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Shape Abnormalities of the Caudate Nucleus Correlate With Poorer Gait and Balance: Results from a Subset of the LADIS Study

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Abstract

Objective—Functional deficits seen in several neurodegenerative disorders have been linked with dysfunction in fronto-striatal circuits and with associated shape alterations in striatal structures. The severity of visible white matter changes (WMC) on MRI has been found to

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Author Contributions

MM wrote the first draft of this paper, planned and performed the volumetric neuroimaging and statistical analyses as a component of his MPhil thesis. JCLL conceived and coordinated the overall project, co-wrote first draft, was principal supervisor for MM's thesis, is primary investigator for the Australian National University and is guarantor for the study. MW was a secondary supervisor for MM, and performed pre-processing and shape and ICV analysis. For the purposes of attribution of contribution, MM, JCLL and MW assert they are equal first co-authors. GS selected the MRI images from the LADIS database, and coordinated data transfer from the Karolinska Institute with EÖ. MC contributed to study recruitment at Huddinge. DV contributed image analysis infrastructure and is principal investigator for the University of Melbourne. TE is principal investigator for Helsinki, EG is an investigator for Copenhagen, GW is principal investigator for Copenhagen, and AW is principal investigator for Gothenburg respectively for LADIS. MGH (principal), HB, CB are investigators for the motor function workgroup of LADIS. LOW is principal investigator for the Karolinska Institute and LADIS for this project. All authors contributed to the writing of the paper.

correlate with poorer performance on measures of gait and balance. This study aimed to determine whether striatal volume and shape changes were correlated with gait dysfunction.

Method—MRI scans and clinical gait/balance data (scores from the SPPB - Short Physical Performance Battery) were sourced from 66 subjects in the previously-published LADIS trial, which was performed in >65 y.o. non-disabled individuals with WMC at study entry. Data were obtained at study entry and at three-year follow-up. Caudate nuclei and putamina were manually traced using a previously published method, and volumes calculated. The relationships between volume and physical performance on the SPPB were investigated with shape analysis utilising the SPHARM toolkit.

Results—There was no correlation between the severity of WMC and striatal volumes. Caudate nuclei volume correlated with performance on the SPPB at baseline, but not at follow-up, with subsequent shape analysis showing regionalisation of left caudate changes in areas corresponding to inputs of the dorsolateral prefrontal, premotor and motor cortex. There was no correlation between putamen volumes and performance on the SPPB.

Conclusion—Disruption in frontostriatal circuits may play a role in mediating poorer physical performance in individuals with white matter changes. Striatal volume and shape changes may be suitable biomarkers for functional changes in this population.

Introduction

The Implications of White Matter Changes

White matter changes (WMC), defined as focal and confluent white matter hyperintensities on T2-weighted MRI brain scans, are particularly prominent in individuals over the age of 65 [1, 2]. Previous studies have examined the correlation of white matter changes and cognitive ability in this older age group, with the largest being the Leukoaraiosis and Disability Study (LADIS). The LADIS study is a multi-centre European study which investigated the effect of WMC on a number of different clinical indicators over a three-year prospective follow-up [3, 4]. The LADIS study has demonstrated a number of associations between severity of WMC and adverse outcomes, which included increased transition to disability [5], greater incidence of depression [6, 7], as well as declining cognitive ability [8-12].

The LADIS study also demonstrated a significant association between the severity of WMC/WMH and the prevalence of gait and balance disorders – both in the frequency of falls and in poorer scores obtained on scales such as the Short Physical Performance Battery (SPPB) [13, 14]. This is consistent with recent literature identifying gait and balance disorders in the elderly as a marker of other serious morbidity and mortality, particularly through proxy measures such as walking speed, which has been linked to all-cause and cardiovascular mortality [15, 16] as well as subsequent development of dementia [17].

Fronto-Striatal Circuits and Striatal Shape Analysis

The link between the basal ganglia of the brain and motor co-ordination and planning is well documented [18-20]. While basal ganglia volumes have been the mainstay of MRI studies, studies of three dimensional shape alterations in the striatal areas of the basal ganglia,

particularly in the caudate nucleus, have been demonstrated in a number of studies examining different neurodegenerative disorders characterised by both motor abnormalities and dementia [21-25]. Our group has previously examined caudate nucleus volumetrics in patients with stroke and vascular dementia [26].

Afferents to the caudate arise from different areas of the cortex, making the caudate nucleus an important part of parallel fronto-striatal circuits [27]. This model, first described by Alexander et al, and confirmed through a number of different modalities [28-31], indicates that different areas of the cortex ‘map’ on to different areas of the caudate nucleus and putamen (Figure 1). Specifically, the cognitive and behavioural circuits arising from dorsolateral prefrontal cortex, anterior cingulate and orbitofrontal cortex primarily project to the caudate, while the frontal eye fields and motor cortex project to both caudate and putamen [27, 32]. Accordingly, functional changes in cognition, behaviour and movement may arise from structural change in caudate and putamen. Therefore, we hypothesized that motor function may be correlated with the structural integrity and hence morphology of the caudate and putamen and sought to examine this hypothesis through three dimensional shape analyses of these structures.

This study aimed to determine whether subjects entering the LADIS study had striatal shape reductions - ‘deflation’ - in specific areas at baseline, corresponding to the site of afferent connections from cortical motor circuits. Our chief hypothesis was that we would detect shape deflation in striatal regions corresponding to areas of the motor cortex, and that this deflation would correlate with poorer performance on the Short Physical Performance Battery. Gait, measured via walking speed in the SPPB, has been associated with cognitive impairment and progression to dementia [33-35]. We further hypothesised that striatal morphology would be associated with walking speed. Finally, as LADIS is a longitudinal study, we sought to investigate these structure-function relationships with clinical data at 3 year follow-up.

Methods

LADIS Study Data Collection and Details

The recruitment methods and other clinical data for LADIS have been documented elsewhere [3] in brief: 639 subjects were recruited from 11 centres in Europe: Florence, Helsinki, Graz, Lisboa, Amsterdam, Gothenburg, Huddinge, Paris, Mannheim, Copenhagen, and Newcastle-upon-Tyne. Inclusion criteria were an age range between 65 and 84 years, white matter changes as rated by the Fazekas Scale (as mild, moderate and severe) on T2 and FLAIR MRI [36] – during the course of the study. WMC were also assessed via total WMC volume and through the Scheltens scale [37] but the different measurement methods did not result in any differences in correlations with gait or balance outcomes [38]. The other criterion for entry was a score on the International Activities of Daily Living (IADL) [39] scale indicating no or mild disability. The exclusion criteria were the presence of severe medical or psychiatric illness, severe unrelated neurological diseases (specifically, this included any comorbid diagnoses of neurodegenerative disorders affecting the caudate nucleus such as Huntington’s Disease), non-vascular leukoencephalopathy, or inability to give informed consent.

MRI scans were performed at baseline and at three years. A number of clinical indicators were measured at baseline and at yearly intervals, including measurements of disability, cognition, mood, gait, and medical events such as stroke.

The gait and balance measure utilised for the current study was the Short Physical Performance Battery (SPPB), which tests the ability of subjects to hold themselves in various standing positions (feet in side-by-side, semi-tandem or tandem), measures walking speed over an 8-foot course, and tests ability and speed at rising from a chair [40]. The SPPB is scored out of 15, with a higher score indicating a better performance.

MRI Acquisition

The MRI-protocol consisted of 3D sagittal or coronal T1-weighted magnetization prepared rapid acquisition gradient echo (MPRAGE) images (TE=4–7 ms; TR=10–25 ms; TI=100–950 ms; flip angle=10–30°; voxel size=1×1×1–1.5 mm³; FOV=250mm), axial T2-weighted fast spin echo images (TE=100–120 ms, TR=4000–6000 ms, FOV=250 mm, slice thickness: 5–7.5 mm, interslice gap 0.5 mm) and fluid attenuated inversion recovery (FLAIR) images (TE=100–140 ms, TR=6000–10,000 ms, TI=2000–2400 ms, FOV=250mm, slice thickness 5–7.5mm, interslice gap 0.5mm). The scans were acquired at 1.5 T [preceding description modified from [41]].

Ethical Approval

The LADIS study received ethical approval from local ethics committees in each centre. We received permission from the principal investigators for our analysis of a subset of the MRI scans and associated clinical data, as well as local approval from the Australian National University Human Research Ethics Committee.

Caudate Nucleus and Putamen Tracing

A subset comprising approximately 10% of the sample (n=66) from the LADIS study were selected by the LADIS study group (by GS) from four LADIS centres – Copenhagen, Stockholm (Huddinge), Gothenburg and Helsinki. These centres were chosen in collaboration with one of the authors (GS) and selected due to image quality for tracing and availability. Scans were anonymised by LADIS group researchers before transfer to a MacBook Pro (Apple, Cupertino, CA, USA) computer provided by University of Melbourne based at the Department of Psychological and Addiction Medicine, Australian National University. Subjects with infarcts in the caudate or putamen were excluded.

DICOM (Digital Imaging and Communications in Medicine) files of T1-weighted images were converted to ANALYZE 7.5 format (Mayo BIR, Rochester, NY, USA) using MRIConvert (<http://lcn.uoregon.edu/~jolinda/MRIConvert/>) to prepare for analysis. Image intensity was standardised by using preset threshold values, based on a pilot analysis of the data, and voxel size was reconstructed as isotropic at 1x1x1mm. The intracranial volume (ICV) was determined in a semi-automated fashion using FSL software (FMRIB Group, Oxford) as a measure to control for brain size. First, brains were skull-stripped with the Brain Extraction Tool (BET) and were then linearly aligned to the MNI152 1mm T1-weighted template. The inverse of the determinant of the affine transformation matrix was

multiplied by the ICV of the MNI152 template to produce a measure of ICV for use as a covariate [42].

Caudate nuclei and putamen were manually traced within ANALYZE 10.0b (Mayo BIR, Rochester, NY, USA) through a Region of Interest (ROI) approach on, by one investigator (MM) who was blind to clinical data, using a previously published protocol [43, 44] applied in a number of studies [26, 45-48]. Briefly, this involved tracing images in the axial plane, using the inferior border of the anterior commissure as the inferior boundary (see Figure 2). The resulting binary objects were checked in the sagittal plane, and volumes calculated. Reliability of the tracing was checked by an experienced tracer (JCLL) tracing basal ganglia on a representative sample of the 66 subjects; MM also retraced the representative sample to serve as test-retest reliability. Intraclass correlation coefficients were used to determine reliability of volumetric measurement – intra-rater reliability was 0.944, with inter-rater reliability 0.890. Decisions on whether to proceed to shape analysis were guided by volumetric results: if there was no significant volume change, shape analysis was not attempted. While it is possible to have shape change without volumetric change, and vice versa, our group's experience is that shape analysis allows localisation of where significant volumetric differences occur. Furthermore, given that volumetric change is very rarely uniform, it follows that overall volume change is driven by a significant localised shape change.

Shape Analysis

Shape analysis was undertaken in a semi-automated fashion using the University of North Carolina shape analysis toolkit (<http://www.nitrc.org/projects/spharm-pdm/>); a detailed description of the methodology is available elsewhere [49, 50]. Segmented 3D binaries are initially processed to ensure interior holes are filled, followed by morphological closing and minimal smoothing. These are then subjected to spherical harmonic shape description (SPHARM), whereby boundary surfaces of each shape are mapped onto the surface of a sphere and the surface coordinates were represented through their spherical harmonic coefficients [51]. The correspondence between surfaces is established by parameter-based rotation, itself based on first-order expansion of the spherical harmonics. The surfaces are uniformly sampled into a set of 1002 surface points and aligned to a study-averaged template for each structure (left and right caudate and putamen) using rigid-body Procrustes alignment [52]. Scaling normalization was performed to remove the effect of head size/intracranial volume, using a surface scaling factor: f_i , where $f_i = \{\text{Mean(ICV)/ICV}_i\}^{1/3}$ [53].

Statistical Analyses

Volumetric data were analysed with paired t-tests to determine change in volume from baseline to 3-year follow-up. ANCOVA was performed to determine whether volume differences were present between severity subgroups as measured by baseline Fazekas score. Relationships between basal ganglia volumes and SPPB scores/walking speeds were assessed with hierarchical regression, with covariates (age, gender and intracranial volume) entered at the first step and the volumes entered at the second step.

With regard to shape analysis, we compute non-parametric statistical tests that compare the local surface coordinates for group mean differences at the 1002 surface locations [49, 50, 53]. A local group difference metric between groups of surface coordinates is derived from the Hotelling T^2 two-sample metric [53]. As the shape analysis involves computing 1002 hypothesis tests, one per surface location, a correction for multiple testing is necessary, as an uncorrected analysis would be overly optimistic. The shape analysis uses permutation tests over the Hotelling T^2 metric for the computation of the raw uncorrected p-values and uses false discovery rate (FDR) [54] for multiple comparison correction. Correlational analyses were undertaken using Spearman's rank-correlation co-efficient r , and maps of both r and FDR-corrected p-values are generated.

Results

Demographics, Longitudinal Change and Severity of White Matter Disease

Demographic details of the entire LADIS dataset have been reported [3]. The demographic details and severity of WMC in the LADIS subgroup included in this study were similar to that of the larger dataset. The rates of subsequent transition to disability or death were significantly lower in the study group compared to the rest of the LADIS group, while SPPB scores were not significantly different (Table 1). There was no significant relationship between basal ganglia volumes and the severity of WMC, whether the severity was assessed via the Fazekas scale, total summed WMC volume or Schelten scores (please see online supplementary materials). Longitudinal paired t-tests on baseline and follow-up basal ganglia volumes showed little change in volume over time, apart from some weakly significant increases in caudate volumes in some subsets (<5% of volume, see online supplementary material). I think you mean decreases in caudate volume Table 3 in the appendix reports shrinkage of the right caudate in the mild group and shrinkage of left caudate in the moderate group. This table is a bit confusing as a positive mean difference signifies shrinkage. It might be better to reverse the sign ie make Mean difference = follow up volume minus baseline volume. Or have I got myself mixed up!!!

Volumetry

Initially, volumetric analysis was performed on the manually segmented 3-D objects of caudate and putamen. The results of these analyses guided the shape analysis explorations, based upon our group's previous experience with shape analysis [24, 46-48]. Regression analysis on these volumes is shown in Table 2. A significant correlation was found between caudate nucleus volumes and both SPPB scores and the walking speed subcomponent of the SPPB at study baseline, but this was not reproduced at three-year follow-up. Intracranial volume was negatively correlated with SPPB at baseline, but not follow-up. There was no significant correlation between putamen volume and measures of gait or balance.

Shape Analysis

We applied the shape analysis method to the segmented caudate for the entire dataset. All results were scale-normalised for total intracranial volume. The results presented are based upon FDR corrected p-value maps, together with corresponding local displacement maps.

The details of the legend for the analyses are described below the images for ease of reference when reading the images (Figure 4).

Shape deflation was seen unilaterally in the left caudate nucleus, with no significant differences seen in the right caudate. Inward deformation of left caudate shape was found in regions corresponding to the inputs of the dorsolateral prefrontal, premotor and motor cortex, correlating with SPPB ($p=0.0017$) [32, 55, 56]. Localised shape changes were seen when analysing the walking speed subcomponent of the SPPB, but these did not persist when corrected for FDR.

Discussion

The current study, of older patients with white matter changes, has identified highly significant shape and volume deflation in areas of the left caudate nucleus that subserve motor portions of the fronto-striatal circuits. These results support our hypothesis, and demonstrate patterns similar to those seen in a number of neurodegenerative disorders that manifest structural change in the caudate nucleus such as Huntington's Disease [57-59], Alzheimer's Disease [60-63], Progressive Supranuclear Palsy [25, 64], Corticobasal Syndrome and Multiple System Atrophy [65-67]. Accordingly, morphometric (shape and volume) analysis of the caudate may be used as a biomarker which could aid in diagnostic clarity and as an additional marker to track the progression and treatment [68].

Within frontostriatal circuits, the caudate subserves a role in the supplementary motor circuit, connecting to premotor and motor cortex involved in the planning and execution of movements [32]. Impairment of gait and balance was correlated with altered morphology of the caudate. This finding suggests that motor dysfunction is associated with disruption of the supplementary motor frontostriatal circuit. This is borne out by the specific regional atrophy in the postero-lateral aspect of the left caudate. It has been proposed that a purpose of hemispheric lateralisation is to encode constrained repertoires of cognition, emotion and behaviour within the left hemisphere [69]. Thus, the specific atrophy of the left caudate may, in part, reflect the process of loss of the physical substrate of the entrained gait and balance behaviours under frontal control in frontostriatal circuits. A parsimonious explanation for lateralization may be that the corresponding morphologic change was not detected in the right caudate due to sample size.

The lack of correlation between white matter lesion load and striatal volumes, and between caudate morphology and SPPB at follow-up may be partially explained by a survivor effect, i.e. the selection of a group for which MRI were available in 3-year follow-up necessarily resulted in a sample biased to lesser severity of disability in general (as seen in Table 1). Thus a correlation evident at baseline may have much less predictive value and hence correlation at follow-up. This survivor effect may also, in part, be responsible for the lack of atrophy demonstrated in basal ganglia volumes over this period (see online supplementary material) – indeed, there was a statistically significant (although small, <5%) increase in caudate volumes of some subsets, which may reflect some compensation as the patient ages but is more likely to be a statistical artefact. The small but highly significant negative correlation between intracranial volume and SPPB at baseline implies higher ICV is

correlated with lower SPPB, signifying poorer motor function. That this is not replicated in the 3-year follow-up may also represent a survivor effect, but is admittedly difficult to explain.

The possible mechanisms of caudate morphology alterations in WMC are admittedly speculative. These mechanisms comprise: possible deafferentation of striatal inputs through direct anatomical disruption by white matter hyperintensities [68], direct vascular damage to the caudate and generalised cerebral atrophy as a result of WMC. We consider the former most likely, and at least in our study, the latter two factors were controlled for by exclusion and as a covariate/scaling respectively.

Limitations of this study include the small sample size. However, as manual tracing is a time-intensive process, the size of this study compares favourably to other shape analysis studies utilising similar methodology [46-48]. Replication of these results, particularly the preponderance of left-sided deflation, will be useful in order to confirm the degree and laterality of shape deflation in individuals with diffuse white-matter hyperintensities. Analysing the rest of the LADIS dataset would be a useful next step, but the large number of scans (600+) involved may require a more automated and less manually intensive segmentation method.

Conclusion

We have demonstrated that the caudate nucleus may be a possible physical substrate and hence, a potential biomarker, for gait and balance in persons with WMC. Recent related research has highlighted that impaired gait, measured as walking speed, is associated with both progression to dementia and increased mortality [33-35]. Thus having identified a possible physical substrate and component of frontostriatal circuits implicated in cortical control of gait and balance is a significant advance. In addition, we have demonstrated a correlation between caudate morphology, responsible for mediation of motor function, and a measure of gait, balance and walking speed. We propose that these methods of shape analysis of the striatum should be applied, with the advance of automated segmentation, to the entire LADIS dataset, and similar datasets to determine if our findings may be replicated, and extended by correlation with automated quantification of white matter hyperintensities. Thus we may derive a reliable neuroimaging biomarker of cognitive and gait dysfunction in cerebrovascular disease, suitable for monitoring disease progression and potentially predictive of dementia and adverse outcomes.

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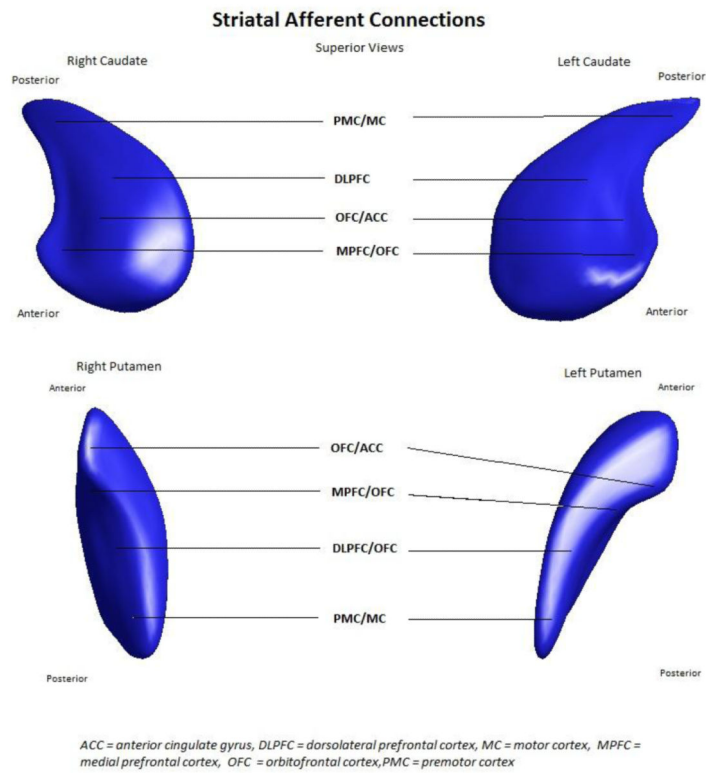


Figure 1. Striatal afferent connections, showing the location on the caudate and putamen that each cortical region preferentially connects, based on the circuit diagrams from Alexander et al 1986.

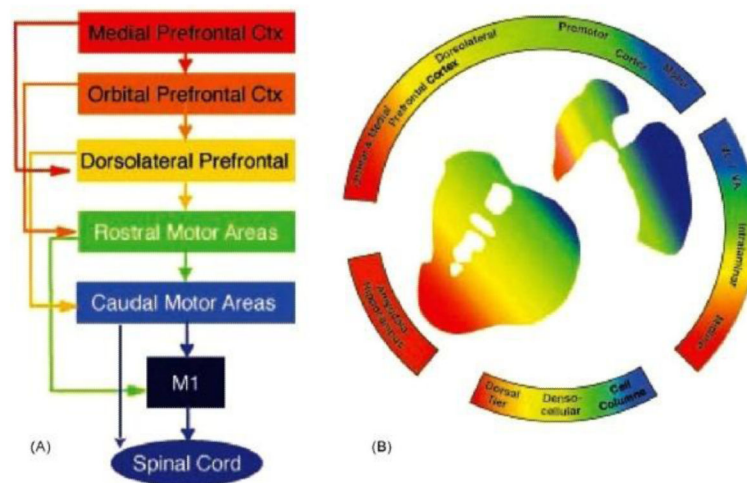


Figure 2.

Diagram demonstrating the functional organisation of A. frontal cortex and B. striatal afferent projections. (A) Schematic illustration of functional connections linking frontal cortical brain regions. (B) Organisation of cortical and subcortical inputs to the striatum. In both (A) and (B), the colours denote functional distinctions. Blue: motor cortex, execution of motor actions; green: premotor cortex, planning of movements; yellow: dorsal and lateral prefrontal cortex, cognitive and executive functions; orange: orbital prefrontal cortex, goal-directed behaviours and motivation; re: medial prefrontal cortex, goal-directed behaviours and emotional processing. Reproduced with permission from Haber, 2003.

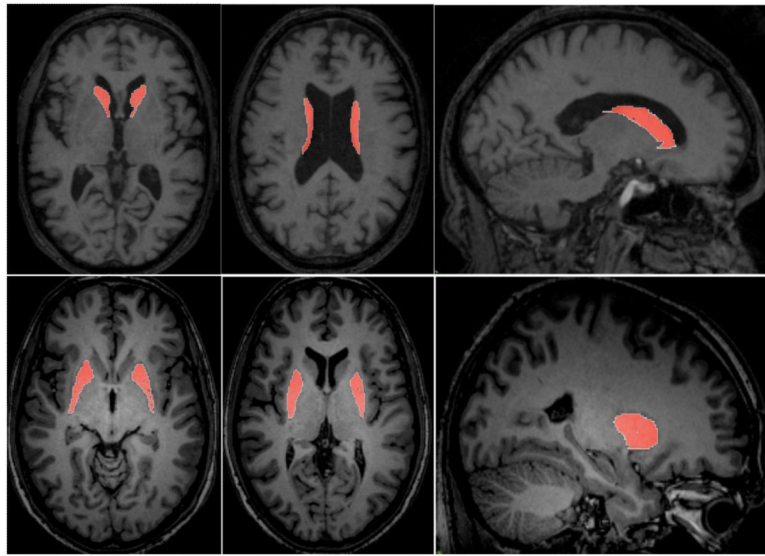


Figure 3. Representative slices from manual tracing of the caudate nuclei, above, and the putamina, below.

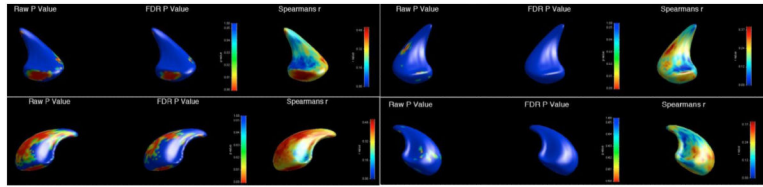


Figure 4.

Shape analysis correlating specific areas of the caudate nucleus with performance on the Short Physical Performance Battery (SPPB) at study entry. Clockwise from L top (three images per structure) : **1a,b,c**: Left caudate ventral aspect, **2a,b,c**: R caudate ventral aspect, **3a,b,c**: R dorsal aspect, **4a,b,c**: L caudate dorsal aspect. The anterior aspect of the caudate is oriented towards the bottom of the image. Raw P value: unadjusted P value; FDR P value: false discovery rate P value (adjustment for family-wise error); Spearman's r: Spearman's rank correlation coefficient for SPPB with caudate surface. Scale for images is displayed in the colour bar at the side of the respective images.

Table 1

Demographic Details

Variable	Study group n=66	Rest of LADIS study (n=573)	Significance of Difference on t- test/chi-square
Age in years – mean (SD)	73.2 (4.97)	74.2 (5.05)	0.115 (NS)
Gender – % male	51.5	44.3	0.262 (NS)
Mean Caudate Volumes (mm ³)*	2695.4	N/A	N/A
Mean Putamen Volumes (mm ³)*	2195.5	N/A	N/A
Mean Intracranial Volume (cm ³)	1567.9	N/A	N/A
Leukoaraiosis – % mild	39.7	45	0.705 (NS)
Leukoaraiosis – % mod	33.8	30.5	0.705 (NS)
Leukoaraiosis – % severe	26.5	24.5	0.705 (NS)
% who transitioned to disability or death at 3 years	25.8	39.6	0.035*
Average SPPB scores at Baseline	9.80	9.74	0.846 (NS)
Average SPPB scores at 3-Year Follow-Up	9.69	9.11	0.119 (NS)
Average Walking Speed at Baseline (m/sec)	1.15	1.19	0.127 (NS)
Average Walking Speed at 3-Year Follow-up (m/sec)	1.17	1.11	0.508 (NS)

* Right plus left volumes

Table 2

Caudate Nucleus Volumetry Regression Analyses (Model 2)

Variable	Time Point	Variable	Standardized Beta	Sig.	Correlations	
					Partial	Part
SPPB Score	Baseline/Study Entry	Age	-.243	.040*	-.278	-.232
		Gender	-.159	.261	-.154	-.125
		Intracranial Volume	-.370	.009*	-.350	-.300
		Bilateral Caudate Volume	.350	.003*	.390	.340
	3-Year Follow-up	Age	-.314	.027*	-.307	-.302
		Gender	-.059	.721	-.051	-.048
		Intracranial Volume	.095	.555	.084	.079
		Bilateral Caudate Volume	.191	.167	.194	.186
Walking Speed	Baseline/Study Entry	Age	-.427	.001*	-.449	-.412
		Gender	-.185	.194	-.176	-.147
		Intracranial Volume	-.274	.047*	-.266	-.227
		Bilateral Caudate Volume	.340	.005*	.373	.330
	3-Year Follow-up	Age	-.383	.005*	-.385	-.368
		Gender	-.130	.412	-.117	-.104
		Intracranial Volume	-.266	.086	-.243	-.221
		Bilateral Caudate Volume	.220	.096	.236	.214

Model 1 = Age, Gender, Intracranial volume Model 2 = Age, Gender, Intracranial volume, Bilateral caudate volume

Table 3

Putamen Volumetry Regression Analyses (Model 2)

Variable	Time Point	Variable	Standardized Beta	Sig.	Correlations	
					Partial	Part
SPPB Score	Baseline/Study Entry	Age	-.259	.046*	-.268	-.248
		Gender	-.288	.059	-.254	-.233
		Intracranial Volume	-.441	.005	-.371	-.355
		Bilateral Putamen Volume	-.084	.519	-.088	-.079
	3-Year Follow-up	Age	-.290	.045*	-.257	-.279
		Gender	-.097	.569	-.068	-.081
		Intracranial Volume	.077	.642	.099	.066
		Bilateral Putamen Volume	.001	.993	.077	.001
Walking Speed	Baseline/Study Entry	Age	-.400	.002*	-.371	-.397
		Gender	-.271	.074	.007	-.241
		Intracranial Volume	-.328	.032	-.216	-.286
		Bilateral Putamen Volume	.022	.863	.008	.024
	3-Year Follow-up	Age	-.355	.012*	-.344	-.350
		Gender	-.173	.295	.073	-.149
		Intracranial Volume	-.288	.077	-.229	-.250
		Bilateral Putamen Volume	.008	.954	-.011	.008

Model 1 = Age, Gender, Intracranial volume Model 2 = Age, Gender, Intracranial volume, Bilateral putamen volume