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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 degeneration of the striatum and substructures to cognitive decline and dementia in subjects with a wide range of cognitive function. Data are 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 sub-sample (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 cerebro-vascular damage, global brain atrophy, and hippocampal volume. Diagnosis of dementia before, during, and after brain scanning was associated with smaller volumes of n. accumbens and putamen, but not with caudate nucleus volume. Subjects in the lowest quartile of n. accumbens, 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 n. accumbens and putamen are closely associated with the occurrence of dementia and n. 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. cerebro-vascular damage and hippocampal volume. The present study suggests a role for the ventral striatum in the development of clinical dementia.

Keywords

MRI; volumetry; striatum; ventral striatum; nucleus accumbens; putamen; caudate nucleus; dementia

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1. 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, depicted in figure 1, 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 neo-cortex. 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 motorcortex and the somato-sensory 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 organised into subnuclei (Brockhaus, 1942). The n. accumbens projects to, and receives input from, several limbic regions including the medial temporal lobe and anterior cingulate cortex. Functionally, the ventral striatum (n. 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 cerebro-vascular damage, global brain atrophy, or hippocampal volume, mediate this relationship 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 cerebro-vascular 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 sub-study.

2. Methods

2.1 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

IRB of the Kuakini Hospital 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 multi-step 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 neuro-psychological tests based on the CERAD 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-III-R was applied for dementia, the NINDS-ADRDA-criteria (McKhann et al., 1984) for AD, and the CADDTC-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 LS, 1977).

During the first follow-up examination (exam 5 1994–1996), whole brain Magnetic Resonance Imaging (MRI) was obtained on a stratified sub-sample of the total cohort. This sub-sample included a random sample of approximately 10 percent 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 apolipoprotein E type $\epsilon 4$ (ApoE $\epsilon 4$ positive), and subjects with clinical stroke (Scher et al., 2007). Successful brain MR images were obtained from 575 subjects.

2.2 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). 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, lacunes, 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 lacune identified (0= no lacunar infarcts, 1=1–2, and 2=3–5 lacunes). 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, we measured the bi-frontal distance, on 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 intra cranial volume (Korf et al., 2004). Manually measured intra cranial volume (ICV) and hippocampal volume were acquired using a protocol described previously (Korf et al., 2004).

2.3 Segmentation of cortical and deep grey 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, 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 n. accumbens.

2.4 Statistical analysis

Analytical sample; demented and not demented cases—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.

Comparison striatal volumes by time of dementia diagnosis relative to brain scan—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, bifrontal distance (corrected for inner table distance), hippocampal volume, and striatal volumes by one-way ANOVA, and compared on presence of cerebral and lacunar infarcts, WMH grade, and presence of ApoE 4 allele (yes = 34 and 44, no=all other genotypes) (Hixson and Powers, 1991) by a Pearson's chi square test. Tests for linear association and pairwise comparison of striatal volumes between the study groups were performed.

Assessment of the association of striatal volume to cognitive decline—For the longitudinal analyses the total sample was divided by quartile of volume of the striatum and sub-structures. Slopes from quartiles 1 – 3 were, separately, compared to the slope of the 4th 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 to the 4th quartile. We adjusted for age at baseline exam, educational level, ICV, CES-D, lacune grade, presence of cerebral infarcts, WMH grade, bifrontal distance, presence of ApoE 4 allele, and quartiles 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 (supplementary table 1), so we proceeded with the linear model.

3. Results

3.1 Dementia and smaller striatal volumes

The dementia study groups differ in age ($p = 0.0083$), CASI-score ($p < 0.0001$), volumes of the striatum ($p = 0.0004$), putamen and accumbens volume ($p < 0.0001$), all three indicators of cerebro-vascular damage, i.e. the presence of cerebral and lacunar infarcts and WMH grade ($p < 0.0001$), bi-frontal distance ($p < 0.0001$), and hippocampal volume ($p < 0.0001$) (Table 1). Pairwise comparison between no dementia group and each of the three dementia groups shows significantly smaller volumes of the total striatum, n. accumbens, and putamen in the prevalent (all $p < 0.001$) and incident dementia ($p = 0.002$ for total striatum, $p < 0.001$ for n. 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 ($p = 0.032$), putamen ($p = 0.012$), and accumbens ($p = 0.001$) in future dementia and comparison of prevalent dementia with incident dementia shows larger a volume of the accumbens ($p = 0.014$) in incident dementia.

3.2 Striatal volume and prediction of cognitive decline

Figure 2 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 is a significant difference in decline of CASI score in quartile IV compared to quartile I for the n. accumbens (slope $\Delta \pm SE = -1.39 \pm 0.21$, p -value < 0.0001). There are no significant differences between quartile IV and I for the putamen (slope $\Delta \pm SE = -0.33 \pm 0.22$, p -value $= 0.13$), caudate nucleus (slope $\Delta \pm SE = -0.01 \pm 0.22$, p -value $= 0.98$), or total striatal volume (slope $\Delta \pm SE = -0.34 \pm 0.21$, p -value $= 0.11$).

A summary of the longitudinal analysis with the no-dementia group only ($n=347$) is shown in Figure 3. Similar to the analysis on the total sample, a significant slope difference between quartile IV and I for the n. accumbens is seen (slope $\Delta \pm SE = -1.39 \pm 0.21$, p -value < 0.0001), but not for the putamen (slope $\Delta \pm SE = 0.14 \pm 0.15$, p -value $= 0.47$), caudate nucleus (slope $\Delta \pm SE = 0.07 \pm 0.19$, p -value $= 0.71$), or striatum (slope $\Delta \pm SE = -0.03 \pm 0.19$, p -value $= 0.89$).

The overall significance of the models estimating the cognitive change slope by quartile of striatal volume are shown in Table 2; results are adjusted for age, education in years, gender, ICV, CES_D score, presence of cerebral infarcts, lacune grade, WMH grade, bi-frontal distance, and the presence of ApoE 4 allele. For comparison we show similar analyses for the hippocampus. We find overall the slope of the cognitive decline to significantly differ among the quartiles of the hippocampus volume. Adjusting for the hippocampus quartiles, as well as other markers of brain pathology and CVD risk factors, we find there is still a significant difference among quartiles of the n. accumbens ($p < 0.0001$). As shown in Figures 2 and 3, this largely reflects the steeper slope in decline of the 4th quartile relative to the first quartiles. Volumes of the total striatum, caudate nucleus, and putamen, are not associated with cognitive decline.

4. Discussion

The present study assessed the relation of the volume of the striatum and its sub-structures and global cognitive performance in the entire spectrum of cognitively healthy to demented older people. We found volumes of the n. 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 n. 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 4 allele, or the amount of cerebrovascular damage. Thus, our findings suggest, the ventro-anterior striatal sub-structure, the n. accumbens, is a significant indicator for cognitive decline. Prospective studies of people who are not demented at baseline are 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 cm³, 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 et al., 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 et al., 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 n. 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 n. 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 cerebro-vascular 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 (Lehericy et al., 1989; Selden et al., 1994). Studies are needed to determine the processes leading to smaller accumbens volumes in older (demented) subjects, as well as the temporal relationship with other neurodegenerative changes in the brain. It has been postulated that the n. 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 n. 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 n. 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 n. 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 n. accumbens, and that we were able to study these sub-structures in association with longitudinal changes in cognition and dementia status. However, the limitations in the extent to which the “borders” between the striatal sub-structures 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 sub-structures based on a functional division, because of overlapping functional zones and low contrast within the neo-striatal 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 grey matter. This may lead to a potential over-estimation of striatal volume. To minimize this effect we excluded subjects with large infarcts (>20mm) in the deep grey matter region, and controlled for the presence of lacunar infarcts.

5 Conclusion

The present study shows that the volume of the n. 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 of community-based individuals

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Anatomical and functional division of striatum

Presented is a 3D model of the striatum, based on the segmentation of those voxels that were labeled striatum in > 20% of the segmentation masks. Model was created with GAMES (Ferrarini et al., 2007) and displayed here for explanatory purposes.

Figure 2. Predicted CASI-score over time per quartile of striatal volume

X-axis: Age = Age of observation

Y-axis: 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, lacunes grade, presence of cerebral infarcts, WMH grade, bi-frontal distance/invertible distance, ApoE 4 allele, hippocampal volume quartiles.

Spaghetti plots of a random sample of 10 subjects per striatal volume quartile are displayed.

Figure 3. Predicted CASI-score over time per quartile of striatal volume (non-demented people only)

X-axis: Age = Age of observation

Y-axis: 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, lacunes grade, presence of cerebral infarcts, WMH grade, bi-frontal distance/invertable distance, ApoE 4 allele, hippocampal volume quartiles.

Spaghetti plots of a random sample of 10 subjects per striatal volume quartile are displayed.

Table 1

Group characteristics according to identification of dementia relative to MRI^a: HAAS MRI sub-sample

	No dementia (n=347)	Future dementia (n=42)	Incident dementia (n=58)	Prevalent dementia (n=30)	p-value ^b
Age [years]	81.3 (5.0)	82.7 (5.1)	82.2 (4.9)	84.2 (5.1)	0.0082
ICV [cm ³]	1436 (110)	1429 (116)	1440 (107)	1442 (100)	0.9525
Education [years]	10.4 (3.0)	10.2 (3.1)	9.9 (3.2)	9.4 (2.6)	0.2293
CASI-score	79.8 (9.8)	72.5 (8.5)	60.3 (16.2)	44.8 (19.8)	< 0.0001
CES-D score	3.7 (3.5)	4.5 (4.5)	4.3 (2.2)	3.0 (2.2)	0.3172
Bi-frontal distance	0.34 (0.03)	0.34 (0.04)	0.36 (0.03)	0.36 (0.03)	< 0.0001
Striatum [cm ³]	20.0 (2.3)	19.7 (2.6)	18.9 (3.3)	18.5 (2.0)	< 0.0004
Accumbens [cm ³]	1.38 (0.24)	1.26 (0.23)	1.21 (0.28)	1.08 (0.18)	< 0.0001
Putamen [cm ³]	9.7 (1.2)	9.4 (1.4)	9.1 (1.7)	8.7 (1.1)	< 0.0001
Caudate nucleus [cm ³]	8.9 (1.3)	9.0 (1.3)	8.6 (1.7)	8.7 (1.6)	0.2972
Hippocampus [cm ³]	5.6 (0.8)	5.2 (0.7)	4.9 (0.9)	4.3 (0.9)	< 0.0001
Apolipoprotein E ε4 genotype [%]	37	29	26	30	< 0.0001
Cerebral infarcts [%]					
0 infarcts	93	93	88	81	
1 infarcts	6	7	7	15	> 0.0001
2 infarcts	1	0	5	4	
Lacune grade [%]					
0 lacunes	58	61	47	46	
1–2 lacunes	31	34	32	35	> 0.0001
3–5 lacunes	10	5	21	19	
WMH grade [%]					
0–3	75	71	60	46	
4–6	20	24	29	35	> 0.0001
7–9	4	5	10	7	

Abbreviations: MRI = Magnetic Resonance Imaging; ICV = Intra Cranial Volume; CASI-score = Cognitive Ability Screening Instrument - score; CES-D score = Center for Epidemiologic Studies Depression score; WMH grade = White Matter Hyperintensity grade.

^a All values are means with standard deviations in parenthesis, unless otherwise noted.

b *p-values* are for the overall association of the characteristics to study group.

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Table 2
Effects of volume of striatum and hippocampus in model for prediction of cognitive decline

Model:	Effects ^a :	Full sample (n=477)		No dementia sample (n=347)	
		F-value	p-value	F-value	p-value
Hippocampus	HIPP quartiles	9.8	< 0.0001	5.4	0.0010
	Age * HIPP quartiles	12.8	< 0.0001	6.4	0.0003
N. accumbens	NACC quartiles	14.9	< 0.0001	6.5	0.0002
	HIPP quartiles	12.7	< 0.0001	2.9	0.0352
Caudate nucleus	Age * NACC quartiles	17.1	< 0.0001	7.3	< 0.0001
	CN quartiles	0.6	0.6460	1.5	0.2186
Putamen	Hipp quartiles	19.5	< 0.0001	3.8	0.0101
	Age * CN quartiles	0.5	0.6512	1.5	0.2228
Striatum	PUT quartiles	1.1	0.3644	1.6	0.1858
	HIPP quartiles	15.8	< 0.0001	3.7	0.0123
Striatum	Age * PUT quartiles	1.4	0.2540	1.7	0.1631
	STR quartiles	1.4	0.2308	1.7	0.1607
Striatum	HIPP quartiles	16.2	< 0.0001	3.2	0.0227
	Age * STR quartiles	1.7	0.1577	1.7	0.1587

Abbreviations: HIPP = hippocampus; NACC = nucleus accumbens; CN = caudate nucleus; PUT = putamen; STR = striatum.

^a Separate effects of age, education in years, gender, ICV, CES_D score, presence of cerebral infarcts, lacune grade, WMH grade, bi-frontal distance, and presence of ApoE 4 allele are not displayed.