetic resonance imaging may indicate a subcortical contribution to the progression of FTD. ***Methods:*** This cross-sectional case-control study compared striatal and thalamic gray matter volumes and functional levels from 30 FTD cases and 30 age- and gender-matched controls. ***Results:*** The FTD group had significantly more atrophy in all gray matter subcortical regions, correlating with ipsilateral frontocortical atrophy. Subcortical atrophy was also associated with functional disability. Subcortical asymmetry was most marked in subjects with primary progressive aphasia. ***Conclusion:*** Subcortical gray matter atrophy may contribute as significantly to symptoms of FTD as cortical atrophy.

Introduction

The frontotemporal dementias (FTD) are an important cause of early-onset dementia [1]. The illness strikes in the sixth decade of life and includes a spectrum of clinical presentations and pathological findings related to frontal lobe functions. There are both behavioral (bvFTD) and aphasic [either fluent or nonfluent primary progressive aphasia (PPA)] clinical variants of the disease, determined by the topography of the neuropathology [2]. Cortical atrophy in frontal or temporal regions, as seen on structural neuroimaging, is supportive of the diagnosis but not required, because without the use of volumetric processing, it might be difficult to distinguish from atrophy due to normal aging [3].

The constellations of impairments characteristic of FTD include changes in personality, social behavior and motivation, all of which have been described in frontal-subcortical (FSC) syndromes [4–7]. Cognitive losses in FTD follow the pattern of the dorsolateral prefrontal subcortical circuit syndrome, affecting attention, planning, and problem solving. Neuropsychiatric symptoms in-

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Table 1. Characteristics of the sample

	Controls (n = 30)	PPA (n = 14)	bvFTD (n = 16)
Men, %	33	43	31.3
Mean age at onset, years	n/a	59.5 (46–73)	59.7 (49–78)
Mean age at time of MRI, years	65 (52–80)	64.3 (54–75)	63.5 (51–80)
Mean duration of illness at the time of the MRI scan, years	n/a	4.8 (1.5–11), n = 14	3.3 (1–6), n = 14
Mean education level	16 (11–21), n = 29	14 (4–20)	14 (5–23)
Mean MMSE score*	29 (27–30), n = 21	13 (1–26)	26.3 (19–30), n = 15

* $p < 0.0001$ (one-way ANOVA, for control vs. either FTD group and between bvFTD vs. PPA). Figures in parentheses indicate ranges.

clude depression, anxiety, impulsivity and compulsive behaviors [8–10]. Lesions to the dorsolateral prefrontal cortex (DLPFC) can result in depression, in addition to difficulties with goal-directed activities and self-monitoring. Degeneration of the orbitofrontal cortex (OFC) results in problems with social behavior and affect, such as irritability, loss of empathy, and obsessive-compulsive behaviors. Finally, lesions of the superior medial frontal cortex lead to amotivational syndromes, such as apathy. Patients with PPA variants develop similar behavioral disturbances to patients with bvFTD, implying that eventually FSC structures are also affected in this subgroup of FTD [11].

Despite the resemblance of clinical manifestations of FTD to FSC syndromes, there are scarce reports about the potential contribution of subcortical degeneration during the course of FTD. Autopsy reports have documented the eventual development of atrophy in the caudate, putamen, globus pallidus and thalamus in FTD [4, 12]. Due to the critical roles of subcortical nuclei within each FSC circuit, it would be reasonable to inquire if atrophy in the striatum and thalamus as measured by structural imaging correlates with frontocortical atrophy and functional disability due to degeneration in FTD. We conducted a cross-sectional, volumetric comparison of magnetic resonance imaging (MRI) scans from subjects with FTD and healthy controls to assess subcortical atrophy in FTD, its relation to ipsilateral cortical atrophy, and its relation to independence in activities of daily living (ADLs). Our four hypotheses were: (1) subcortical atrophy scores will be significantly smaller in subjects with FTD than in controls; (2) striatal, anterior thalamic, and posterior thalamic regions will be more asymmetric in PPA than in bvFTD; (3) within the FTD group, subcortical volumes of interest (VOIs) will be proportional to frontal VOIs, and (4) within the FTD group, subcortical atrophy scores will be lower in the more functionally disabled subjects.

Materials and Methods

Subjects were diagnosed with FTD at Memory Disorders Clinics of the Sunnybrook Health Sciences Centre (S.E.B.) and Baycrest (T.W.C. and M.F.), Toronto, Canada, between 1995 and 2004. Ethics committees at both institutions approved the protocols for collecting the data. We conducted a retrospective search for subjects with FTD diagnosed according to clinical criteria published from a consensus meeting in which three co-authors had participated [1]. One subject had a clinical diagnosis of frontal-variant Alzheimer's disease but had frontotemporal lobar degeneration (FTLD) with tau-positive inclusions at autopsy. The combined autopsy confirmation rate for clinical diagnosis of FTD among these 3 clinicians has been 96%. Ten of the FTD subjects (33%) in this study had autopsy confirmation of their diagnoses (table 1). As in the consensus diagnostic criteria [1], functional imaging (SPECT or PET) abnormalities in frontotemporal cortices were not required for the diagnosis of FTD in our sample.

Patients evaluated for FTD at the two neurocognitive clinics routinely undergo a standardized MRI of the brain research protocol for dementia at the Sunnybrook Health Sciences Centre [13] unless the procedure is contraindicated (e.g. status after pacemaker placement). MRI took place in a 1.5-tesla Signa scanner (GE Medical Systems, software v. 8.4M4, with CV 40 mT/m gradients), acquiring a high-resolution T_1-weighted image (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). This was followed by an interleaved proton density and T_2-weighted image set (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). The T_1-weighted and proton density/T_2-weighted imaging parameters have been selected to provide optimal intensity separation and are routinely used for the tissue segmentation protocol below [13]. MRI scans for this

study were typically performed within 3 months of the clinical diagnosis of FTD, with the exception of 4 cases of FTD who had their first MRI for research purposes 1–2 years after diagnosis. In some of those cases, the MRI scan was useful in ruling out secondary diseases (e.g. stroke) in the differential diagnosis, but findings of atrophy did not bias inclusion or exclusion from this study.

For a description of the sample, please see table 1. Although FTD typically has an early onset age, there are some autopsy-confirmed, late-onset FTD cases with slow progression (aged 75–85 years) [14], which indicates that we should not exclude our oldest subjects on the basis of age at onset. We determined duration of illness as the time from the informant's first recollection of symptoms related to dementia. Mini Mental State Examination (MMSE) scores from the PPA group were lower than from the bvFTD group ($p = 0.0002$ for unequal variances), reflecting the impact of language ability on MMSE performance [15]. Dementia Rating Scale scores in the study by Mattis [16] were available for 17 FTD subjects and averaged 107.5 (range 48–142). For medication data, please see a previous study by this group [3].

Sixteen subjects within the FTD group (53%) had bvFTD [2]; 1 of the 16 bvFTD subjects had the motor neuron variant of FTD, confirmed by autopsy. Fourteen FTD subjects (47%) presented with progressive aphasia for the first 2 years of illness and constituted the PPA group [2]. Of the 14 PPA subjects, 5 were left-handed.

Methods of evaluating daily function varied among the 3 clinicians. Disability Assessment for Dementia (DAD) [17] scores were available for 18 subjects, Bristol Activities of Daily Living Scale (BADLS) scores [18] for 3, and clinical qualification of independence for basic and instrumental activities of daily living (IADLs) for 6. Functional ability data were unavailable for 3 of the 30 subjects.

Parkinsonism was defined as the presence of any of the following: resting tremor, bradykinesia, cogwheeling, postural instability or parkinsonian gait. The FTD subjects were evaluated at neurocognitive clinics where parkinsonism is assessed, even if not by formal use of the United Parkinson Disease Rating Scale [19]. We reviewed clinic notes from evaluations within 6 months of the MRI for this study, seeking the observations of parkinsonism. Chart data regarding parkinsonism were unavailable for 2 subjects.

Control subjects had no current or recent history of stroke, Parkinson's disease, head trauma with loss of consciousness, psychotic disorders, psychoactive substance abuse, or major depressive disorder. Control subjects were excluded if MRI revealed silent cortical infarct but not for silent white matter hyperintensities of any size.

Image Analysis

A three-step procedure (brain extraction, tissue segmentation and parcellation) was applied by 2 operators to the MR images to obtain regional volumetric information (C.J.M.S. and J.R., mean interrater correlation coefficient of 0.990 across regions, range 0.95–1.0). After a semi-automatic tri-feature brain extraction procedure, the T_1-weighted image was segmented into gray matter, white matter, and cerebrospinal fluid tissue compartments [12]. Regional parcellations were obtained with the semi-automatic brain region extraction (SABRE) methods described by Dade et al. [20]. Using ANALYZE software (Biomedical Imaging Resource, Mayo Clinic, Rochester, Minn., USA), an operator (J.R.) identified 8 major landmarks (central sulcus, sylvian fissure, parieto-occipital sulcus, anterior and posterior commissure) on each T_1-weighted image and a 3-dimensional surface-rendered MR image to guide the automated delineation of frontal regions, divided into left and right sides. Additional left and right SABRE parcellations were applied to yield gray matter component VOIs for striatal and thalamic regions (fig. 1a). Medial temporal regions were masked out of these SABRE zones. A separate thalamus mask was used to indicate left and right, anterior and posterior thalamic volumes (fig. 1b). The anterior thalamic region contains the ventral anterior thalamic nucleus, which is a component of the DLPFC and OFC. The posterior thalamic region includes the mediodorsal thalamic nucleus, which contributes to all three FSC circuits: DLPFC, OFC, and superior medial frontal cortex [21].

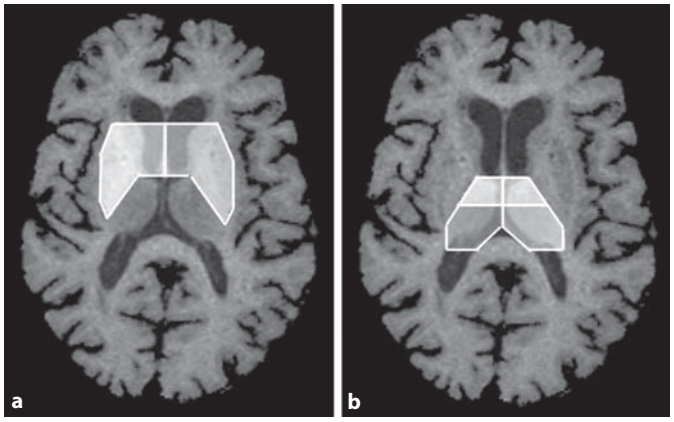

Fig. 1. Axial view of additional SABRE regions overlaid on a T_1-weighted eroded image in the AC-PC stereotactic space. **a** Striatal region with left and right delineations. **b** Thalamic region with left and right, anterior and posterior delineations. The figure displays only one demonstrative slice of the full 3-dimensional masks used to calculate volumes of interest (VOIs).

We used two steps to process the six subcortical volumes. The first calculation of the ratio of VOI to total supratentorial intracranial volume for each individual accounted for normal variation in head size per individual. The ratio was then multiplied by the mean total supratentorial intracranial volume for the control sample (1,219.27 ml, n = 30) to yield a normalized volume for each brain region.

To quickly grasp the hemispheric asymmetry, we created atrophy score variables to represent the proportion of atrophy relative to control volumes standardized to account for normally occurring asymmetry of the striatum and thalamus. The atrophy score is calculated as follows:

$$2 \times \frac{\left(\text{left or right volume}\left(\text{e.g., striatum}\right)\right)}{\left(\text{average control left} + \text{right volumes from control}\right)}$$

Atrophy scores serve as a Z score for the degree of atrophy exhibited by a group or an individual subject, ranging between zero and 1, with 1 indicating no atrophy. At a glance, a lower atrophy score

Table 2. Mean volumes and atrophy scores for 30 controls versus 30 FTD patients, in order of descending effect size

	Control VOI ml	FTD VOI ml	Effect size *d*	Control atrophy score	FTD atrophy score	p value
Left striatum	6.97 ± 0.99	5.26 ± 1.41	1.43	0.95 ± 0.13	0.71 ± 0.19	0.0000005
Left frontal gray matter	92.07 ± 5.31	80.88 ± 11.01	1.37	1.00 ± 0.06	0.88 ± 0.12	0.000005
Right striatum	7.77 ± 0.99	6.15 ± 1.43	1.33	1.05 ± 0.13	0.84 ± 0.19	0.000002
Left posterior thalamus	3.05 ± 0.41	2.42 ± 0.58	1.29	0.96 ± 0.13	0.76 ± 0.18	0.000004
Left anterior thalamus	1.36 ± 0.23	1.04 ± 0.29	1.23	0.93 ± 0.15	0.71 ± 0.20	0.000005
Right frontal gray matter	92.58 ± 4.93	83.41 ± 10.98	1.15	1.00 ± 0.05	0.90 ± 0.12	0.0001
Right anterior thalamus	1.58 ± 0.27	1.32 ± 0.27	0.96	1.07 ± 0.18	0.90 ± 0.18	0.0003
Right posterior thalamus	3.32 ± 0.36	2.89 ± 0.58	0.90	1.04 ± 0.11	0.91 ± 0.18	0.0005

Effect sizes were calculated from volumes; p values are listed for one-tailed independent-samples t tests between atrophy scores.

indicates more severe atrophy relative to the expected volume of that structure for an average control, as well as smaller size relative to the contralateral subcortical structure. For example, as shown in the first row of table 2, mean VOIs for the left striatum were larger for controls than for FTD patients (6.97 vs. 5.26 ml). The atrophy scores (0.95 and 0.71, respectively) provide not only the same indication of control versus FTD differences, but also relate the sense that the left striatum is smaller than the right striatum for both groups (atrophy score <1.0).

Statistical Analysis

There were four hypotheses to test in this study:

(1) Subcortical Atrophy Scores Will Be Significantly Smaller in Subjects with FTD than in Controls. One-tailed independent-samples t tests compared the 8 atrophy scores for the FTD group versus their controls. Where atrophy scores differed between control and FTD groups with $p < 0.05$, effect sizes, *d,* were calculated for the VOIs as follows:

$$d = \frac{\text{mean}_{\text{control}} - \text{mean}_{\text{FTD}}}{0.5 \times (\text{sum of standard deviations})}$$

(2) Striatal, Anterior Thalamic, and Posterior Thalamic Regions Will Be More Asymmetric in PPA than in bvFTD. To compare effects of diagnosis, laterality, and specific subcortical region, we subjected the subcortical atrophy scores to a 2 × 3 repeated-measures ANOVA. Within-subject factors were left/right side and striatum versus anterior thalamus versus posterior thalamus; diagnosis (control vs. FTD) was the between-subject factor. This analysis was rerun with controls, bvFTD and PPA subgroups as the between-subject factor, in case one subgroup was driving the difference between subjects with FTD and controls.

(3) Within the FTD Group, Subcortical VOIs Will Be Proportional to Frontal VOIs. Bivariate correlations identified ipsilateral associations between frontal gray matter VOIs and subcortical VOIs, seeking Pearson correlation coefficients with $p < 0.05$. In order to reduce extrapolation bias, we examined frontocortical-subcortical volume associations in subjects whose averaged frontocortical volume exceeded that of the second smallest value (trimmed minimum, 86 ml) in the control group. To further explore the findings among FTD cases, we compared regression fit lines between FTD patients and controls using an interaction between the linear effect of averaged frontal volume × diagnostic group in a linear regression model.

(4) Within the FTD Group, Subcortical Atrophy Scores Will Be Lower in the More Functionally Disabled Subjects. Because the functional levels of the subjects created an ordinal variable, the ordinal regression was used. In order to examine the influence of 2 subjects with low atrophy scores but relatively high independence in ADLs, we reran the ordinal regression, withholding these subjects, and compared parameter estimates to those obtained using the full sample.

All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software version 15.0.

Results

Subcortical atrophy scores were significantly smaller in the FTD than in the control group (table 2). All mean atrophy scores were less than 1.0 in the FTD group. Hypothesis tests were significant using a Bonferroni adjustment to the alpha level with 8 comparisons. Left subcortical atrophy scores for 19/30 controls were also less than 0.98, indicating left-right asymmetry of volumes in these structures. The 2 × 3 repeated-measures ANOVA testing reaffirmed that left-sided subcortical structures were smaller than those on the right ($F = 88.12$, $p < 0.00001$). Neither age nor handedness were correlates of the left-right asymmetry in controls.

Our second hypothesis predicted that there would be more asymmetry in the PPA than the FTD group. The interaction of laterality and diagnosis did not reach statistical significance at the level of control versus FTD ($p = 0.163$), but reanalysis with three diagnostic groups yielded a significant laterality × diagnosis interaction

Table 3. Correlations (r) among subcortical and frontocortical VOIs

	Ipsilateral		
	striatum	anterior thalamus	posterior thalamus
PPA (n = 14)			
L frontal	0.82**	0.89**	0.67**
R frontal	0.52	0.79*	0.53
bvFTD (n = 16)			
L frontal	0.58*	0.24	0.41
R frontal	0.60*	0.26	–0.29
Control (n = 30)			
L frontal	0.07	0.08	0.28
R frontal	0.01	0.28	0.30

Among controls, frontocortical VOIs did not significantly correlate with ipsilateral subcortical VOIs. L = Left; R = right. * $p < 0.05$ (2-tailed); ** $p < 0.01$ (2-tailed).

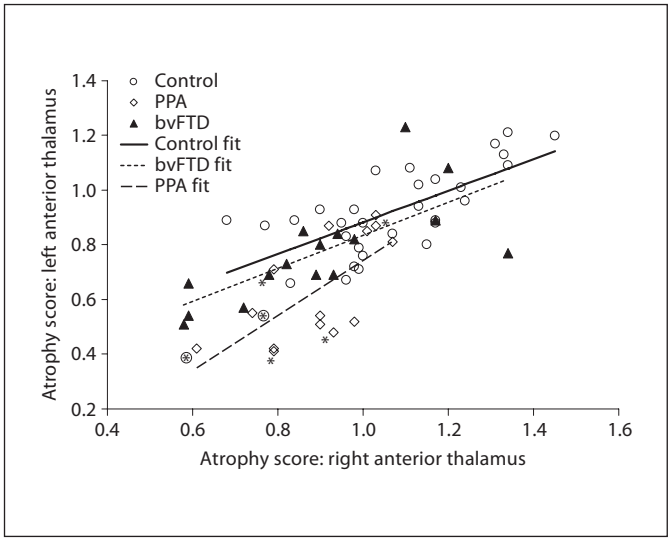

Fig. 2. The PPA group showed greater asymmetry of subcortical atrophy than controls or bvFTD patients. Scatterplot of atrophy scores shows relative overlap between diagnostic groups for anterior thalamic regions. The asterisks (*) indicate the 4 subjects who developed parkinsonism 2–7 years after the MRI for this study was performed. The circled asterisks indicate the 2 subjects who had cogwheeling at the time of the MRI.

(F = 7.44, p = 0.001). The PPA group had more marked asymmetry than controls and bvFTD patients. Figure 2 shows the three diagnostic groups on one scatterplot. Regression fit lines for bvFTD and controls were parallel (β slopes 0.61 and 0.58, $R^2 = 0.61$ and 0.58, respectively), but the PPA fit line had a steeper slope of 0.99 ($R^2 = 0.47$). Figure 3 exemplifies a further breakdown of the results by the specific PPA subgroup. Of the two types of PPA, the progressive nonfluent aphasia (PNFA) group shared the least overlap with controls, as seen in left anterior thalamic atrophy scores.

The next study objective was to assess the relationship between subcortical and frontocortical atrophy. The control group showed no significant bivariate correlations between any of the subcortical VOIs and ipsilateral frontocortical VOIs (table 3). The FTD group, on the other hand, showed statistically significant bivariate correlations between subcortical and ipsilateral frontocortical VOIs. We did not determine a significant effect of diagnostic group (control vs. FTD) on the relationship between a specific subcortical VOI and the averaged frontal VOI. Figure 4 and table 4 show that, for both striatal regions (left p = 0.09, right p = 0.07) and right posterior thalamic region (p = 0.11), unstandardized linear parameter estimates (β) for FTD patients were slightly larger than those for control participants, although without statistical significance. This may have resulted, at least in part, from the incomplete overlap of

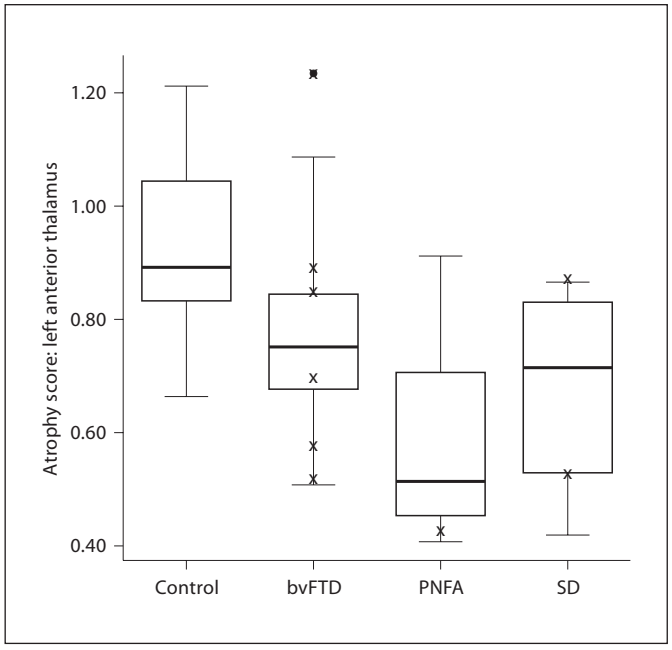

Fig. 3. Boxplot of left anterior thalamus atrophy scores. Atrophy scores for autopsy-confirmed cases are designated with an X. One of the autopsy-confirmed cases was an outlier of the bvFTD group. SD = Semantic dementia.

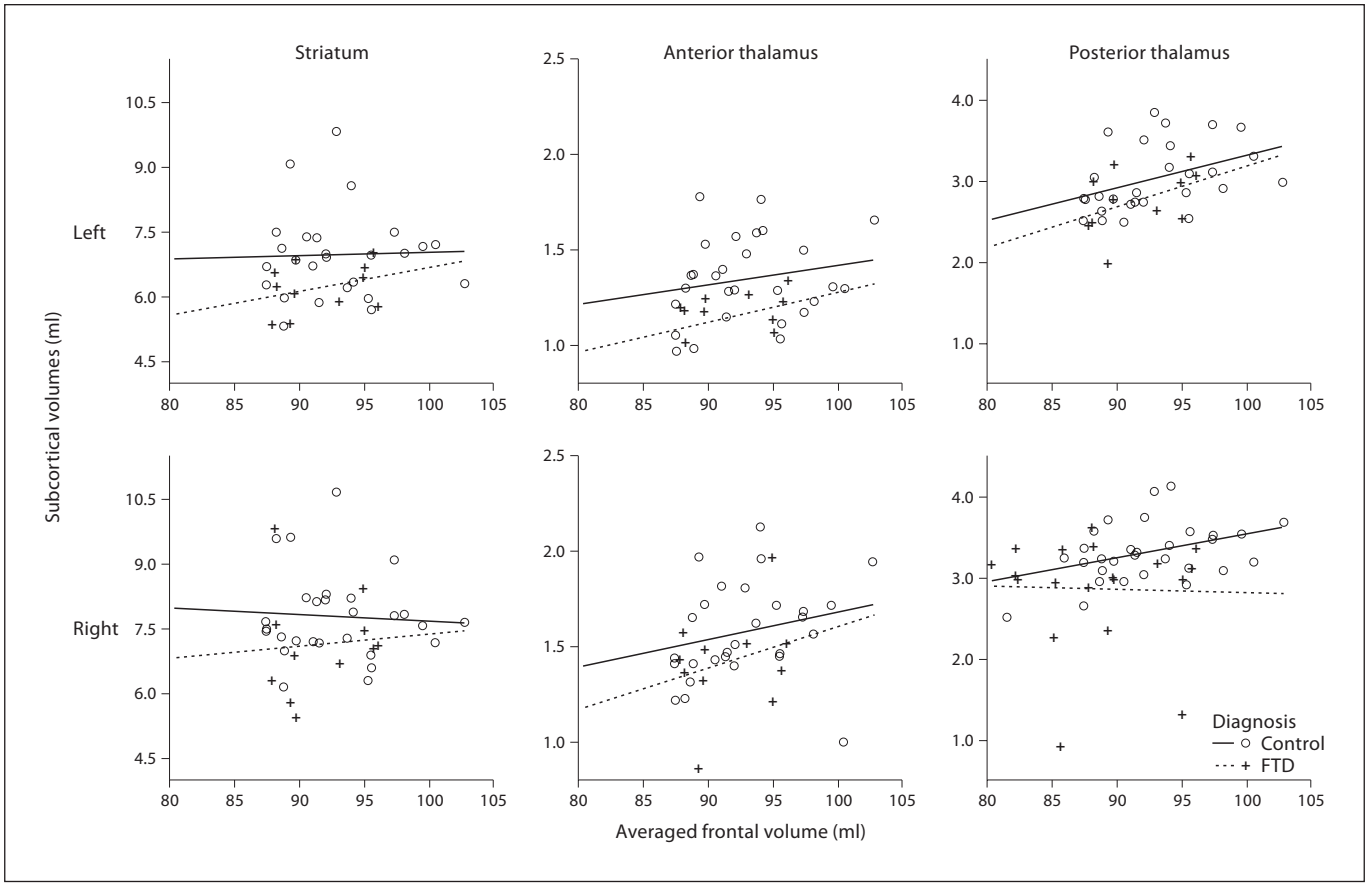

Fig. 4. Scatterplots illustrating correlation of right and left subcortical volumes to averaged frontal cortical volumes (control n = 30, FTD n = 30). Regression fit lines for FTD more consistently resemble a reference line with $\beta = 1.0$.

Table 4. Parameter estimates for regression fit lines in figure 4, cases with averaged frontal volume >86 ml

	Striatum	Anterior thalamus	Posterior thalamus
Left			
control	0.007	0.01	0.02
FTD	0.06	0.02	0.05
Right			
control	–0.02	0.02	0.02
FTD	0.03	0.02	–0.04

the FTD and control groups across the range of averaged frontal volumes.

With regard to the fourth objective, to link subcortical atrophy scores in FTD to the level of functional disability, most of the subjects with FTD were split between needing assistance for IADLs only (n = 12, equivalent to a range of 19–85% on the DAD IADL subscore) or for both BADLS and IADLs (n = 8, corresponding to 19–85% on the DAD BADL subscore). Seven FTD subjects and all 30 controls were independently functioning. Ordinal regression found statistically significant relationships between functional status and atrophy in all subcortical VOIs except the right posterior thalamus (table 5; fig. 5). Ordinal regression without the 2 FTD subjects with small volumes but relatively high independence in ADLs resulted in enhanced β parameter estimates and improved the p value of the regression on the right posterior thalamus to <0.05.

Although 2 of the subjects manifested cogwheeling at the time of the MRI, all subjects would have had a largely negative United Parkinson Disease Rating Scale motor examination subscale score, no greater than 7. Both sub-

Table 5. Parameter estimates for ordinal regression describing relationship between subcortical volumes and functional level (accompanies fig. 5)

	All cases (n = 60)		58 Subjects	
	β (standard error)	p value	β (standard error)	p value
Left				
Striatum	–0.9 (0.2)	0.0003	–1.1 (0.3)	0.0002
Anterior thalamus	–3.5 (1.1)	0.002	–5.6 (1.5)	0.0002
Posterior thalamus	–2.0 (0.6)	0.0005	–2.3 (0.7)	0.001
Right				
Striatum	–1.1 (0.3)	0.0002	–1.2 (0.3)	0.0002
Anterior thalamus	–4.5 (1.3)	0.001	–4.9 (1.4)	0.001
Posterior thalamus	–1.1 (0.5)	0.05	–1.6 (0.7)	0.03

The second column shows the influence of 2 subjects with small volumes but relatively high independence in ADLs.

jects with cogwheeling present required assistance for ADLs at the time of MRI. Signs of parkinsonism developed 2, 3, 6, and 7 years after MRI in 4 further subjects (3 PPA, 1 bvFTD; fig. 2). The sample did not include a sufficient number of subjects with parkinsonism at the time of MRI for us to significantly explore an association among parkinsonism, atrophy scores, and functional disability.

Discussion

Structural MRI did reveal subcortical atrophy in FTD, as hypothesized based on FSC circuit connectivity. Patients with PPA had especially asymmetric subcortical atrophy. This subcortical atrophy may play an important contribution to the progression of FTD. Our cross-sectional sample demonstrated a specific impact of subcortical atrophy on functional disability that has not been reported previously.

This study showed that subcortical volumes, especially those on the left, were more consistently atrophied among the FTD group than were frontocortical volumes. A number of previous studies have identified subcortical atrophy in FTD at autopsy [3, 11, 22–26]. Brun [23] first described marked striatal atrophy in Pick's disease that was not appreciable in frontotemporal lobar degeneration (FTLD). More recent autopsy studies have described basal ganglia atrophy in FTLD [3, 11, 22, 24–26]. We demonstrated the presence of subcortical atrophy in living patients near the time of their initial presentation to neurocognitive clinics. Our sample was comprised of FTD patients still able to score 20 on the MMSE on average.

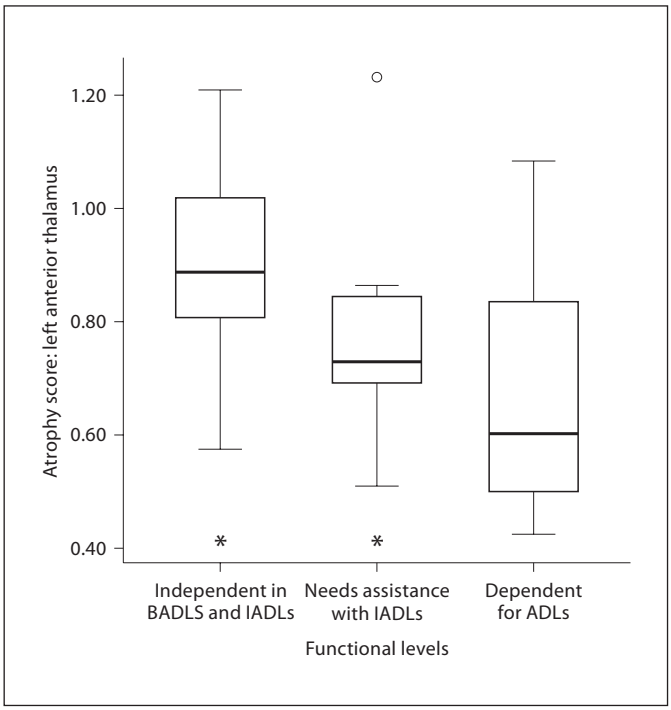

Fig. 5. Smaller subcortical structures associate with greater dependence for ADLs in subjects with FTD. Boxplots of atrophy scores for the left anterior thalamus are shown here. Group sizes: independent n = 6, requiring assistance for IADLs only n = 11, dependent for both BADLS and IADLs n = 8. The two asterisks (*) represent subjects with low atrophy scores yet relatively independent functional levels. The circle represents 1 subject with a large left anterior thalamus atrophy score who needed assistance with IADLs.

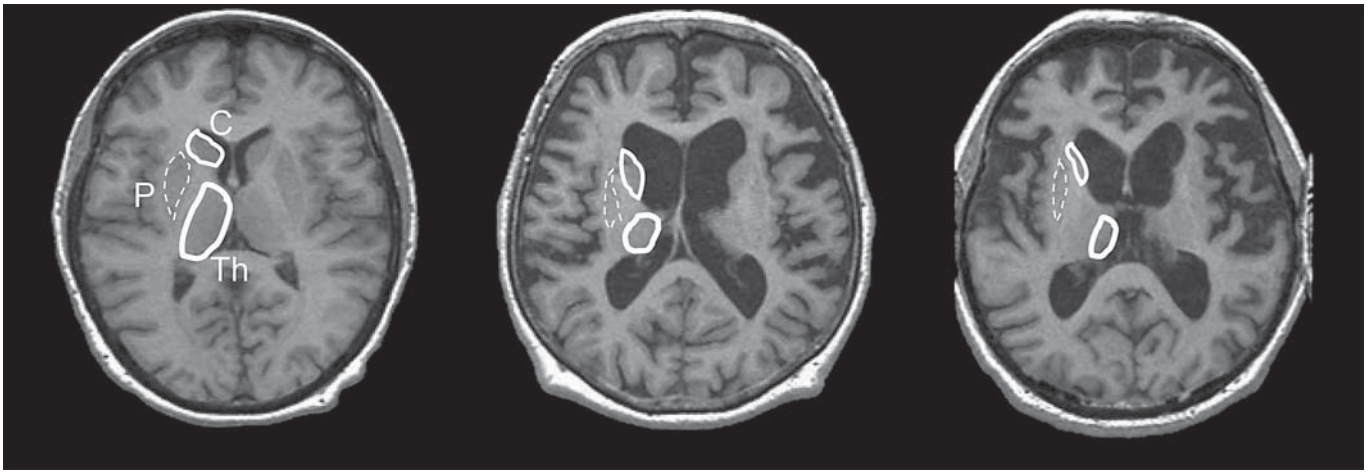

Fig. 6. Axial views of control (left) and FTD subjects (middle and right) demonstrating atrophy in the caudate (C), putamen (P), and thalamus (Th). Marked cortical atrophy in the FTD subject on the right may distract the eye from atrophy in subcortical structures.

Our choice of age- and gender-matched controls helped to compensate for effects of age and gender upon striatal atrophy [27]. According to reported mortality in FTD [28], MRI data for this study were collected approximately 2 years prior to the terminal state. Williams et al. [29] and Seeley et al. [30] have made similar reports of atrophy in these brain regions of living patients with FTD, using different methodology (voxel-based morphometry).

The PPA group, as might be expected for individuals with left-hemisphere dominance with aphasia, showed much more asymmetry, whereas the bvFTD group's left/right atrophy scores were similar to the control group. The finding of marked asymmetry in PPA may be even more remarkable, considering that one third of the subjects with PPA were left-handed. It will be interesting to learn through longitudinal studies if the subcortical atrophy in PPA correlates with the severity of the aphasia. Our findings are important in the consideration of how structural imaging data might be helpful to the management of FTD. First, clinicians may need to attend more to subcortical structures on diagnostic MRI. Figure 6 shows a subject with subcortical atrophy in the absence of severe frontal atrophy. The degree of subcortical atrophy and its asymmetry, although they did not correlate with duration of illness, were indicative of the variant of FTD (worst in PNFA). Longitudinal studies may further clarify the relationship of subcortical atrophy to duration of illness and prognosis.

Among FTD subjects, subcortical atrophy correlated with ipsilateral frontocortical atrophy and with the level of functional disability. The small sample size in the current study precludes statistical analysis of the relative impact of atrophy scores on ADLs in bvFTD versus PPA groups, but the distribution of disability in our sample did not differ between those two groups, unlike in a recent report showing that ADLs are more impaired in patients with bvFTD than in those with PPA [31]. The presence or later development of parkinsonism appeared to correlate with atrophy score, but the sample for this was too small to analyze statistically. It is beyond the scope of this cross-sectional data set whether frontotemporal atrophy or subcortical atrophy began first.

The finding of subcortical atrophy could not have been due to bias of our sample toward patients with FTD who had extrapyramidal symptoms. The subgroup of FTD patients with extrapyramidal symptoms who have manifested basal ganglia degeneration has been described elsewhere [24, 25]. Subcortical gliosis and neuronal loss have been reported in patients with motor neuron disease and FTD [25]. Corticobasal syndrome has also been included as one of the FTD by many investigators. We included only 2 subjects who already showed signs of cogwheeling in our sample, but they did not meet diagnostic criteria for corticobasal syndrome [32], which would necessarily involve atrophy of basal ganglia [33]. Our sample was not biased toward finding FTD subjects with smaller basal ganglia.

Having established the basal ganglia as an area of atrophy during the progression of FTD, subsequent investigations could elucidate the clinical consequences of this pathology. Our findings warrant future longitudinal imaging evaluation of patients from the time of diagnosis and through the course of the illness with correlation to FSC circuit syndromes, parkinsonism, ADLs, and neuropathology. Other potential lesions to the FSC circuits could arise from TDP-43, tauopathy, or neuronal intermediate filament inclusions in the basal ganglia [34, 35]. Subcortical atrophy may contribute as significantly to symptoms of FTD as cortical atrophy.

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