

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

Matthew D. Macfarlane, M.B.Ch.B., F.R.A.N.Z.C.P.,

Jeffrey C.L. Looi, M.B.B.S., M.D., F.R.A.N.Z.C.P., A.F.R.A.C.M.A.,

Mark Walterfang, M.B.B.S., Ph.D., F.R.A.N.Z.C.P., Gabriela Spulber, M.D., Ph.D.,

Dennis Velakoulis, M.B.B.S., D.Med.Sc., F.R.A.N.Z.C.P., Martin Styner, Ph.D.,

Milita Crisby, M.D., Ph.D., Eva Örndahl, Ph.D., Timo Erkinjuntti, M.D., Ph.D.,

Gunbild Waldemar, M.D., D.M.Sc., Ellen Garde, M.D., Ph.D., Michael G. Hennerici, M.D.,

Hansjörg Bänzner, M.D., Christian Blabak, M.D., Anders Wallin, M.D., Ph.D.,

Lars-Olof Wahlund, M.D., Ph.D., and the LADIS Study Group

Objective: *Functional deficits seen in several neurodegenerative disorders have been linked with dysfunction in frontostriatal circuits and with associated shape alterations in striatal structures. The severity of visible white matter hyperintensities (WMHs) on magnetic resonance imaging has been found to 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.*

Methods: *Magnetic resonance imaging scans and clinical gait/balance data (scores from the Short Physical Performance Battery [SPPB]) were sourced from 66 subjects in the previously published LADIS trial, performed in nondisabled individuals older than age 65 years with WMHs at study entry. Data were obtained at study entry and at 3-year follow-up. Caudate nuclei and putamina were manually traced using*

Received November 20, 2012; revised April 18, 2013; accepted April 24, 2013. From the Research Centre for the Neurosciences of Ageing, Academic Unit of Psychiatry and Addiction Medicine (MDM, JCLL), Australian National University Medical School, Canberra Hospital, Canberra, Australian Capital Territory, Australia; Division of Clinical Geriatrics, Department of Neurobiology, Care Science and Society (JCLL, GS, MC, L-OW), and Division of Medical Imaging and Technology, Department of Clinical Science, Intervention and Technology (EÖ), Karolinska Institute, Stockholm, Sweden; Melbourne Neuropsychiatry Centre (MW, DV), Royal Melbourne Hospital and University of Melbourne, Melbourne, Victoria, Australia; Neuroimaging Research and Analysis Laboratories, Carolina Institute of Developmental Disabilities, Departments of Psychiatry and Computer Science (MS), University of North Carolina, Chapel Hill, NC; Department of Radiology (EÖ), Karolinska University Hospital in Huddinge, Stockholm, Sweden; Department of Neurological Sciences (TE), University of Helsinki, Finland and Department of Neurology (TE), Helsinki University Central Hospital, Helsinki, Finland; Memory Disorders Research Group, Department of Neurology, Rigshospitalet (GW), Copenhagen University Hospital, Copenhagen, Denmark; Danish Research Centre for Magnetic Resonance (EG), Copenhagen University Hospital, Hvidovre, Denmark; Department of Neurology (MGH, HB, CB), Universitätsmedizin Mannheim UMM, University of Heidelberg, Mannheim, Germany; and Institute of Neuroscience and Physiology (AW), Sahlgrenska University Hospital, Gothenburg, Sweden. Presented in part as a poster at the 16th Congress of the European Federation of Neurological Societies, Stockholm, Sweden, September 8–11, 2012. Send correspondence and reprint requests to Matthew D. Macfarlane, M.B.Ch.B., F.R.A.N.Z.C.P., Academic Unit of Psychiatry and Addiction Medicine, Level 2 Building 4, Canberra Hospital, Yamba Dr, Garran ACT 2605, Australia. e-mail: mmacfarlane1@gmail.com

Supplemental digital content is available for this article in the HTML and PDF versions of this article on the journal's Web site (www.ajgponline.org).

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<http://dx.doi.org/10.1016/j.jagp.2013.04.011>

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a previously published method and volumes calculated. The relationships between volume and physical performance on the SPPB were investigated with shape analysis using the spherical harmonic shape description toolkit. Results: There was no correlation between the severity of WMHs and striatal volumes. Caudate nuclei volume correlated with performance on the SPPB at baseline but not at follow-up, with subsequent shape analysis showing left caudate changes occurred 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 WMHs. Striatal volume and shape changes may be suitable biomarkers for functional changes in this population. (Am J Geriatr Psychiatry 2013; ■:■–■)

Key Words: Striatum, caudate nucleus, MRI, gait, white matter disease

INTRODUCTION

Implications of White Matter Hyperintensities

White matter hyperintensities (WMHs), observed on T2-weighted magnetic resonance imaging (MRI) brain scans, are particularly prominent in individuals over the age of 65.^{1,2} Previous studies examined the correlation of WMHs and cognitive ability in this older age group, with the largest being the Leukoaraiosis and Disability Study (LADIS), a multi-center European study that investigated the effect of WMHs on a number of different clinical indicators over a 3-year prospective follow-up.^{3,4} The LADIS study has demonstrated a number of associations between severity of WMHs and adverse outcomes, which included increased transition to disability,⁵ declining cognitive ability,^{6–10} and greater incidence of depression.^{11–13}

The LADIS study also demonstrated a significant association between the severity of WMHs 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).^{14,15} This is consistent with 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,^{16,17} as well as subsequent development of dementia¹⁸ and association with

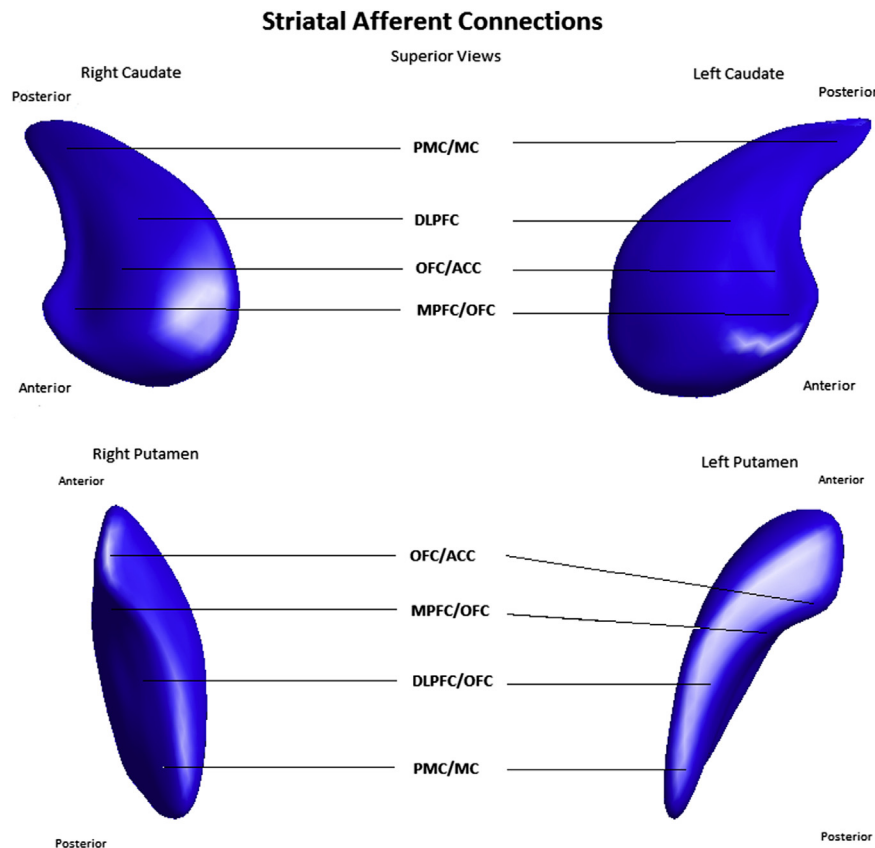
depression.¹⁹ A recent study also demonstrated a correlation between slower walking speeds with smaller volumes of caudate nuclei.²⁰

Frontostriatal Circuits and Striatal Shape Analysis

The link between the basal ganglia of the brain and motor coordination and planning is well documented.^{21–23} Afferents to the caudate arise from different areas of the cortex, making the caudate nucleus an important part of parallel frontostriatal circuits. The frontostriatal circuit model, first described by Alexander et al.,²⁴ has been confirmed through a number of different modalities, including diffusion tensor imaging and transcranial magnetic stimulation combined with functional MRI, showing anatomic and functional links between the frontal cortex and striatum.^{25–28} In addition, strokes in frontostriatal circuits correlate with increased rates of vascular depression.

Many of these studies indicate that different areas of the cortex “map” on to different areas of the caudate nucleus and putamen (Fig. 1). Specifically, the cognitive and behavioral circuits arising from dorsolateral prefrontal cortex, anterior cingulate, and orbitofrontal cortex primarily project to the caudate, whereas the frontal eye fields and motor cortex project to both caudate and putamen.^{24,29} Accordingly, functional changes in cognition, behavior, and movement may arise from structural change in caudate and putamen.

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.²⁴



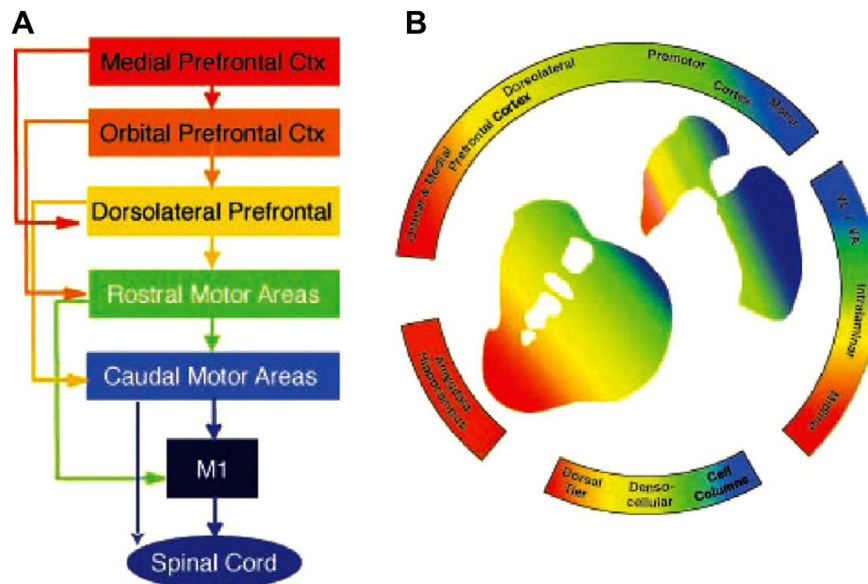
ACC = anterior cingulate gyrus, DLPFC = dorsolateral prefrontal cortex, MC = motor cortex, MPFC = medial prefrontal cortex, OFC = orbitofrontal cortex, PMC = premotor cortex.

Although basal ganglia volumes have been the mainstay of MRI studies (our group has previously examined caudate nucleus volumetrics in patients with stroke and vascular dementia),³⁰ studies of three-dimensional shape alterations in the striatal areas of the basal ganglia, particularly in the caudate nucleus, show promise in elucidating correlation between specific deficits and specific shape change in striatal structures as predicted by Alexander's model. Differential shape changes in these structures have been correlated with differing functional deficits in subtypes of frontotemporal lobar degeneration,³¹ have aided in distinguishing Parkinson disease and multiple system atrophy,³² and in progressive supranuclear palsy.³³ Shape changes have also been used as biomarkers for diagnosis of Huntington disease³⁴ and chorea-acanthocytosis.^{35,36}

Based on these results, 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 (Fig. 2). This study aimed to determine whether subjects entering the LADIS study demonstrated a correlation between volume of striatal structures and performance on measures of gait and balance and that, in turn, striatal shape reductions (sometimes referred to as "shape deflation") would correspond to the smaller volumes seen in those with poorer performance. Our chief hypothesis was that we would detect shape deflation in striatal regions corresponding to the site of afferent connections to areas of the motor cortex and that this deflation would correlate with poorer performance on the

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FIGURE 2. Diagram demonstrating the functional organization of [A] frontal cortex and [B] striatal afferent projections. [A] Schematic illustration of functional connections linking frontal cortical brain regions. [B] Organization of cortical and subcortical inputs to the striatum. In both [A] and [B], the colors 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 behaviors and motivation; red: medial prefrontal cortex, goal-directed behaviors and emotional processing. Reproduced with permission from Haber.²⁹



SPPB. Gait, measured via walking speed in the SPPB, has been associated with cognitive impairment and progression to dementia.^{37,38} In addition, because LADIS is a longitudinal study, we sought to investigate these structure–function relationships with clinical data at 3-year follow-up.

METHODS

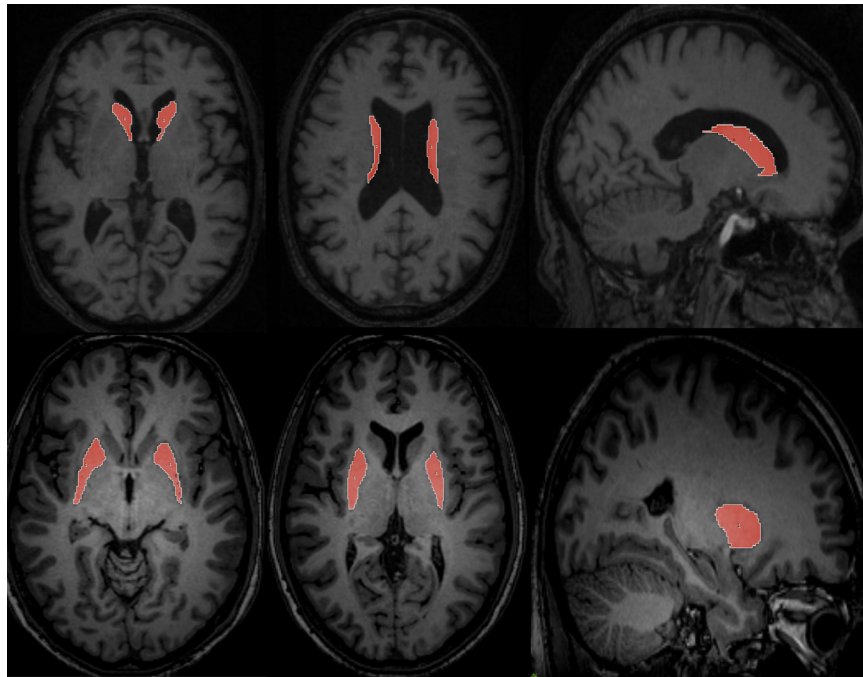
LADIS Study Data Collection and Details

This study used a subset ($N = 66$) of the larger LADIS study. The recruitment methods and other clinical data for LADIS are documented elsewhere³ but are described briefly here: 639 subjects were recruited from 11 centers in Europe: Florence, Helsinki, Graz, Lisboa, Amsterdam, Gothenburg, Huddinge, Paris, Mannheim, Copenhagen, and Newcastle-upon-Tyne. Inclusion criteria were age between 65 and 84 years and the presence of WMHs as rated by the Fazekas visual-rating scale (as mild, moderate, and severe) on

T2-weighted and fluid attenuated inversion recovery MRI³⁹ at study entry. WMHs were also assessed via total WMH volume and through the Scheltens visual-rating scale,⁴⁰ but the different measurement methods did not result in any differences in correlations with gait or balance outcomes.⁴¹ Thus, the Fazekas scale score was used in the present study as a covariate rather than more complex measurement methods. The other criterion for entry was a score on the International Activities of Daily Living⁴² scale indicating no or mild disability. The exclusion criteria were the presence of severe medical or psychiatric illness, severe unrelated neurodegenerative disorders (such as Huntington disease, frontotemporal lobar degeneration, Alzheimer disease, and dementia with Lewy bodies), nonvascular leukoencephalopathy, or inability to give informed consent.

MRI scans were performed at baseline and at 3 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.

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



The gait and balance measure used for the current study was the SPPB, which tests the ability of subjects to hold themselves in various standing positions (feet in side-by-side, semitandem, or tandem), measures walking speed over an 8-foot course, and tests ability and speed at rising from a chair.⁴³ The SPPB is scored out of 12, with a higher score indicating a better performance.

MRI Acquisition

The MRI-protocol consisted of three-dimensional sagittal or coronal T1-weighted magnetization prepared rapid acquisition gradient echo images (TE: 4–7 ms; TR: 10–25 ms; TI: 100–950 ms; flip angle: 10–30 degrees; voxel size: $1 \times 1 \times 1\text{--}1.5 \text{ mm}^3$; FOV: 250 mm), axial T2-weighted fast spin echo images (TE: 100–120 ms; TR: 4,000–6,000 ms; FOV: 250 mm; slice thickness: 5–7.5 mm; interslice gap: 0.5 mm), and fluid attenuated inversion recovery images (TE: 100–140 ms; TR: 6,000–10,000 ms; TI: 2,000–2,400 ms; FOV: 250 mm; slice thickness: 5–7.5 mm; interslice gap: 0.5 mm). The scans were acquired at 1.5 Tesla. (Preceding description was modified from Ryberg *et al.*⁴⁴)

Ethical Approval

The LADIS study received ethical approval from local ethics committees in each center. 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 centers: Copenhagen, Stockholm (Huddinge), Gothenburg, and Helsinki. These centers were chosen in collaboration with one of the authors (GS), and images were selected for readable image quality and availability of follow-up scans. Scans were rendered anonymous by LADIS group researchers before transfer to a MacBook Pro (Apple, Cupertino, CA) computer provided by University of Melbourne based at the Department of Psychological and Addiction Medicine, Australian National University.

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Subjects with infarcts in the caudate or putamen were excluded to eliminate the possibility of measured volume or shape change being a result of direct vascular damage to striatal structures.

Digital Imaging and Communications in Medicine files of T1-weighted images were converted to ANALYZE 7.5 format (Mayo BIR, Rochester, NY) using MRIConvert (<http://lcn.uoregon.edu/~jolinda/MRIConvert/>) to prepare for analysis. Image intensity was standardized by using preset threshold values, based on a pilot analysis of the data, and voxel size was reconstructed as isotropic at $1 \times 1 \times 1$ mm.

Intracranial volume (ICV) was determined in a semiautomated fashion using FSL software (FMRIB Group, Oxford, Oxfordshire, United Kingdom) as a measure to control for brain size. First, brains were skull-stripped with the Brain Extraction Tool (<http://www.fmrib.ox.ac.uk/analysis/research/bet/>) and were then linearly aligned to the MNI (Montreal Neurological Institute, McGill University Montreal, Canada) 152 1-mm T1-weighted template.⁴⁵ 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.^{45,46}

Caudate nuclei and putamen were manually traced within ANALYZE 10.0b (Mayo BIR) through a region of interest approach by one investigator (MM) who was blind to clinical data using a previously published protocol^{47,48} applied in a number of studies.^{30,36,49–51} Briefly, this involved tracing images in the axial plane, using the inferior border of the anterior commissure as the inferior boundary (Fig. 3). The resulting binary objects were checked in the sagittal plane and volumes calculated (mean volumes are given in Appendix A; available online). COMP: Please provide a hyperlink for the Appendix. Reliability of the tracing was checked by an experienced tracer (JCLL) tracing basal ganglia on a representative sample of the 66 subjects; one author (MM) also retraced the representative sample to serve as test–retest reliability. Intraclass correlation coefficients were used to determine reliability of volumetric measurement: Intrarater reliability was 0.944, with inter-rater reliability at 0.890. The decisions on whether to proceed to shape analysis were guided by volumetric results based on experience in our prior shape analysis studies in neurodegenerative disease:

If there was no significant volume change, shape analysis was not attempted.^{33,52}

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.^{53,54} Segmented three-dimensional binaries are initially processed to ensure interior holes are filled, followed by morphologic closing and minimal smoothing. These are then subjected to spherical harmonic shape description, 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.⁵⁵ 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 1,002 surface points and aligned to a study-averaged template for each structure (left and right caudate and putamen) using rigid-body Procrustes alignment.⁵⁶ Scaling normalization was performed to remove the effect of head size/ICV, using a surface scaling factor: f_i , where $f_i = \{\text{Mean (ICV)}/\text{ICV}_i^{1/3}\}$.⁵⁷

Statistical Analyses

Differences in this subset of the LADIS study compared with the larger LADIS dataset were assessed via two-tailed independent samples *t* tests for means and χ^2 tests for frequencies. Volumetric data were analyzed with two-tailed paired *t* tests to determine change in volume from baseline to 3-year follow-up. Analysis of covariance was performed to determine whether volume differences were present between severity subgroups as measured by baseline Fazekas score, controlling for age, gender, and ICV. Relationships between basal ganglia volumes and SPPB scores were assessed with hierarchical regression, with covariates (age, gender, Fazekas score, number of frontal lacunar infarcts, and ICV) entered at the first step and the volumes entered at the second step.

With regard to shape analysis, we compute nonparametric statistical tests that compare the local surface coordinates for group mean differences at the

TABLE 1. Clinical Details

Variable	Study Group (N = 66)	Rest of LADIS Study (N = 573)	T Score on Two-Tailed Independent Sample t Test/Pearson χ^2	Significance of Difference on t Test/ χ^2
Age, y, mean (SD)	73.2 (4.97)	74.2 (5.05)	-1.579	0.115
Gender, % male	51.5	44.3	1.126	0.303
MMSE scores, mean (SD)	27.74 (2.1)	27.31 (2.47)	1.349	0.178
Hypertension, %	75.8	69.9	1.824	0.402
Diabetes, %	6.1	14.6	10.810	0.004
Hypercholesterolemia, %	33.3	50.9	9.494	0.009
History of gait disturbance, %	25.8	41.2	0.630	0.529
History of falls, %	36.4	28.8	1.666	0.435
History of syncopal events, %	22.1	16.8	5.432	0.143
History of cardiac arrhythmia, %	10.6	18.8	0.523	0.470
Transitioned to disability or death at 3 years, %	25.8	39.6	4.462	0.035

Notes: SD: standard deviation; MMSE: Mini-Mental State Exam; df = 635 for t test, df = 2 for χ^2 .

TABLE 2. MRI and Gait/Balance Statistics

Variable	Study Group (N = 66)	Rest of LADIS Study (N = 573)	T Score on Two-Tailed Independent Sample t Test/Pearson χ^2	Significance of Difference on t Test/ χ^2
Mean ^a caudate volumes, mm ³ (SD)	2,695.4 (498)	N/A	N/A	N/A
Mean ^a putamen volumes, mm ³ (SD)	2,195.5 (349)	N/A	N/A	N/A
Mean intracranial volume, cm ³ (SD)	1567.9 (175)	N/A	N/A	N/A
WMH severity, % mild	39.7	45	0.699	0.485
WMH severity, % mod	33.8	30.5	0.699	0.485
WMH severity, % severe	26.5	24.5	0.699	0.485
Average SPPB scores at baseline (SD)	9.85 (2.29)	9.79 (2.25)	0.220	0.846
Average SPPB scores at 3-year follow-up (SD)	9.77 (2.44)	9.10 (2.86)	1.751	0.081
Average walking speed at baseline, m/s (SD)	1.15 (0.262)	1.19 (0.318)	-1.128	0.260
Average walking speed at 3-year follow-up, m/s (SD)	1.17 (0.248)	1.11 (0.402)	0.972	0.332

Notes: SD: standard deviation; WMH severity: white matter hyperintensities as measured by Fazekas scale.³⁹ df = 635 baseline data, df = 445 follow-up data for t test, df = 3 for χ^2 .

^aMean of right and left volumes.

1,002 surface locations.^{53,54,57} A local group difference metric between groups of surface coordinates is derived from the Hotelling T² two-sample metric.⁵⁷ Because the shape analysis involves computing 1,002 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 T² metric for the computation of the raw uncorrected p values and uses false discovery rate (FDR)⁵⁸ for multiple comparison correction. Correlational analyses were undertaken using Spearman rank-correlation coefficient *r*, and maps of both *r* and FDR-corrected p values were generated (details of the shape statistical analyses are included in Appendix B; available online).

RESULTS

Demographics, Clinical Details, Longitudinal Change, and Severity of White Matter Disease

Demographic details of the entire LADIS dataset have been reported.³ The demographic and clinical details and severity of WMHs in the LADIS subgroup included in this study were compared with that of the larger dataset (Tables 1 and 2). The rates of subsequent transition to disability or death were significantly lower in the study group compared with the rest of the LADIS group (25.8% versus 39.6%, Pearson's $\chi^2 = 4.462$, df = 2, *p* = 0.035), whereas SPPB scores were not significantly different (9.8 versus 9.74 at baseline, *t* = 0.220, df = 637, *p* = 0.846;

*Caudate Nucleus Abnormalities and Gait Dysfunction***TABLE 3. Caudate Nucleus Volumetry: Linear Regression Analyses (Model 2)**

Variable	Time Point	Variable	Standardized Beta	t	Sig.	Correlations	
						Partial	Part
SPPB score	Baseline/study entry	Age	−0.243	—	0.039 ^a	−0.0282	—
				2.117			0.0232
		Gender	−0.137	—	0.335	−0.0134	—
				0.973			0.0107
		WMC severity	−0.247	—	0.047 ^a	−0.0271	—
				2.033			0.0223
	3-Year follow-up	ICV	−0.361	—	0.010 ^a	−0.346	−0.292
				2.663			
		Frontal lacunes	0.147	1.235	0.223	0.169	0.135
		Bilateral caudate volume	0.339	2.994	0.004 ^a	0.383	0.329
		Age	−0.275	—	0.058	−0.270	−0.256
				1.940			
		Gender	−0.018	—	0.914	−0.016	−0.014
				0.108			
		WMC severity	−0.219	—	0.137	−0.213	−0.200
				1.512			
		ICV	0.154	0.935	0.354	0.134	0.123
		Frontal lacunes	0.055	0.387	0.701	0.056	0.051
		Bilateral caudate volume	.186	1.361	.186	.193	.180

Notes: Model 1 (not shown): age, gender, ICV, WMC severity (Fazekas score), number of frontal lacunes. df = (5,53). Model 2: age, gender, ICV, WMC severity (Fazekas score), number of frontal lacunes, bilateral caudate volume. Sig: significance. df = (1,52).

^ahighlights statistically significant results (p < 0.05).

TABLE 4. Putamen Volumetry: Linear Regression Analyses (Model 2)

Variable	Time Point	Variable	Standardized Beta	t	Sig.	Correlations	
						Partial	Part
SPPB score	Baseline/study entry	Age	−0.232	—	0.068	−0.250	−0.220
				1.864			
		Gender	−0.221	—	0.143	−0.202	−0.175
				1.486			
		WMC severity	−0.277	—	0.039 ^a	−0.281	−0.249
				2.113			
	3-Year follow-up	ICV	−0.369	—	0.018 ^a	−0.322	−0.289
				2.449			
		Frontal lacunes	0.170	1.334	0.188	0.182	0.157
		Bilateral putamen volume	−0.108	—	0.398	−0.117	−0.101
				0.853			
		Age	−0.251	—	0.090	−0.243	−0.233
				1.732			
		Gender	−0.058	—	0.739	−0.048	−0.045
				0.335			
		WMC severity	−0.227	—	0.132	−0.216	−0.206
				1.534			
		ICV	0.146	0.853	0.398	0.122	0.115
		Frontal lacunes	0.070	0.470	0.640	0.068	0.063
		Bilateral putamen volume	−0.020	—	.897	−0.019	−0.018
				0.131			

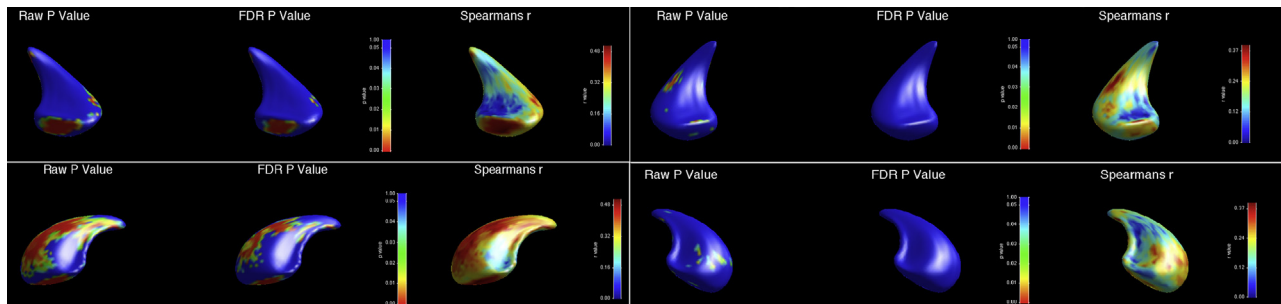
Notes: Model 1 (not shown): age, gender, ICV, WMC severity (Fazekas score), number of frontal lacunes. df = (5,53). Model 2: age, gender, ICV, WMC severity (Fazekas score), number of frontal lacunes, bilateral putamen volume. Sig: significance. df = (1,52).

^ahighlights statistically significant results (p < 0.05).

9.69 versus 9.11 at follow-up, $t = 1.751$, $df = 455$, $p = 0.119$). There was no significant relationship between striatal volumes and the severity of WMHs

(Appendix A; available online). Longitudinal two-tailed paired t tests on baseline and follow-up striatal volumes showed little change in volume over

FIGURE 4. Shape analysis correlating specific areas of the caudate nucleus with performance on the SPPB at study entry. Clockwise from left top (three images per structure): 1a,b,c: Left caudate inferior aspect, 2a,b,c: right caudate inferior aspect, 3a,b,c: right superior aspect, 4a,b,c: left caudate superior aspect. The anterior aspect of the caudate is oriented toward 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 color bar at the side of the respective images. p Values are calculated using permutation methods (see [Appendix B](#); available online).



time, apart from some weakly significant increases in caudate volumes in some subsets (<5% of volume, [Appendix A](#); available online).

Volumetry

Initially, volumetric analysis was performed on the manually segmented three-dimensional objects of caudate and putamen. The results of these analyses guided the shape analysis explorations, based on our group's previous experience with shape analysis.^{31,36,50,51} Regression analysis on these volumes is shown in [Tables 3](#) and [4](#). A significant correlation was found between caudate nucleus volumes and SPPB scores at study baseline (regression analysis as above, standardized beta = 0.339, $t = 2.994$, $df = 1, 53$, partial correlation = 0.383, $p = 0.004$), but this was not reproduced at the 3-year follow-up (standardized beta = 0.186, $t = 1.361$, $df = 1, 53$, partial correlation = 0.193, $p = 0.180$). ICV was negatively correlated with SPPB at baseline when analyzed in models with caudate and putamen volumes but not at follow-up. There was no significant correlation between putamen volume and measures of gait or balance ([Table 4](#)).

Shape Analysis

We applied the shape analysis method to the segmented caudate for the entire dataset. All results were scale-normalized for total ICV. The results presented are based on 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 ([Fig. 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, as seen in [Figure 4](#). The FDR-corrected p value for these deformations was 0.0017.^{29,59,60}

DISCUSSION

This study of older patients with WMHs has identified highly significant shape and volume deflation in areas of the left caudate nucleus that subserve motor portions of the frontostriatal circuits. This study expands on the results of a previous volumetric study that correlated caudate sizes with walking speed: Of note, this also failed to find a significant correlation with putamen volumes.²⁰ 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 disease,^{61–63} Alzheimer disease,^{64–67} progressive supranuclear palsy,^{33,68} corticobasal syndrome, and multiple system atrophy.^{69–71} Accordingly, morphometric (shape and volume) analysis of the caudate

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may be used as a biomarker that could aid in diagnostic clarity and as an additional marker to track the progression and treatment.⁷²

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.²⁹ 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 shape deflation in the posterolateral aspect of the left caudate. It has been proposed that a purpose of hemispheric lateralization is to encode constrained repertoires of cognition, emotion, and behavior within the left hemisphere.⁷³ Thus, the specific shape deflation of the left caudate may, in part, reflect the process of loss of the physical substrate of the entrained gait and balance behaviors under frontal control in frontostriatal circuits, although this explanation is speculative and would require replication before any conclusions could be drawn. A parsimonious explanation for lateralization may be that the corresponding morphologic change was not detected in the right caudate due to a Type 2 error caused by a low sample size. Equally, a chance positive finding in the left caudate is also possible; further replication will help to clarify this matter.

The lack of correlation between WMHs and striatal volumes and between caudate morphology and SPPB at follow-up may be partially explained by a survivor effect, that is, 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 artifact.

The possible mechanisms of caudate morphology alterations in WMHs are admittedly speculative. These mechanisms comprise possible deafferentation

of striatal inputs through direct anatomic disruption by WMHs,⁷² direct vascular damage to the caudate, and generalized cerebral atrophy as a result of WMHs. 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.

The correlation of SPPB with caudate morphology but not with putaminal morphology remains puzzling, given that the motor frontostriatal circuit connections are predominant in the putamen. A speculative explanation may be that altered caudate morphology impacts more significantly on prefrontal control of motor function (dorsolateral prefrontal, orbitofrontal [planning /executive aspects]), as opposed to putaminal atrophy more directly affecting motor (premotor and motor [direct motoric]) function. This has been observed in premotor/putaminal control of micturition.⁷⁴ Other studies have also failed to find any links between putaminal size or functioning with walking speed.^{20,75}

Although the focus of this study has been the correlation of clinical measures relevant to the motor frontostriatal circuit and altered striatal (caudate and putamen) morphology, we acknowledge that altered striatal morphology may be even more salient to the cognitive and emotional frontostriatal circuits arising from dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortex; altered executive functioning and planning may be a mediating link between caudate volumes and SPPB scores. We are currently investigating the correlation of striatal morphology with cognitive and behavioral clinical measures in this subset of LADIS.

Limitations of this study include the small sample size. Manual tracing is a time-intensive process, and the size of this study compares favorably to other shape analysis studies using similar methodology.^{36,50,51} Replication of these results, particularly the preponderance of left-sided deflation, will be useful to confirm the degree and laterality of shape deflation in individuals with WMHs. Analyzing 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.

In conclusion, we have demonstrated that the caudate nucleus may be a possible physical substrate for gait and balance in persons with WMHs. Related

research has highlighted that impaired gait, measured as walking speed, is associated with both progression to dementia and increased mortality.^{37,38} Thus, having identified a possible physical substrate and component of frontostriatal circuits implicated in cortical control of gait and balance is an advance, potentially further localizing the pathway of the neurons involved with coordinating these complex movements. 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 to similar datasets to determine if our findings may be replicated and extended by correlation with automated quantification of WMHs. 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.

This study was supported by the European Union (grant QLRT-2000-00446, Impact of age-related brain white matter hyperintensities on transition to disability in the elderly "Leukoaraiosis and Disability"). The Danish cohort study was supported, in part, by the Danish Velux Foundation. JCLL self-funded travel costs to assist in conduct of this research in Melbourne and Stockholm. This research has

made use of the SMILE medical imaging laboratory at Karolinska University Hospital and Karolinska Institute, Stockholm, Sweden. MS was supported by National Institutes of Health grant U54 EB005149, National Alliance for Medical Image Computing (NA-MIC).

MDM wrote the first draft of this paper and planned and performed the volumetric neuroimaging and statistical analyses as a component of his MPhil thesis. JCLL conceived and coordinated the overall project, cowrote the first draft, was principal supervisor for MDM's thesis, is primary investigator for the Australian National University, and is guarantor for the study. MW was a secondary supervisor for MDM and performed preprocessing and shape and ICV analysis. For the purposes of attribution of contribution, MM, JCLL, and MW assert they are equal first coauthors. 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 for LADIS. MGH (principal), HB, and 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.

A preliminary version of the data analysis was published as an abstract in the European Journal of Neurology.⁷⁶

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