Ventral striatal atrophy in Alzheimer's disease : exploring a potential new imaging marker for early dementia

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CHAPTER 4

Ventral striatal volume is associated with cognitive decline in older people: a population based MR-study

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ABSTRACT

Striatal degeneration may contribute to cognitive impairment in older people. Here, we examine the relation of atrophy of the striatum and its substructures to cognitive decline and dementia in study participants ranging from normal cognition to dementia. Data were from the prospective community-based Honolulu Asia Aging Study of Japanese American men born 1900–1919. Brain MRI (1.5T) was acquired on a stratified subsample ($n = 477$) that included four groups defined by cognitive status relative to the scan date: subjects without dementia ($n = 347$), subjects identified as demented 2–3 years prior to brain scanning ($n = 30$), at the time of scanning ($n = 58$), and 3–5 years after scanning ($n = 42$). Volumes of the striatum, including the accumbens, putamen, and caudate nucleus were automatically estimated from T1 MR images. Global cognitive function was measured with the CASI, at four exams spanning an 8-year interval. Trajectories of cognitive decline were estimated for each quartile of striatal volume using mixed models, controlling for demographic variables, measures of cerebrovascular damage, global brain atrophy, and hippocampal volume. Diagnosis of dementia before, during, and after brain scanning was associated with smaller volumes of nucleus accumbens and putamen, but not with caudate nucleus volume. Subjects in the lowest quartile of nucleus accumbens volume, both in the total sample and in the subjects not diagnosed with dementia during the study, had a significantly ($p < 0.0001$) steeper decline in cognitive performance compared to those in the highest quartile. In conclusion, volumes of the nucleus accumbens and putamen are closely associated with the occurrence of dementia and nucleus accumbens volume predicts cognitive decline in older people. These associations were found independent of the magnitude of other pivotal markers of cognitive decline, i.e., cerebrovascular damage and hippocampal volume. The present study suggests a role for the ventral striatum in the development of clinical dementia.

INTRODUCTION

The effects on cognition of degenerative changes in the medial temporal lobe have been widely studied. However, other structures atrophy with age as well and may also contribute significantly to late-life cognitive impairment. The striatum is of particular interest because it is part of two systems prone to degeneration in older people, the limbic and the fronto-striatal system. The striatum, is anatomically divided by the capsula interna into the caudate nucleus, putamen, and nucleus accumbens. The caudate nucleus and putamen are histologically similar and their functions are thought to be congruous with their somato-topographical connections to the neocortex. The caudate nucleus is part of circuits to the dorsolateral prefrontal cortex, lateral orbital prefrontal cortex, and posterior parietal cortex. The putamen is part of circuits with the motor cortex and the somatosensory cortex (Utter and Basso 2008). The nucleus accumbens, located ventro-anterior, differs histologically and functionally from the caudate nucleus and putamen. Its cells have smaller dimensions and are organized into subnuclei (Brockhaus 1942) The nucleus accumbens projects to, and receives input from, several limbic regions including the medial temporal lobe and anterior cingulate cortex. Functionally, the ventral striatum (nucleus accumbens and fundi of the caudate and putamen) participates in processing limbic information and the dorsal striatum (caudate nucleus and putamen) in sensorimotor information (Voorn et al. 2004).

The role of the striatum in cognitive processes has been studied in specific basal ganglia disorders and as part of basal forebrain atrophy in Alzheimer's disease (AD). In Huntington's disease (HD), atrophy of the caudate nucleus is associated with impaired executive functioning (Peinemann et al. 2005), bicaudate ratio with impaired language learning (De Diego-Balaguer et al. 2008), and smaller volumes of the putamen with worse psychomotor function (Jurgens et al. 2008). Apart from classical basal ganglia diseases, in a recent volumetric study it was observed that AD cases had significantly decreased volumes of the putamen compared to memory complainers (de Jong et al. 2008). Also, basal forebrain atrophy, including parts of the ventral striatum, was observed as long as 4.5 years before the development of clinical symptoms (Hall et al. 2008; Teipel et al. 2005). Despite the data on striatal volumes in dementia and basal ganglia diseases, little is known on the relation between striatal volume and cognitive decline in older people, varying from cognitively "normal" to impaired. Also not known is, whether other predictors of cognitive impairment, such as cerebrovascular damage, global brain atrophy, or hippocampal volume, mediate this relation or whether striatal volumes can improve our ability to predict cognitive decline in older people.

Here, we examine the relation of striatal volume to dementia and global cognitive function and decline, in the entire spectrum from cognitively healthy to demented older

subjects. We account for the presence and extent of several pivotal cerebrovascular damage parameters, hippocampal volume, and global brain atrophy. Subjects are from the well-characterized population based cohort of the Honolulu-Asia Aging Study (HAAS), who participated in an MRI substudy.

METHODS

Subjects and study design

Study subjects were older Japanese-American men, born between 1900–1919, who participated in the HAAS, an expansion of the Honolulu-Heart Program. A detailed description of the HAAS can be found elsewhere (White et al. 1996). In short, subjects were examined in 1991–1993 (baseline exam 4), and in three follow-up exams in 1994–1996 (exam 5), 1997–1999 (exam 6), and 1999–2000 (exam 7). The study was approved by the institutional review board of the Kuakini Medical Center and all respondents signed informed consent forms, except those who were demented, for whom an informed caretaker signed the consent

Assessment of cognitive function and dementia

During each exam all subjects were evaluated on cognitive performance and dementia cases were ascertained using a multistep procedure described elsewhere (White et al. 1996). Briefly, all subjects were screened with the Cognitive Ability Screening Instrument (CASI), which ranges in score from 0–100 (Teng et al. 1994). If subjects were screened positive, they were further evaluated with neuropsychological tests based on the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) battery (Morris et al. 1989), a neurologic exam, a proxy interview, and a diagnostic brain scan. Diagnoses were made in a consensus meeting in which the DSM-IIIR (American Psychiatric Association 1987) was applied for dementia, the NINCDS-ADRDA criteria (McKhann et al. 1984) for AD, and the CADDTC (California Alzheimer's Disease Diagnostic and Treatment Centers) criteria were applied for vascular dementia (VaD) (Chui et al. 1992). Depressive symptomology was measured in the first exam, using the Center for Epidemiologic Studies-Depression scale (CES-D) (Radloff 1977).

During the first follow-up examination (exam 5 1994–1996), whole brain Magnetic Resonance Imaging (MRI) was obtained on a stratified subsample of the total cohort. This subsample included a random sample of approximately 10% of the cognitively unimpaired participants and a selected over-sample of subjects with prevalent dementia (exam 4), subjects who scored poorly on cognitive testing but did not meet the criteria

for clinical dementia, subjects who possessed the apoliprotein E type $\varepsilon 4$ (APOE $\varepsilon 4$ positive), and subjects with clinical stroke (Scher et al. 2007). Successful brain MR images were obtained from 575 subjects.

MRI acquisition and readings

Magnetic Resonance Imaging (MRI) was performed using a 1.5 Tesla MRI system (GE Signa Advantage) in the Kuakini Medical Center in Honolulu. The protocol has been described (Scher et al. 2007) elsewhere. Standardized MR readings were performed by readers at the John Hopkins Reading Center, blinded to the subject's medical history or health status at the time of scanning. The number of cerebral infarcts, lacunar infarcts, subcortical infarcts, and white matter lesions was evaluated according to Cardiovascular Health Study protocols (Longstreth et al. 1998). lacunar infarcts were defined having a maximal diameter of 3.0–20 mm. For this analysis, subjects were grouped according to the number of lacunar infarcts identified (0 = no lacunar infarct, 1 = 1–2, and 2 = 3–5 lacunar infarcts). White matter hyperintensities (WMH) on proton density images were scored on a scale from 0–9 (0 = no white matter hyperintensities and 9 = all white matter involved), and for the analyses grouped as follows: 1 = 1–3, 2 = 4–6, and 3 = 7–9. As an indicator of global brain atrophy, bi-frontal distance was measured, defined on T1 weighted axial slices as the largest right-left distance between the lateral borders of the right and left frontal horns. Inner table distance, the right-left dimension between the inner tables of the skull, was measured at the same level of the bi-frontal distance, and used to correct the bi-frontal distance for intracranial volume (Korf et al. 2004). Manually measured intracranial volume (ICV) and hippocampal volume were acquired using a protocol described previously (Korf et al. 2004).

Segmentation of cortical and deep gray matter structures

The algorithm FIRST (FMRIB's Integrated Registration and Segmentation Tool), of the FSL package (Smith et al. 2004) was used for automated segmentation of left and right nucleus accumbens, caudate nucleus, and putamen (Patenaude et al. 2007). This software package has been evaluated relative to manual tracing methods and other automated segmentation tools and an average Dice coefficient for the striatum of 0.81 was estimated (Babalola et al. 2009; Morey et al. 2009). We used the *run_first_all*-script with default options, followed by a boundary correction with a z-score of 3. The output of FIRST consisted of non-normalized striatal volumes. Total striatal volume was calculated by adding up the volumes of the caudate nucleus, putamen, and nucleus accumbens.

Statistical analysis

Analytical sample

There were 549 scanned subjects with successfully processed ICV and hippocampal volume (Korf et al. 2006). For the present study we excluded subjects whose scans could not be successfully processed by FIRST ($n = 18$), those with subcortical infarcts > 20 mm ($n = 20$), which may cause large errors in the computed volumes, and those who were diagnosed with or developed types of dementia other than AD, VaD, or mixed type of AD/VaD dementia ($n = 34$). Our final study sample included 477 subjects. In general, the sample of prevalent and incident dementia cases in this analysis tended to be of mild severity and to have a slower rate of functional decline than cases who were not scanned. Of those who were not diagnosed with dementia during the study about 30% did not survive the total 8-year follow-up time.

Relation of striatal volumes and time of dementia diagnosis

Each striatal structure volume was normally distributed across the total study sample of 477 subjects. To assess whether the striatal volumes are smaller in subjects with dementia or will be diagnosed with dementia in the future, we assigned each subject to one of 4 exhaustive and mutually exclusive categories; 1) those who had been identified as demented at the first HAAS examination 4 (baseline prevalent dementia cases: $n = 30$), 2) those who were identified as demented at the first follow-up examination 5 (incident dementia cases when scanned $n = 59$), 3) those who were identified as demented in follow-up exams 6 or 7 ($n = 42$), and 4) all others ($n = 347$). For descriptive purposes, we will refer to these groups as: prevalent dementia, incident dementia, future dementia, and no dementia. The groups were compared on age, ICV, years of education, CASI-score, CES-D score, bi-frontal distance (corrected for inner table distance), hippocampal volume, and striatal volumes by one-way ANOVA, and compared on cerebral and lacunar infarcts, WMH, and presence of APOE $\varepsilon 4$ allele (yes = 34 and 44, no = all other genotypes) (Hixson and Powers 1991) by a Pearson's χ^2 test. Tests for linear association and pairwise comparison of striatal volumes between the study groups were performed.

Association of striatal volume and cognitive decline

For the longitudinal analyses the total sample was divided by quartile of volume of the striatum and substructures. Slopes from quartiles 1–3 were, separately, compared to the slope of the 4^{th} quartile (highest volume quartile). For this, a mixed model approach was used, with random intercepts and age at each of the four HAAS exams as the

time line. The mixed model accounted for varying time intervals between the exams of different subjects, differences in the number of measurements per subject (unbalanced data), and differences in age at baseline exam. Whether or not slopes differed across quartiles and over time, was tested with an interaction term of age (the time scale) and quartile of volume, compared with the 4th quartile. We adjusted for age at baseline exam, educational level, ICV, CES-D, lacunar infarcts, cerebral infarcts, WMH, bifrontal distance, presence of APOE $\varepsilon 4$ allele, and quartile of hippocampal volume. To check whether potential associations were not due to overrepresentation of demented subjects in the lower quartiles of volume, we reran the mixed model analysis on the no dementia group only ($n = 347$). Furthermore, we tested non-linearity in the cognitive trajectories by adding a quadratic term into the model. This term was not significant, and the linear model was more parsimonious without sacrificing the model fit (table 1), so we proceeded with the linear model.

Table 1: Test of linear vs. quadratic cognitive deterioration by quartile of striatal volume

Structure	Quartile	Full sample ($n = 477$)			No dementia sample ($n = 347$)		
		p	AIC linear	AIC quadratic	p	AIC linear	AIC quadratic
Striatum							
	I	0.83	2524	2530	0.03	1704	1706
	II	0.55	2744	2750	0.14	2254	2258
	III	0.07	2787	2789	< 0.01	2347	2347
	IV	< 0.01	2617	2616	< 0.01	2261	2257
Nucleus accumbens							
	I	0.93	2337	2343	0.02	1311	1311
	II	0.21	2766	2771	0.08	2338	2341
	III	0.30	2626	2631	0.52	2312	2318
	IV	0.52	2747	2753	0.29	2520	2525
Putamen							
	I	0.15	2519	2523	0.26	1662	1667
	II	0.23	2718	2722	0.28	2246	2251
	III	0.91	2811	2817	0.96	2241	2248
	IV	0.01	2616	2615	< 0.01	2375	2372
Caudate nucleus							
	I	0.12	2550	2554	0.03	2055	2057
	II	0.91	2808	2814	0.87	2088	2094
	III	0.62	2673	2679	0.47	2142	2148
	IV	0.71	2621	2627	0.31	2235	2240

AIC, Akaike's information criterion

RESULTS

Dementia and smaller striatal volumes

The dementia study groups differ in age ($p = 0.008$), CASI-score ($p < 0.0001$), volumes of the striatum ($p = 0.0004$), putamen and accumbens volume ($p < 0.0001$), all three indicators of cerebrovascular damage, i.e., cerebral and lacunar infarcts and WMH ($p < 0.0001$), bi-frontal distance ($p < 0.0001$), and hippocampal volume ($p < 0.0001$) (Table 2). Pairwise comparison between no dementia group and each of the three dementia groups shows significantly smaller volumes of the total striatum, nucleus accumbens, and putamen in the prevalent (all $p < 0.001$) and incident dementia ($p = 0.002$ for total striatum, $p < 0.001$ for nucleus accumbens, $p = 0.002$ for putamen) groups, and also smaller volumes of the accumbens in the future dementia group ($p = 0.003$). Comparison of prevalent dementia with future dementia shows larger volumes of the striatum ($p = 0.03$), putamen ($p = 0.01$), and accumbens ($p = 0.001$) in future dementia and comparison of prevalent dementia with incident dementia shows a larger volume of the accumbens ($p = 0.01$) in incident dementia.

Striatal volume and prediction of cognitive decline

Figure 1 summarizes the results of the longitudinal analysis, showing the predicted decline in CASI scores over time per quartile of striatal volume; spaghetti plots of a random sample of 10 subjects of each quartile are also included in the figure. There was a significant difference in decline of CASI score in quartile IV compared to quartile I for the nucleus accumbens (slope Δ (SE) $= -1.39$ (0.21), $p < 0.0001$). There were no significant differences between quartile IV and I for the putamen (slope Δ (SE) $= -0.33$ (0.22), $p = 0.13$), caudate nucleus (slope Δ (SE) $= -0.01$ (0.22), $p = 0.98$), or total striatal volume (slope Δ (SE) $= -0.34$ (0.21), $p = 0.11$).

A summary of the longitudinal analysis with the no-dementia group only (n=347) is shown in Figure 2. Similar to the analysis on the total sample, a significant slope difference between quartile IV and I for the nucleus accumbens was seen (slope Δ (SE) $= -1.39$ (0.21), $p < 0.0001$), but not for the putamen (slope Δ (SE) $= 0.14(0.15)$, $p = 0.47$), caudate nucleus (slope Δ (SE) $= 0.07$ (0.19), $p = 0.71$), or striatum (slope Δ(SE) $= -0.03$ (0.19), $p = 0.89$).

The overall significance of the models estimating the cognitive change slope by quartile of striatal volume are shown in Table 3; results were adjusted for age, education in years, gender, ICV, CES-D score, cerebral infarcts, lacunar infarcts, WMH, bi-frontal distance, and the presence of APOE $\varepsilon 4$ allele. For comparison we show similar analyses

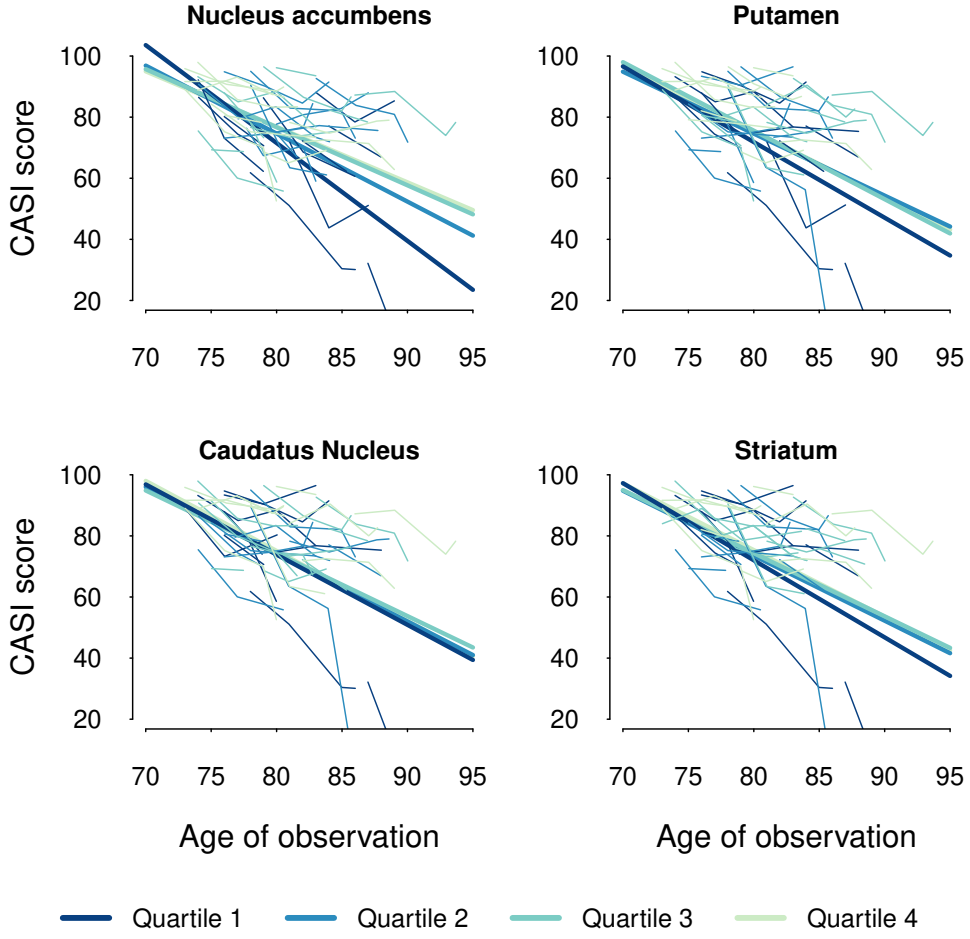
Table 2: Group characteristics according to identification of dementia relative to MRI: HAAS MRI subsample

Mean (SD) or %	No dementia ($n = 347$)	Future dementia ($n = 42$)	Incident dementia ($n = 58$)	Prevalent dementia ($n = 30$)	p ANOVA or χ^2
Age[a]	81.3 (5.0)	82.7 (5.1)	82.2 (4.9)	84.2 (5.1)	0.008
ICV	1436 (110)	1429 (116)	1440 (107)	1442 (100)	0.95
Education[a]	10.4 (3.0)	10.2 (3.1)	9.9 3(.2)	9.4 (2.6)	0.23
CASI-score	79.8 (9.8)	72.5 (8.5)	60.3 (16.2)	44.8 (19.8)	<.0001
CES-D score	3.7 (3.5)	4.5 (4.5)	4.3 (2.2)	3.0 (2.2)	0.32
Bi-frontal dist.	0.34 (0.03)	0.34 (0.04)	0.36 (0.03)	0.36 (0.03)	<.0001
Striatum	20.0 (2.3)	19.7 (2.6)	18.9 (3.3)	18.5 (2.0)	<.0004
Accumbens	1.38 (0.24)	1.26 (0.23)	1.21 (0.28)	1.08 (0.18)	<.0001
Putamen	9.7 (1.2)	9.4 (1.4)	9.1 (1.7)	8.7 (1.1)	<.0001
Caudate	8.9 (1.3)	9.0 (1.3)	8.6 (1.7)	8.7 (1.6)	0.30
Hippocampus	5.6 (0.8)	5.2 (0.7)	4.9 (0.9)	4.3 (0.9)	<.0001
APOE $\varepsilon 4$	37	29	26	30	<.0001
Cerebral infarcts					
0	93	93	88	81	
1	6	7	7	15	<.0001
$\geqslant 2$	1	0	5	4	
Lacunar infarcts					
0	58	61	47	46	
1–2	31	34	32	35	<.0001
3–5	10	5	21	19	
White Matter Hyperintensity					
0–3	75	71	60	46	
4–6	20	24	29	35	<.0001
7–9	4	5	10	7	

CASI, Cognitive Ability Screening Instrument; CES-D, Center for Epidemiologic Studies Depression.
a in years

for the hippocampus. We found the slope of the cognitive decline to significantly differ among the quartiles of hippocampal volume. Adjusting for the hippocampus quartiles, as well as other markers of brain pathology and cardiovascular disease risk factors, we found there was still a significant difference among quartiles of the nucleus accumbens ($p < 0.0001$). As shown in Figures 1 and 2, this largely reflected the steeper slope in decline of the 4th quartile relative to the first quartiles. Volumes of the total striatum, caudate nucleus, and putamen, were not associated with cognitive decline.

Figure 1: Predicted CASI-score over time per quartile of striatal volume



CASI Score, predicted mean CASI (Cognitive Ability Screening Instrument) score over 8-year interval, adjusted for age, age at baseline, educational level, ICV, CES-D score, lacunar infarcts, cerebral infarcts, WMH, bi-frontal distance/inner table distance, APOE $\varepsilon 4$ allele, hippocampal volume quartiles.

DISCUSSION

The present study assessed the relation of the volume of the striatum and its substructures and global cognitive performance in the entire spectrum of cognitively healthy to

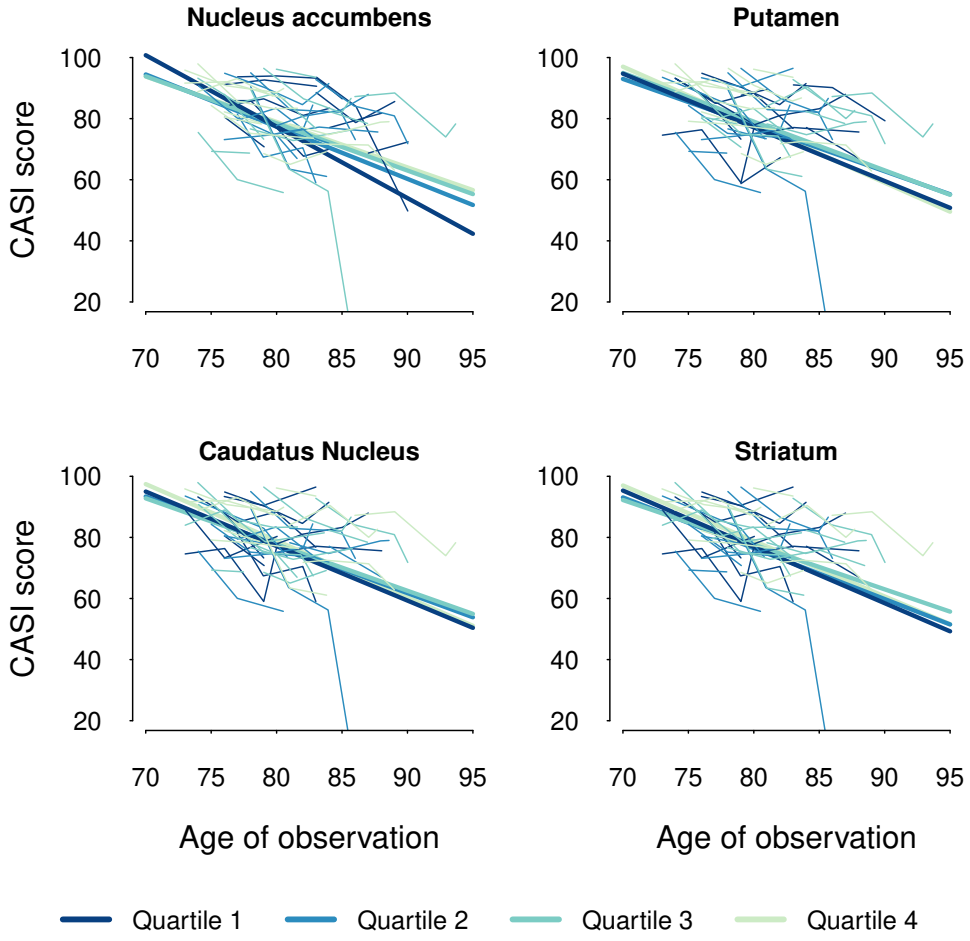
Table 3: Volume of striatum and hippocampus in predicting cognitive decline

		Full sample ($n = 477$)		No dementia sample ($n = 347$)	
Model	Effects[a]	F-value	p-value	F-value	p-value
Hippocampus (Hipp)					
	Hipp quartiles	9.8	<.0001	5.4	0.001
	Age × Hipp quartiles	12.8	<.0001	6.4	0.0003
Nucleus accumbens (NAcc)					
	NAcc quartiles	14.9	<.0001	6.5	0.0002
	Hipp quartiles	12.7	<.0001	2.9	0.04
	Age × NAcc quartiles	17.1	<.0001	7.3	<.0001
Caudate nucleus (CN)					
	CN quartiles	0.6	0.65	1.5	0.22
	Hipp quartiles	19.5	<.0001	3.8	0.01
	Age × CN quartiles	0.5	0.65	1.5	0.22
Putamen (Put)					
	Put quartiles	1.1	0.36	1.6	0.19
	Hipp quartiles	15.8	<.0001	3.7	0.01
	Age × Put quartiles	1.4	0.25	1.7	0.16
Striatum (Str)					
	Str quartiles	1.4	0.23	1.7	0.16
	Hipp quartiles	16.2	<.0001	3.2	0.02
	Age × Str quartiles	1.7	0.16	1.7	0.16

[a] Separate effects of age, education in years, gender, ICV, CES-D score, cerebral infarcts, lacunar infarcts, WMH, bi-frontal distance, and presence of APOE $\varepsilon 4$ allele are not displayed.

demented older people. We found volumes of the nucleus accumbens (as they were at the time of scanning) to be lower in subjects diagnosed with dementia 2–3 years prior to, at the time of, and 3–5 years after, the brain MR-scan was acquired. Total volumes of the striatum, and separately the putamen were smaller in subjects diagnosed with dementia prior to and at the time of scanning. Furthermore, we found that quartiles of nucleus accumbens volume significantly differed in the rate of cognitive decline both in the total sample and the sample of subjects who were not identified with dementia during the course of the study. Specifically, subjects in the lowest quartile of accumbens volume had a significantly steeper slope of cognitive decline measured over an 8-year period, independent of global brain atrophy, hippocampal volume, presence of APOE $\varepsilon 4$ allele, or the amount of cerebrovascular damage. Thus, our findings suggest, the ventro-anterior striatal substructure, the nucleus accumbens, is a significant indicator for cognitive decline. Prospective studies of people who are not demented at baseline are

Figure 2: Predicted CASI-score over time per quartile of striatal volume (non-demented people only)



CASI Score, Predicted mean CASI (Cognitive Ability Screening Instrument) score over 8-year interval, adjusted for age, age at baseline, educational level, ICV, CES-D score, lacunar infarcts, cerebral infarcts, WMH, bi-frontal distance/inner table distance, APOE $\varepsilon 4$ allele, hippocampal volume quartiles.

needed to investigate whether atrophy in the accumbens is a marker for some specific cognitive trajectories, such as a fast or steep decline.

These findings contribute to our understanding of the stages of cognitive decline.

The striatum is the largest structure of the basal ganglia, both hemispheres together measuring approximately 20 cm^3, and is regarded as an input nucleus for cortical projections (Utter and Basso 2008). Several studies have described the topographical arrangement of the human striatum in distinct, sometimes partially overlapping, circuits serving motor and cognitive functions (Alexander, DeLong, and Strick 1986; Draganski et al. 2008; Leh et al. 2007; Middleton and Strick 2000). Of interest here is the anterior cingulate loop described by Alexander (Grahn, Parkinson, and Owen 2008). This loop includes the ventral striatum, which receives input from the anterior cingulate cortex, hippocampal cortex, entorhinal cortex, and the superior and inferior temporal gyri. The ventral striatum consists of the nucleus accumbens, fundi of the caudate and putamen, and olfactory stria (Brockhaus 1942). Since the accumbens is part of the limbic circuit, we had postulated that it shared the limbic circuits' vulnerability to degenerate during the dementing process. In our study the nucleus accumbens was significantly smaller in subjects with dementia and subjects who were going to become demented. Volume of the accumbens contributed independently to the model explaining cognitive decline in older people. This contribution was independent of more generally used indicators of cognitive decline hippocampal volume, global brain atrophy, and cerebrovascular damage parameters. The results were similar in the sample not diagnosed with dementia during the 8-year follow-up period.

Pathological studies of the striatum in AD have shown that in particular, the cholinergic interneurons contain neurofibrillary tangles and are lost in the ventral striatum, which may be a potential explanation for our findings (Lehéricy et al. 1989; Selden, Mesulam, and Geula 1994). Studies are needed to determine the processes leading to smaller accumbens volumes in older (demented) subjects, as well as the temporal relation with other neurodegenerative changes in the brain. It has been postulated that the nucleus accumbens plays a pivotal role in memory and learning processes (Goldenberg et al. 1999; Gonzalez-Burgos and Feria-Velasco 2008; Graybiel 2008), possibly explaining the association of smaller volumes with more rapid cognitive decline. However, the nucleus accumbens is part of the intricate basal forebrain system and detailed knowledge of how this system facilitates cognitive functioning is still lacking, as is our understanding of the precise role of the nucleus accumbens (Alheid and Heimer 1988).

We also found associations between the volume of the putamen and diagnosis of dementia, although not with cognitive decline. Previously, smaller volumes of the putamen were observed in people with dementia (de Jong et al. 2008). It is possible that decrease in the volume of the putamen becomes evident in more progressed stages of dementia and not in preclinical stages, which may explain the association with dementia but not with prediction of cognitive decline. Contrary to expectation, the caudate nucleus was not associated with dementia or cognitive decline in our study, whereas other studies

have pointed out the occurrence of degeneration of the head of the caudate nucleus in AD (Frisoni et al. 2002; Karas et al. 2003; Rombouts et al. 2000). Possibly, this inconsistency reflects differences in where the borders were placed between the nucleus accumbens and the caudate nucleus, but it may also be that the volume differences for the caudate nucleus are too small to detect by our method.

A major advantage of our study was the highly reproducible separate segmentation of caudate, putamen, and nucleus accumbens, and that we were able to study these substructures in association with longitudinal changes in cognition and dementia status. However, the limitations in the extent to which the "borders" between the striatal substructures can be identified, need to be taken into account when interpreting the data. The borders of these structures are better viewed as transition zones with overlapping functions. Currently, it is not possible to delineate substructures based on a functional division, because of overlapping functional zones and low contrast within the neostriatal structure on MR. Finally, the striatal volume calculations were based on the delineation of the surface or boundary voxels, which does not account for within structure changes, including lacunar infarcts, iron accumulation, and enlarged Virchow Robin spaces in the deep gray matter. This may lead to a potential overestimation of striatal volume. To minimize this effect we excluded subjects with large infarcts ($>$ 20mm) in the deep gray matter region, and controlled for the presence of lacunar infarcts.

CONCLUSION

The present study shows that the volume of the nucleus accumbens is closely associated with cognitive performance in older subjects, independent of other common brain changes in older persons. Additional studies are needed to further determine the clinical significance of atrophy in the striatum in community-based individuals

BIBLIOGRAPHY

Alexander GE, DeLong MR, and Strick PL (1986). "Parallel organization of functionally segregated circuits linking basal ganglia and cortex". *Annu. Rev. Neurosci.* 9: 357–381. DOI: 10.1146/annurev.ne.09.030186.002041.

Alheid GF and Heimer L (1988). "New perspectives in basal forebrain organization of special relevance for neuropsychiatric disorders: the striatopallidal, amygdaloid, and corticopetal components of substantia innominata". *Neuroscience* 27 (1): 1–39. DOI: 10.1016/0306-4522(88)90217-5.

American Psychiatric Association (1987). *Diagnostic and statistical manual of mental disorders DSM-III-R (3rd ed. revised)*. Washington, DC: Authors.

Babalola KO, Patenaude B, Aljabar P, Schnabel J, Kennedy D, et al. (2009). "An evaluation of four automatic methods of segmenting the subcortical structures in the brain". *Neuroimage* 47 (4): 1435–1447. DOI: 10.1016/j.neuroimage.2009.05.029.

Brockhaus H (1942). "Zur feineren anatomie des septum und des striatum". *Journal für Psychologie und Neurologie* 5 (1): 56. URL: http://www.thehumanbrain.info/database/db_literature/brockhaus_striatum1942d.pdf (visited on 09/10/2018).

Chui HC, Victoroff JI, Margolin D, Jagust W, Shankle R, and Katzman R (1992). "Criteria for the diagnosis of ischemic vascular dementia proposed by the State of California Alzheimer's Disease Diagnostic and Treatment Centers". *Neurology* 42 (3): 473–480. DOI: 10.1212/WNL.42.3.473.

De Diego-Balaguer R, Couette M, Dolbeau G, Durr A, Youssov K, and Bachoud-Levi AC (2008). "Striatal degeneration impairs language learning: evidence from Huntington's disease". *Brain* 131 (11): 2870–2881. DOI: 10.1093/brain/awn242.

de Jong LW, van der Hiele K, Veer IM, Houwing JJ, Westendorp RG, et al. (2008). "Strongly reduced volumes of putamen and thalamus in Alzheimer's disease: an MRI study". *Brain* 131 (12): 3277–3285. DOI: 10.1093/brain/awn278.

Draganski B, Kherif F, Kloppel S, Cook PA, Alexander DC, et al. (2008). "Evidence for segregated and integrative connectivity patterns in the human Basal Ganglia". *J. Neurosci.* 28 (28): 7143–7152. DOI: 10.1523/JNEUROSCI.1486-08.2008.

Frisoni GB, Testa C, Zorzan A, Sabattoli F, Beltramello A, et al. (2002). "Detection of grey matter loss in mild Alzheimer's disease with voxel based morphometry". *J. Neurol. Neurosurg. Psychiatr.* 73 (6): 657–664. DOI: 10.1136/jnnp.73.6.657.

Goldenberg G, Schuri U, Grömminger O, and Arnold U (1999). "Basal forebrain amnesia: does the nucleus accumbens contribute to human memory?" *J. Neurol. Neurosurg. Psychiatr.* 67 (2): 163–168. DOI: 10.1136/jnnp.67.2.163.

Gonzalez-Burgos I and Feria-Velasco A (2008). "Serotonin/dopamine interaction in memory formation". *Prog. Brain Res.* 172: 603–623. DOI: 10.1016/S0079-6123(08)00928-X.

Grahn JA, Parkinson JA, and Owen AM (2008). "The cognitive functions of the caudate nucleus". *Prog. Neurobiol.* 86 (3): 141–155. DOI: 10.1016/j.pneurobio.2008.09.004.

Graybiel AM (2008). "Habits, rituals, and the evaluative brain". *Annu. Rev. Neurosci.* 31: 359–387. DOI: 10.1146/annurev.neuro.29.051605.112851.

Hall AM, Moore RY, Lopez OL, Kuller L, and Becker JT (2008). "Basal forebrain atrophy is a presymptomatic marker for Alzheimer's disease". *Alzheimers. Dement.* 4 (4): 271–279. DOI: 10.1016/j.jalz.2008.04.005.

Hixson JE and Powers PK (1991). "Restriction isotyping of human apolipoprotein A-IV: rapid typing of known isoforms and detection of a new isoform that deletes a conserved repeat". *J. Lipid Res.* 32 (9): 1529–1535. URL: http://www.jlr.org/content/32/9/1529.full.pdf (visited on 09/10/2018).

Jurgens CK, van de Wiel L, van Es AC, Grimbergen YM, Witjes-Ane MN, et al. (2008). "Basal ganglia volume and clinical correlates in 'preclinical' Huntington's disease". *J. Neurol.* 255 (11): 1785–1791. DOI: 10.1007/s00415-008-0050-4.

Karas GB, Burton EJ, Rombouts SA, van Schijndel RA, O'Brien JT, et al. (2003). "A comprehensive study of gray matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry". *Neuroimage* 18 (4): 895–907. DOI: 10.1016/S1053-8119(03)00041-7.

Korf ESC, White LR, Scheltens P, and Launer LJ (2004). "Midlife blood pressure and the risk of hippocampal atrophy: the Honolulu Asia Aging Study". *Hypertension* 44 (1): 29–34. DOI: 10.1161/01.HYP.0000132475.32317.bb.

Korf ESC, White LR, Scheltens P, and Launer LJ (2006). "Brain aging in very old men with type 2 diabetes: the Honolulu-Asia Aging Study". *Diabetes Care* 29 (10): 2268–2274. DOI: 10.2337/dc06-0243.

Leh SE, Ptito A, Chakravarty MM, and Strafella AP (2007). "Fronto-striatal connections in the human brain: a probabilistic diffusion tractography study". *Neurosci. Lett.* 419 (2): 113–118. DOI: 10.1016/j.neulet.2007.04.049.

Lehéricy S, Hirsch EC, Cervera P, Hersh LB, Hauw JJ, et al. (1989). "Selective loss of cholinergic neurons in the ventral striatum of patients with Alzheimer disease". *Proc. Natl. Acad. Sci. U.S.A.* 86 (21): 8580–8584. URL: http://www.pnas.org/content/pnas/86/21/8580.full.pdf (visited on 09/10/2018).

Longstreth WT, Bernick C, Manolio TA, Bryan N, Jungreis CA, and Price TR (1998). "Lacunar infarcts defined by magnetic resonance imaging of 3660 elderly people: the Cardiovascular Health Study". *Arch. Neurol.* 55 (9): 1217–1225. URL: https://jamanetwork.com/journals/jamaneurology/fullarticle/774257 (visited on 09/10/2018).

McKhann G, Drachman D, Folstein M, Katzman R, Price D, and Stadlan EM (1984). "Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease". *Neurology* 34 (7): 939–944. DOI: 10.1212/WNL.34.7.939.

Middleton FA and Strick PL (2000). "Basal ganglia and cerebellar loops: motor and cognitive circuits". *Brain Res. Brain Res. Rev.* 31 (2-3): 236–250. DOI: 10.1016/S0165-0173(99)00040-5.

Morey RA, Petty CM, Xu Y, Hayes JP, Wagner HR, et al. (2009). "A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes". *Neuroimage* 45 (3): 855–866. DOI: 10.1016/j.neuroimage.2008.12.033.

Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, et al. (1989). "The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease". *Neurology* 39 (9): 1159–1165. DOI: 10.1212/WNL.39.9.1159.

Patenaude B, Smith SM, Kennedy DN, and Jenkinson M (2007). *Bayesian shape and appearance models, FMRIB technical report TR07BP1*. London. URL: https://www.fmrib.ox.ac.uk/datasets/techrep/tr07bp1/tr07bp1.pdf (visited on 09/10/2018).

Peinemann A, Schuller S, Pohl C, Jahn T, Weindl A, and Kassubek J (2005). "Executive dysfunction in early stages of Huntington's disease is associated with striatal and insular atrophy: a neuropsychological and voxel-based morphometric study". *J. Neurol. Sci.* 239 (1): 11–19. DOI: 10.1016/j.jns.2005.07.007.

Radloff LS (1977). "The CES-D scale: A self-report depression scale for research in the general population". *Appl. Psychol. Meas.* 1 (3): 385–401. DOI: 10.1177/014662167700100306.

Rombouts SA, Barkhof F, Witter MP, and Scheltens P (2000). "Unbiased whole-brain analysis of gray matter loss in Alzheimer's disease". *Neurosci. Lett.* 285 (3): 231–233. DOI: 10.1016/S0304-3940(00)01067-3.

Scher AI, Xu Y, Korf ESC, White LR, Scheltens P, et al. (2007). "Hippocampal shape analysis in Alzheimer's disease: a population-based study". *Neuroimage* 36 (1): 8–18. DOI: 10.1016/j.neuroimage.2006.12.036.

Selden N, Mesulam MM, and Geula C (1994). "Human striatum: the distribution of neurofibrillary tangles in Alzheimer's disease". *Brain Res.* 648 (2): 327–331. DOI: 10.1016/0006-8993(94)91136-3.

Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, et al. (2004). "Advances in functional and structural MR image analysis and implementation as FSL". *Neuroimage* 23 Suppl 1: S208–219. DOI: 10.1016/j.neuroimage.2004.07.051.

Teipel SJ, Flatz WH, Heinsen H, Bokde AL, Schoenberg SO, et al. (2005). "Measurement of basal forebrain atrophy in Alzheimer's disease using MRI". *Brain* 128 (11): 2626–2644. DOI: 10.1093/brain/awh589.

Teng EL, Hasegawa K, Homma A, Imai Y, Larson E, et al. (1994). "The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia". *Int. Psychogeriatr.* 6 (1): 45–58. DOI: 10.1017/S1041610294001602.

Utter AA and Basso MA (2008). "The basal ganglia: an overview of circuits and function". *Neurosci. Biobehav. Rev.* 32 (3): 333–342. DOI: 10.1016/j.neubiorev.2006.11.003.

Voorn P, Vanderschuren LJ, Groenewegen HJ, Robbins TW, and Pennartz CM (2004). "Putting a spin on the dorsal-ventral divide of the striatum". *Trends Neurosci.* 27 (8): 468–474. DOI: 10.1016/j.tins.2004.06.006.

White L, Petrovitch H, Ross GW, Masaki KH, Abbott RD, et al. (1996). "Prevalence of dementia in older Japanese-American men in Hawaii: The Honolulu-Asia Aging Study". *JAMA-J. Am. Med. Assoc.* 276 (12): 955–960. DOI: 10.1001/jama.1996.03540120033030.