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Putaminal Volume and Diffusion in Early Familial Creutzfeldt-Jakob Disease

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Abstract

Background—The putamen is centrally implicated in the pathophysiology of Creutzfeldt-Jakob Disease (CJD). To our knowledge, its volume has never been measured in this disease. We investigated whether gross putaminal atrophy can be detected by MRI in early stages, when diffusion is already reduced.

Methods—12 familial CJD patients with the E200K mutation and 22 healthy controls underwent structural and diffusion MRI scans. The putamen was identified in anatomical scans by two methods: manual tracing by a blinded investigator, and automatic parcellation by a computerized segmentation procedure (FSL FIRST). For each method, volume and mean Apparent Diffusion Coefficient (ADC) were calculated.

Results—ADC was significantly lower in CJD patients ($697 \pm 64 \mu\text{m}^2/\text{sec}$ vs. $750 \pm 31 \mu\text{m}^2/\text{sec}$, $p < 0.005$), as expected, but volume was not reduced. The computerized FIRST delineation yielded comparable ADC values to the manual method, but computerized volumes were smaller than manual tracing values.

Conclusions—We conclude that significant diffusion reduction in the putamen can be detected by delineating the structure manually or with a computerized algorithm. Our findings confirm and extend previous voxel-based and observational studies. Putaminal volume was not reduced in our early-stage patients, thus confirming that diffusion abnormalities precede detectable atrophy in this structure.

Keywords

Putamen; VOI; ADC; CJD; E200K; FIRST; FSL; SPM

1. Introduction

Creutzfeldt-Jakob Disease (CJD) is the most prevalent of human prion diseases. It is thought to be caused by cerebral accumulation of a misfolded protein devoid of conventional genetic

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material [1], and it is invariably fatal. First described clinically and pathologically in the 1920s [2], it is still difficult to diagnose at its early stages [3].

Hyperintensity of the basal ganglia on specific MRI sequences, T2-weighted (T2W), fluid-attenuated inversion recovery (FLAIR), and diffusion-weighted imaging (DWI), has been increasingly used to support CJD diagnosis [4]. Throughout the 1990s, several case reports noted T2W hyperintensities in the caudate nucleus, putamen, and thalamus of CJD patients, correlating them with pathologically proven spongiform changes in the same regions [5–7]. DWI is now recognized as a sensitive diagnostic marker for CJD [8], but all studies to date have relied on visual reading of MRI scans [9,10], or quantitative voxel-based analysis [11, 12]. Both methods have been effective at detecting small foci of abnormal signal in the basal ganglia, but neither method can be considered appropriate for the primary aim of this study, namely to measure Apparent Diffusion Coefficient (ADC) in the whole putamen.

The second aim of our study was to measure putaminal volume. Imaging studies of diffusion in CJD may be confounded by the opposing effects of diffusion reduction (thought to reflect CJD-specific histological effects, mainly vacuolation and prion deposition) and of diffusion increase (due to tissue shrinkage and partial volume effect with CSF accumulation). The net effect of this balance is variable, topographically and chronologically, complicating the interpretation of diffusion findings. In the cerebellum, despite its known involvement in CJD, DWI abnormalities are very rarely detected visually in classic CJD patients, although they may be seen in cases of specific disease variants [13,14]. We have proposed that this inability to detect diffusion reduction is due to atrophy, and similar mechanisms may affect the cortex [15]. In contrast, clear diffusion reduction in the putamen may be easily detectable because this structure does not suffer atrophy in the early stages of CJD or, if it does, there are no adjacent CSF spaces to mask the reduced diffusion. This hypothesis (lack of putaminal atrophy) constituted the second aim of this study.

The third aim of this study was to compare different methods of anatomical delineation. While manual tracing is still considered the gold standard in the field, it is extremely slow and can be subject to bias [16,17]. In recent years, the need for accurate, robust and cost-effective segmentation tools has led to the development of several automated or semi-automated tools for identifying and measuring anatomical regions [18–24]. In this cross-sectional analysis study, we aimed to assess if one such automated method (FIRST, FSL 4.0, <http://www.fmrib.ox.ac.uk/fsl>) [25] could replace the tedious manual tracing.

2 Materials and Methods

2.1 Subjects

As part of a large prospective study of familial CJD, we collected high-resolution structural MR images from 35 subjects: 13 patients and 22 controls. All patients had familial CJD by WHO diagnostic criteria [26], verified by presence of the E200K mutation and follow-up until death. Healthy controls were recruited from the same families, were negative for the E200K mutation, normal by neurological, neuropsychological and MRI examination, and had no significant history of drug or alcohol abuse. One outlying patient (case #2003) had an unusual clinical phenotype (disease duration of 19 months before first MRI) and severe cerebral atrophy that resulted in technical difficulties in manual region of interest (ROI) tracing. This patient was excluded from analysis, leaving 12 patients and 22 controls. The patients were examined on average 3.17 ± 2.95 months (median 2 months, range 0–10 months) after onset of disease, and survived on average 4.50 ± 4.12 months after examination. Specific neurological symptoms were rated by the Clinical Neurological Scale (CNS) [27] and cognitive status assessed by the MMSE [28]. The samples are further characterized in Table 1. The samples differed significantly in gender distribution ($\chi^2=5.99$, $p<0.05$). There was no significant

difference in age between the samples, and the patients demonstrated the expected cognitive deficits and neurological symptoms.

2.2 MRI scanning protocol

Scanning was performed at the Sheba Medical Center, Israel, on a 1.5T General Electric Signa Excite system with a standard quadrature head coil. For each subject, we collected a high resolution anatomical T1-weighted SPGR sequence (axial plane, TR 28ms, TE 6ms, FOV 240 mm, Flip angle 40°, 256 × 256 matrix size, 104 contiguous slices of 1.5 mm thickness, yielding reconstructed voxel dimensions of 0.94×0.94×1.50 mm) and a single-shot echo-planar spin-echo DWI sequence (axial plane, TR 5000 ms, TE 85 ms, FOV 240 mm, 128×128 matrix size zero-filled to 256×256, 48 slices of 3 mm thickness, yielding the reconstructed image resolution of 0.94×0.94×3.0 mm). Each DWI sequence included a non-diffusion-weighted image ($b=0$ s/mm², T2W) and a diffusion weighted image at $b=1000$ s/mm², which was derived automatically as a geometric mean of the individual signal intensities with diffusion gradients along three orthogonal directions. To derive the ADC maps, the acquired DWI images were analyzed with Matlab code (MathWorks, Natick, MA) developed in-house. First, parenchymal regions were delineated by applying the Brain Extraction Tool (BET, FSL 4.0, <http://www.fmrib.ox.ac.uk/fsl/>) [29] onto the $b=0$ s/mm² image. Then, ADC values were derived using the standard Stejskal and Tanner equation in each voxel: $ADC = \ln[S(b1)/S(b2)] / (b2-b1)$, where $S(b1)$ and $S(b2)$ are the signal intensities of diffusion-weighted images with applied b-factors of $b1=0$ s/mm² and $b2=1000$ s/mm², respectively [30].

2.3 Manual ROI tracing

Manual ROI tracing was performed by a single rater (IS) blind to all subjects' information, and required approximately three hours per subject. MedX 3.4 (<http://medx.sensor.com>) was utilized for the visualization and delineation of structures, and for computations of volume and mean ADC. A neuroanatomical atlas [31] was used as reference.

First, brains were visually inspected to identify the most superior slice in which the putamen was visible. Typically, it first appeared as an oval-shaped gray matter mass lateral to the caudate nucleus and delimited by the internal and the external capsule. In more inferior slices, the size of the putamen gradually increased, while its shape departed from that of an oval to resemble that of a "single quote" sign (Figure 1). While the internal capsule remained a clear divider between the putamen and the caudate, the external capsule thinned, so care was taken not to include it in the tracing. At approximately half-brain, as the thalamus began to appear, the globus pallidus emerged adjacent to the putamen. For about ten slices, the globus pallidus bordered the putamen and was carefully excluded from tracing. Between the anterior commissure and the top of the cerebral peduncles, the putamen merged with the nucleus accumbens and moved laterally and posteriorly. At the level of this reallocation, the examiner relied heavily on the atlas to distinguish the structure of interest from bordering nuclei. Tracing ended at the level of the cerebral peduncles, where the putamen was no longer present.

To calculate mean ADC in each structure, ADC maps were coregistered with their respective anatomical scans and resliced to match the SPGRs' image resolutions, using tri-linear interpolation in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/>). The templates previously traced on SPGR were superimposed onto the ADC maps, and mean ADC with standard deviations (SD) were extracted.

2.4 Computerized parcellation

FIRST (FSL v4.0, <http://www.fmrib.ox.ac.uk/fsl/first/index.html>) is a model-based segmentation tool that allows for parcellation of several subcortical brain structures from high resolution T1-weighted images of the brain [32,33]. It makes use of statistical models of shape

and intensity based on a large set of manually labeled T1-weighted images consisting of 317 brains. The models are fit to new data by maximizing the probability of shape given intensity: when exposed to a new anatomical image, FIRST searches through linear combinations of shape modes of variation for the most probable shape instance given the observed intensities in the image.

In our study, bias-field corrected T1-weighted (SPGR) images were used as input images; using a workstation equipped with a Pentium 4 (3.0 Ghz) processor running RedHat WS 4.0, delineation of putamen required about five minutes. It is important to mention that FIRST allows a user to control how much “boundary” should be included in a structure by assigning a z-score to each boundary voxel and by letting the user decide the appropriate z-score for a threshold. Voxels are classified as “boundary” by FIRST when the algorithm cannot determine their anatomical association; such voxels are typically located at the borders of adjacent structures, like the ones represented by white lines in Figure 1. On the other hand, voxels are classified as “no-boundary” when no such ambiguity is present. For our study, we ran FIRST with the most conservative z-score threshold options available, excluding all boundary voxels. We have also performed the analysis including all boundary voxels, but it severely overestimated putaminal volumes and therefore we disregarded this option for the rest of the study.

2.5 Statistical analysis

Data were analyzed using SPSS v16.0 (SPSS, Inc., Chicago, IL) and JMP (SAS Institute, Cary, NC). To compare volumetric and diffusion data across methods, we ran repeated-measures ANOVAs on bilateral mean of ADC or total volume (sum of left and right), using diagnosis (controls vs. patients) as between subjects grouping factor, method (FIRST vs. manual tracing) as within subjects factor, and age covariance (with interaction). We averaged data bilaterally because we did not find any unilateral effect of disease when we ran the ANOVAs with hemisphere as a factor. Linear regressions and product-moment correlations were used to assess relationships between variables.

3. Results

3.1 Face validity of manual tracing

We evaluated the validity of our manual tracing procedures by comparing volumetric estimates in our healthy controls to published values. We collected data from 12 publications [34–45] that measured normal putaminal volume at different ages, and calculated the linear regression of putaminal volume against age from these literature values. The resulting regression equation was $\text{Volume [mm}^3\text{]} = 10,289 - 51 * \text{Age}$. Computing the same regression across normal subjects in our current dataset yielded a similar regression ($\text{Volume (mm}^3\text{)} = 11,120 - 59 * \text{Age}$, $r = -0.55$, $p < 0.01$). The age correlation of the volumes computed by FIRST ($r = -0.36$, $p = 0.11$) failed to reach significance. Further, the volume predicted by the literature regression equation for our sample (mean age 54 years) was $7,535 \text{ mm}^3$, in close agreement to our observed manual value of $7,892 \text{ mm}^3$.

3.2 CJD and Method effects on Putaminal Volume

Figure 2A summarizes total putaminal volumes computed by the two methods: manual ROI and FIRST. Repeated-measures ANOVA was performed with diagnosis as between subjects grouping factor, method (manual tracing and FIRST) as repeated measure, and age covariance. There was a significant main effect of diagnosis ($F_{1,30} = 4.85$, $p < 0.05$) and age ($F_{1,30} = 5.47$, $p < 0.05$). The effect of method was also significant ($F_{1,30} = 4.29$, $p < 0.05$), but no interactions reached significance. Putaminal volume was larger in patients than in controls, and decreased with age. Volumes calculated from the manual tracing ($7,892 \pm 1,179 \text{ mm}^3$ for controls and

8,059± 1,155 mm³ for patients) were larger than those calculated from FIRST (6,533± 942 mm³ for controls and 7,306± 814 mm³ for patients). Figure 3B shows, for each subject, the putaminal volume obtained via FIRST plotted against the respective volume obtained via manual tracing. The figure indicates that the two methods yielded correlated values ($r=0.63$, $p<0.0001$), but that volumes from FIRST were lower than those from the manual ROI, in both patients and controls. Within the patients, manually calculated volume correlated significantly with disease duration ($r=0.68$, $p<0.05$), but this correlation failed to reach significance for FIRST volume ($r=0.27$, NS).

3.3 CJD and Method Effects on ADC

Figure 3A shows the ADC values by method and diagnosis. The main effects of diagnosis ($F_{1,30}=17.31$, $p<0.0002$) and age ($F_{1,30}=4.55$, $p<0.05$) were significant, with patients lower than controls, and ADC increasing with age. Method showed a significant main effect ($F_{1,30}=6.93$, $p<0.02$), with manual tracing values being higher than FIRST values. Finally, there was a significant interaction of method with diagnosis ($F_{1,30}=5.40$, $p<0.05$): the manual tracing method yielded marginally higher ADC values than FIRST, and this difference was greater in patients than in controls. Figure 3B shows, for each subject, mean ADC obtained via FIRST plotted against mean ADC obtained via manual ROI. The correlation between the two methods was excellent for both patients and controls ($r^2=0.945$ and $r^2=0.954$, respectively), although the Figure suggests some noisy data for patients at lower ADC values. Within the patients, ADC reductions were related to symptomatic severity, as expected. ADC was positively correlated with the MMSE ($r=0.72$ for manual and 0.70 for FIRST) and negatively correlated with our CNS scale ($r=-0.60$ for manual and -0.50 for FIRST).

4. Discussion

Reduced diffusion in some parts of the putamen is a prominent feature in CJD, of diagnostic importance and, possibly, pathophysiologic significance. ADC reductions have been repeatedly demonstrated by visual examination of MRI scans [8,9,46–48], as well as quantitative voxel-based analyses [12]. However, it was not clear whether these findings represented only small focal changes within the putamen, or whether the putamen as a whole also displayed such abnormalities. The difficulty of this distinction is illustrated in Figure 4. While putaminal changes of diffusion and T2 can be visually detected in all three sequences shown, it is difficult to assess their extent. In this cross-sectional study, we defined the putamen anatomically, considered the structure as a whole, and demonstrated significant reductions of diffusion. Further, these reductions in our patients were significantly correlated in the expected direction with our clinical severity measures. This finding in familial CJD indicates that the pathological diffusion reductions involve substantial portions of this structure, and confirm previous reports about its centrality in other CJD variants [9,47–53].

In contrast, we did not find any reductions of putaminal volume in our CJD patients, by either of the two methods employed. This is especially noteworthy since our patients were slightly older than the controls, and a slight volume reduction would be expected due to aging effects alone. In fact, putaminal volume was mildly (but significantly) higher in patients than in controls, and positively correlated with disease duration. This slight elevation of volume could be caused by technical artifacts (e.g., blurred boundaries), or could signify an unknown compensatory response, as was hypothesized for the striatum in Parkinson's disease [41]. Alternatively, the longitudinal relaxation time (T1) of the putamen may be reduced, or T1 of the surrounding white matter may be elevated, by prion-related pathology, making the white matter tissue appear as though it is part of the putamen. Consequently, this would lead to overestimation of the drawing boundaries and its volume. Regardless, it is clear that significant putaminal atrophy does not occur in early CJD, despite the substantial diffusion reductions.

We have previously speculated that early CJD is characterized by diffusion reductions in four brain areas (cortex, cerebellum, basal ganglia and thalamus), but cannot be detected in the first two due to atrophy and other technical factors. Atrophy is associated with replacement of tissue with CSF, thus raising the observed diffusion coefficient and masking the underlying diffusion reductions, presumably caused by vacuolation and/or prion deposition [52–54]. The current results are consistent with that hypothesis, in that the lack of atrophy in the putamen would avoid masking the diffusion reductions.

A second aim of our study was to compare methods of ROI delineation. Our manual method, considered the ‘gold standard’, was validated by comparison to age-adjusted literature values, as well as by the robust age regression found within our own healthy subjects. The automated FIRST method, while much faster (5 min per subject Vs 3 hours) and, presumably, bias-free, underestimated manual putaminal volume. The correlation between the two, while highly significant, was noisy (Figure 3B) and explained only about a third of the observed variance. Accurate prediction of manual volumes from the FIRST values is, therefore, difficult. Further, the FIRST volume regression by age within our normal controls was weak and nonsignificant. We conclude, therefore, that the automated method, without inclusion of boundaries, does not currently provide full accuracy for putaminal volume determinations. Whether the enhanced sensitivity of manual tracing is worth the substantial cost in time is probably context-dependent. When very large effects are tested, the superior speed and reproducibility of the FIRST algorithm are a substantial advantage. Further, use of the automated method may be recommended for multi-center studies because it eliminates inter-rater variability.

In contrast, the ADC values determined by the FIRST method were very close to the manual values, and could be substituted for them. The reason for the different behavior of volume and diffusion values deserves a comment. ADC images are relatively ‘flat’. While CSF is starkly different from tissue, the contrast between healthy grey and white matter in adults is minimal on the ADC maps. Because the putamen is surrounded by other grey and white matter without significant CSF boundaries, and is fairly uniform internally, small mistakes in defining its boundaries would not substantially change the observed mean diffusion. In contrast, such mistakes would significantly change the volume estimates. We believe this is the reason that FIRST can be used to derive accurate ADC values in the putamen, even though it underestimates volume.

Our application of the FIRST algorithm was limited in scope, and we did not manipulate its parameters to optimize its performance. It is possible that its performance would be enhanced with more careful optimization. Further, there are other automated parcellation methods that were not tested here, which might have yielded better results [22–24,55–57]. Users should be aware that many algorithms offer different adjustable parameters. The choice of “parameter,” such as exclusion of boundaries, can alter the outcomes significantly. It should also be noted that our patient and control samples were not precisely matched for gender. Gender effects were considered in the analyses, and did not exert significant influence on ADC or on the manually-determined putaminal volume. For the automated volume determination, there was a significant gender effect ($p < 0.05$, males larger than females), but no interaction with diagnosis (i.e., the effect was similar for both patients and controls). Therefore, we do not believe that the lack of precise gender matching affects our results or conclusions. Finally, our results demonstrate that putaminal diffusion reductions precede gross putaminal atrophy detectible with current MRI technology in E200K fCJD, but future work will have to confirm that this is true in sporadic CJD or even in all fCJD.

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Figure 1.

Representative axial slices of manual tracing and FIRST in a healthy control (case# 1054) and a CJD patient (case # 2002). Tracings represent putamen at mid-level, with shape resembling a “single-quote” sign.

Figure 2.

(A) Putaminal total volumes + SD, in manual ROI and FIRST. Dark and light grey bars represent controls and patients, respectively. (B) Correlation plots for putaminal volume between manual tracing and FIRST. Filled and open circles represent controls and patients, respectively, and the dotted line is the line of identity.

Figure 3.

(A) Mean putaminal ADC + SD, in manual tracing and FIRST. Dark and light grey bars represent controls and patients, respectively. (B) Correlation plots for putaminal ADC between manual tracing and FIRST. Filled and open circles represent controls and patients, respectively, and the dotted line is the line of identity.

Figure 4.

Representative imaging findings on a healthy control (case#1093, female, age 61) and a symptomatic patient (case# 2004, female, age 64). Anatomical image, DWI at $b=0 \text{ s/mm}^2$ (T2-weighted image), DWI (diffusion weighted image), and quantitative ADC map are shown. On the anatomical image, putamen tracings by FIRST are superimposed at mid-level.

Table 1

Subjects' characteristics. MMSE: mini-mental state. CNS: Clinical Neurological Scale. Significant differences between the groups were assessed by two-tailed t tests.

Variable	Patients	Controls	<i>p</i>
N (male/female)	12 (9/3)	22 (7/15)	<0.05
Age [years]	59 ± 6 (52~75)	54 ± 11 (39~80)	0.15
MMSE	23 ± 5	29 ± 1	<0.0001
CNS	12.50 ± 5.44	0.32 ± 0.57	<0.0001