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

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CHAPTER 5

Different susceptibility of medial temporal lobe and basal ganglia atrophy rates to vascular risk factors

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ABSTRACT

Atrophy of medial temporal lobe (MTL) and basal ganglia (BG) are characteristic of various neurodegenerative diseases in older people. In search of potentially modifiable factors that lead to atrophy in these structures, we studied the association of vascular risk factors to atrophy of MTL and BG in 368 non-demented men and women (born 1907–1935) who participated in the Age, Gene/Environment, Susceptibility-Reykjavik Study. A fully automated segmentation pipeline estimated volumes of MTL and BG from whole brain MRI performed at baseline and 2.4 years later. Linear regression models showed higher systolic and diastolic blood pressures and the presence of APOE ε4 were independently associated with increased atrophy of MTL but no association of vascular risk factors with atrophy of BG was found. The different susceptibility of MTL and BG atrophy to the presence of vascular risk factors suggests the relatively preserved perfusion of BG when vascular risk factors are present.

INTRODUCTION

Several vascular risk factors are associated with the development of cognitive decline and Alzheimer's disease in the ageing population, among others obesity, high blood pressure, and high serum cholesterol (Debette et al. 2011; EL Kivipelto M.H et al. 2001; Tolppanen et al. 2012). A large body of literature is available that shows great overlap between these risk factors for cognitive decline and Alzheimer's disease on the one hand and risk factors for atrophy of brain structures on the other hand. Of particular interest are risk factors for pathological changes in the medial temporal lobe (MTL) and the basal ganglia and thalamus (BG), since pathological changes in these structures have been associated with an increased risk for Alzheimer's disease and cognitive decline in older people (Barnes et al. 2009; de Jong, van der Hiele, et al. 2008; de Jong, Wang, et al. 2012). Because of the growing ageing population, identification of potentially modifiable risk factors for atrophy of MTL and BG is important. Proper treatment may prevent or postpone the development of cognitive decline and therefore have a major public health impact.

Decreased volumes of MTL have been associated with untreated elevated midlife systolic and diastolic blood pressures (Korf, White, et al. 2004), type 2 diabetes (Korf, White, et al. 2006), high BMI at midlife (Debette et al. 2011), and the presence of APOE 4 allele (den Heijer, Oudkerk, et al. 2002). The APOE genotype is in particular relevant vascular risk factor, since it is involved in cholesterol metabolism and in repair of brain injury (Liu et al. 2013) and therefore may be related to MTL volume decline via multiple mechanisms. APOE $\varepsilon 4$ allele has also been associated with steeper rates of annual decline in hippocampal volume (Moffat et al. 2000). Although the associations of APOE $\varepsilon 4$ and midlife exposure to other vascular risk factors with decreased MTL volumes is supported by many reports, studies of associations of late life vascular risk factor exposure and MTL volume measurements tend to give mixed results or show no association (Gattringer et al. 2012). However, many of these studies are based on cross-sectional data and/or may not use direct measurements of MTL volume (Debette et al. 2011).

Although important in cognitive decline, less is known on vascular risk factors and volumetric changes in the BG. The striatum and thalamus are particularly susceptible to hypertensive cerebral small vessel disease (SVD), which on its turn is associated with cognitive decline (Prins et al. 2005; Smallwood et al. 2012). The striatum is supplied by perforating branches from the medial cerebral artery and the thalamus by perforating branches from the posterior cerebral artery, just shortly after both cerebral arteries have branched from the circle of Willis (Schmahmann 2003). This analogous irrigation may lead to similar effects of vascular risk factors in the striatum and thalamus. Man-

ifestations of SVD that are visible on magnetic resonance images (MRI), i.e., lacunar infarcts, microbleeds, and dilated Virchow Robin spaces, indeed frequently occur simultaneously in the striatum and the thalamus (Vermeer, Longstreth, and Koudstaal 2007; Zhu, Tzourio, et al. 2010; Zhu, Dufouil, et al. 2010). Besides macroscopically visible traits of SVD, microscopic pathology, such as micro infarcts or gliosis, may impact the structural integrity of the BG neural network as well (Gouw et al. 2011) and may lead to general atrophy of the structure. Since vascular risk factors have been related to the occurrence of SVD in the BG, we hypothesize that BG atrophy rates also increases in the presence of vascular risk factors.

In this follow-up brain MRI-study, we examined baseline and follow-up volumes of MTL and BG in relation to various vascular risk factors in late life. We hypothesized that those factors associated with cognitive decline are related to a higher atrophy rate of the MTL, but also a higher atrophy rate of the BG, in particular high blood pressure. Furthermore, we examined whether the effects of different vascular risk factors on the MTL and BG interacted with each other or exerted independent effects. We chose to combine volumes of the striatum (including caudate nucleus, putamen, and globus pallidus) with the thalamic volume, because of their analogous vascularization. For descriptive purposes we refer to these structures as BG. Participants were from the population based Age, Gene/Environment, Susceptibility-Reykjavik Study (AGES-Reykjavik), who took part in a midterm follow-up MR substudy.

METHODS

Study population

Data were from the well-characterized population-based AGES-Reykjavik study, (2002–2006) composed of men and women born between 1907–1935. The design of the study has been described elsewhere (Harris et al. 2007). Participants underwent extensive clinical evaluation, brain MRI, and cognitive testing. Cases of dementia were ascertained in a three-step process, as described previously (Harris et al. 2007), including a screening based on the Mini Mental State Examination and the Digit Symbol Substitution Test, a diagnostic neuropsychological test battery, an informant interview, and a neurological examination. A consensus diagnosis of dementia and MCI was made by a panel including a geriatrician, neurologist, neuropsychologist, and neuroradiologist. Dementia was classified according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria (American Psychiatric Association 1994) A random sample of 410 participants was selected from the cohort that had successfully acquired MRI at baseline between 2004–2006 ($N = 4614$). From this sample we excluded those with missing or low quality

images that could not be adequately segmented ($n = 35$) and demented cases ($n = 3$). Because large areas of ischemic damage may affect the scan analysis, we also excluded those with hemispherical infarcts spanning 3 or more cortical lobes ($n = 2$), and those with parenchymal defects in the BG larger than 30 mm ($n = 2$). Our final study sample consisted of 368 non-demented people with successfully processed brain MR at both time points. This subsample underwent follow-up brain scanning, performed between June 2006 and March 2007, with an average interval of 2.4 (SD = 0.16) years from the first scan.

Protocol approvals, registrations, and patient consents

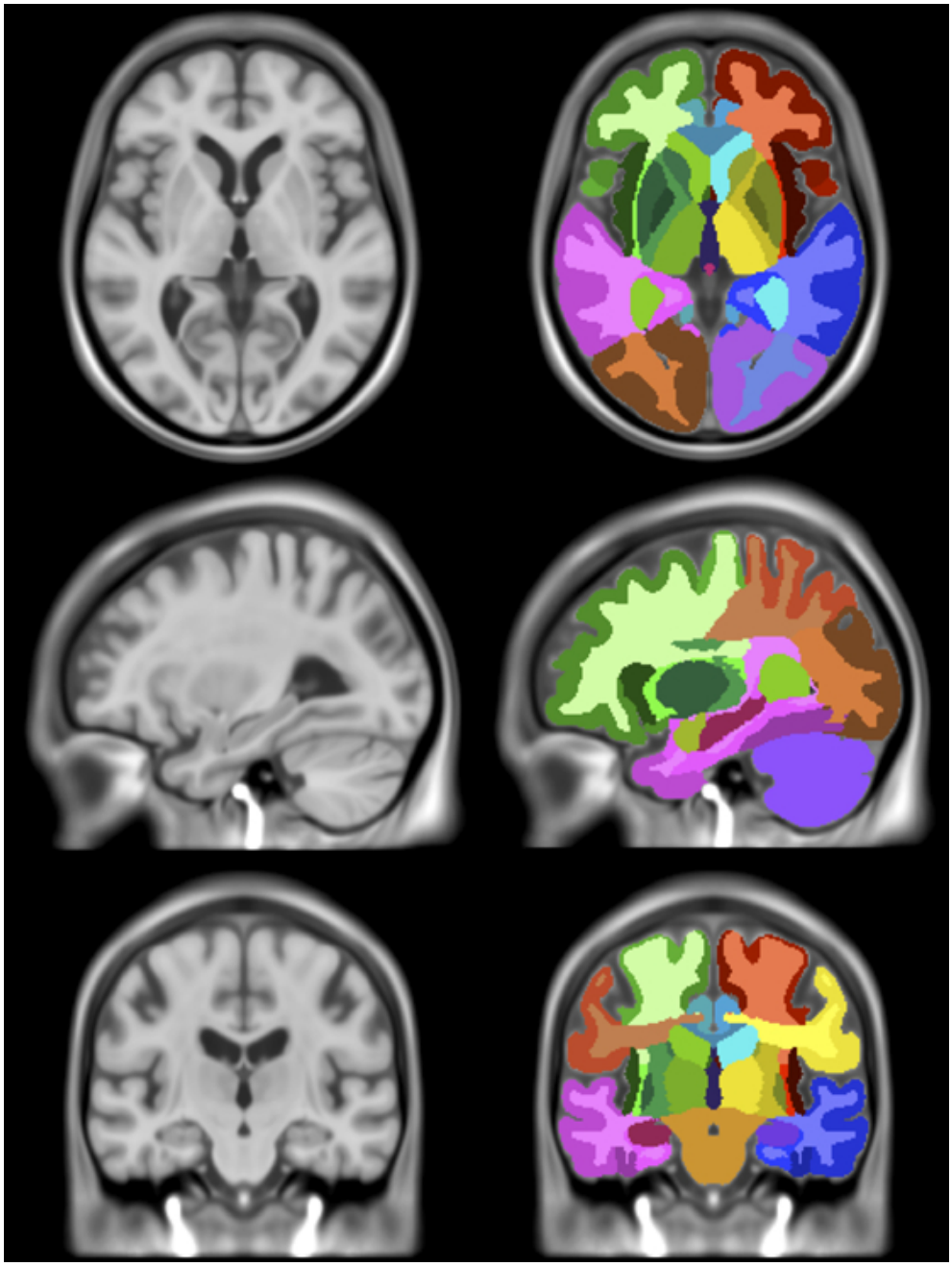
All participants signed an informed consent. The AGES-Reykjavik study was approved by the Intramural Research Program of the National Institute on Aging, the National Bioethics Committee in Iceland (VSN00-063), the Icelandic Data Protection Authority, and the institutional review board of the U.S. National Institute on Aging, National Institutes of Health.

Acquisition and post processing of MRI

MRI was performed in the Icelandic Heart Association Research Institute on a 1.5-T Signa Twinspeed system (General Electric Medical Systems) MRI scanner with 8-channel head coil (General Electric Medical Systems, Waukesha, WI). The image protocol, described previously (Sveinbjornsdottir et al. 2008), included whole brain axial T1-weighted 3-dimensional, FSE PD/T2, and FLAIR sequences, with the same acquisition parameters at both time points. Scans were processed with a fully automated segmentation pipeline described previously (Sigurdsson et al. 2012). Preprocessing of the images included inter slice intensity normalization, noise reduction, and correction for intensity nonuniformity. The pipeline combined the use of a regional probabilistic atlas (figure 1), created with a large sample of the AGES-Reykjavik study ($N = 314$), with a multispectral tissue segmentation method. The atlas was warped non-linearly to the T1-weighted images of each study participant, where the intersection of regional delineation by the atlas with the results from the tissue segmentation was used to calculate the volumes of the regions of interest. The manual segmentation protocols for MTL and BG, used to create the probabilistic atlas, are reported in the appendix.

Substructure volumes of MTL, i.e., amygdala and hippocampus, and substructures of BG, i.e., caudate nucleus, putamen, accumbens, globus pallidus, and thalamus were combined. By combining substructures we reduced the possibility that volume loss due to observational noise in one substructure became volume gain in the adjacent substructure.

Figure 1: Brain regions of the probabilistic atlas in the AGES-Reykjavik atlas



ICV was defined as the sum of CSF, total gray and white matter, and white matter lesion volume.

Validation

Performance of the automated segmentation pipeline of AGES-Reykjavik study was validated against four scans that were manually segmented into different brain regions. Dice-kappa scores were calculated for each region (caudate nucleus: 0.93, putamen: 0.87, accumbens: 0.69, pallidus: 0.66, thalamus: 0.92, hippocampus: 0.79, amygdala: 0.79).

Risk factors and covariates

All covariates and risk factors were measured at baseline. Education level (college or university education versus lower education), smoking history (never, former, or current smoker), and alcohol intake history (never, former or current drinker) were assessed by questionnaire. Body mass index (BMI) was calculated as current weight divided by squared midlife height (taken from data of the Reykjavik Study examination that occurred 25 years (SD = 4.2) earlier). Blood pressure was measured at baseline, 216 (59%) participants were using antihypertensive medication and 152 (41%) were unmedicated. Diabetes was defined as a history of physician diagnosed diabetes, use of glucose-modifying medication, or fasting blood glucose of $\geqslant$ 7.0 mmol/L. MRI infarct-like lesions were identified by trained radiographers as defects in the brain parenchyma with a maximal diameter of at least 4 mm and associated with hyperintensity on T2 and fluid-attenuated inversion recovery images. For lesions in the cerebellum and brain stem or lesions with cortical involvement, no size criterion was required. APOE genotype was successfully determined in 366 participants (Eiriksdottir et al. 2006). Participants were classified by genotype into 3 groups having either one or two APOE $\varepsilon 2$ alleles) (22, 23), two APOE $\varepsilon 3$ alleles (33), or one or two APOE $\varepsilon 4$ alleles (34, 44). Participants with one APOE $\varepsilon 2$ allele and one APOE $\varepsilon 4$ (24) were excluded from the analysis ($N = 5$).

Statistical analysis

Characteristics of the study sample were compared with characteristics of the rest of the AGES-Reykjavik sample that underwent MR scanning ($N = 4246$). The study sample was on average younger (mean 75.5 (SD = 5.3) [range 67–90 yo] vs. mean 76.5 (SD = 5.5) [range 66–98 yo], $p = 0.001$), had lower volume of WML (mean 18.7 (SD = 19.1) vs. mean 21.0 (SD = 21.1), $p = 0.03$) and higher MMSE score (median 28 (20^{th}

percentile = 26, 80th percentile = 29) vs. median 27 (20th percentile = 24, 80th percentile = 29), $p < 0.0001$) (Table 1).

The change in volume of BG and MTL were calculated as annualized percent change as follows:

$$\frac{Volume\ Time_2 - Volume\ Time_1}{Volume\ Time_1 \times (Time_2 - Time_1)} \times 100$$

Mean baseline and follow-up BG and MTL volumes (unadjusted for ICV) and mean annualized percent change in BG and MTL volumes were calculated for the total sample and for women and men separately (table 2). Pearson correlations of baseline BG and MTL volumes with follow-up volumes and with annualized percent changes were also calculated (last two columns of table 2).

Differences in baseline volume and annualized percent change of BG and MTL among groups with different APOE genotype (33, and 34/44, and 23/22), smoking and alcohol status (never, former, current), presence of diabetes and MRI infarct-like lesions were assessed in a general linear model. Continuous variables, i.e., age, BMI, LDL, HDL, glucose, and blood pressure levels, were transformed into z-scores, so coefficients from the different risk factors could be compared. Furthermore, continuous variables were also dichotomized at the median value for age and WML or according to clinically relevant thresholds: BMI $\geqslant$ 25 kg/m^2, LDL $\geqslant$ 4.1 mmol/L, HDL $<$ 1.03 mmol/L for men and $<$ 1.30 mmol/L for women, glucose level $>$ 5.6 mmol/L, systolic blood pressure $\geqslant$ 140 mmHg, diastolic blood pressure $\geqslant$ 90 mmHg. Relations between the continuous variables (z-scored) and dichotomized variables were assessed in a general linear model. Models with baseline BG or MTL volumes as dependent variable were adjusted for age (as a continuous variable), sex, and ICV. Since annualized percent change in MTL volume was significantly related to MTL volume at baseline (table 2), models with annualized percent change in BG or MTL as dependent variables were additionally adjusted for baseline volume of BG or MTL respectively. Models for associations with LDL and HDL level were also adjusted for the use of statins. Models for associations with systolic and diastolic blood pressure were also adjusted for the use of antihypertensive medication.

To assess whether the relations of blood pressure with baseline and percent change in MTL and BG volumes were altered by the use of antihypertensive medication, the interaction terms between blood pressure and use of hypertensive medication were evaluated in these models. Also, to assess whether the relations of blood pressure and different APOE genotypes with baseline volumes and percent changes of BG and MTL varied by age, the interaction terms between age and blood pressure and age and APOE genotype were evaluated in these models. Moreover, to see whether the relations of blood pressure with baseline and percent change of BG and MTL atrophy were potentially driven by APOE genotype, the interaction term between blood pres-

Table 1: Characteristics of AGES-Reykjavik and MRI follow-up samples

Characteristics, Mean (SD)[a]	AGES Reykjavik ($N = 4246$)	Study sample ($N = 368$)	p[b]
Age	76.5 (5.5)	75.5 (5.3)	0.001
Women, % (N)	58 (2464)	59 (216)	0.85
intracranial volume (cm^3)	1501 (148)	1501 (150)	0.86
Apo E genotype, % (N)			
33	63 (2623)	61 (223)	
34/44	27 (1096)	27 (98)	0.67
22/23	10 (403)	11 (40)	
High Education, % (N)	11 (457)	12 (43)	0.65
Dementia, % (N)	5 (202)	0 (0)	
MMSE score	26.5 (3.1)	27.5 (1.8)	$<.0001$
Body mass index (kg/m^2)	26.9 (4.4)	27.1 (4.1)	0.58
Serum low-density lipoprotein (mmol/L)	3.49 (1.04)	3.59 (1.04)	0.08
Serum high-density lipoprotein (mmol/L)	1.60 (0.45)	1.60 (0.44)	0.95
Smoking status, % (N)			
Never	43 (1824)	46 (172)	
Former	45 (1898)	44 (163)	0.12
Current	12 (521)	9 (33)	
Alcohol intake, % (N)			
Never	23 (955)	21 (78)	
Former	12 (523)	9 (33)	0.09
Current	65 (2728)	69 (255)	
Diabetes, % (N)	11 (475)	11 (41)	0.95
Glucose	5.75 (1.14)	5.80 (1.36)	0.56
White matter lesions (cm^3)	21.0 (21.1)	18.7 (19.1)	0.03
MRI infarct-like lesions, % (N)	31 (1320)	30 (110)	0.68
Hypertension[c]	52 (2222)	54 (198)	0.63
Systolic blood pressure (mmHg)	142.3 (20.5)	143.1 (19.2)	0.44
Diastolic blood pressure (mmHg)	73.8 (9.6)	74.5 (9.8)	0.15

a or percentage (N) if stated

b from t-test for continuous variables and χ^2 test for class variables

c defined as systolic blood pressure $\geqslant 140$ and or diastolic blood pressure $\geqslant 90$

Table 2: Descriptive statistics for BG and MTL baseline and follow-up volumes and annualized percent change

Region of interest	Descriptive measures Mean (SD)			Pearson's correlations between:	
	Baseline volume in cm^3	Follow-up volume in cm^3	% change	Baseline volume and follow-up volume	Baseline volume and % change
Basal ganglia					
All	35.4 (3.3)	34.9 (3.3)	−0.57 (0.85)	0.98**	−0.038
Women	34.4 (2.9)	34.0 (3.0)	−0.48 (0.78)	0.98**	0.028
Men	36.9 (3.3)	36.2 (3.3)	−0.69 (0.92)	0.97**	−0.014
Medial temporal lobe					
All	10.6 (1.1)	10.4 (1.2)	−0.83 (1.03)	0.98**	0.14*
Women	10.2 (1.0)	10.0 (1.0)	−0.78 (1.03)	0.97**	0.21*
Men	11.2 (1.1)	11.0 (1.1)	−0.92 (1.04)	0.97**	0.18*

Baseline volume and follow-up volume, raw volume unadjusted for intracranial volume; % change, annualized percent change computed with formula: $100 \times (volume_{time_2} - volume_{time_1})/(volume_{Time_1} \times (time_2 - time_1))$.

* $p < 0.05$; ** $p < 0.0005$.

sure and APOE genotype was tested. Lastly, we tested a three-way interaction term (*age* × *presence of high blood pressure* × *APOE genotype*). All interaction terms were found nonsignificant (all *p*-values > 0.32), therefore they were not included in the models of which the results are displayed in table 4 and table 3.

Finally, we tested the association of annualized percent change in BG and MTL volumes in two separate models with all covariates and risk factors variables (age, sex, APOE genotype, diabetes, smoking status, alcohol status, MRI infarct-like lesions, and z-scores of BMI, HDL, WML, and blood pressure) entered simultaneously. Because of collinearity, separate full risk factor models were made for systolic and diastolic blood pressure. Statistical analyses were conducted with R 2.11.1 (R Core Team 2010). A two-sided alpha level of 0.05 was considered significant.

RESULTS

The sample consisted of 368 participants with a mean age of 75.5 (SD = 5.3 years; range 67–90 years) and 58.7% were women. Mean baseline volume of the BG was 35.4 cm^3 (SD = 3.3) and average annualized percent change in BG was −0.57% per year (−0.5 cm^3/year). Mean baseline volume of the MTL was 10.6 cm^3 (SD = 1.1) and average annualized percent change in MTL was −0.83%/year (−0.2 cm^3/year). Men had a significantly larger decrease in BG compared to women (−0.69%/year vs. −0.48%/year, $p = 0.02$). Annualized percent change in MTL did not differ among men and women (Table 2).

Analysis of baseline volumes

Baseline volumes of BG and MTL were associated with few risk factors (Table 4): a smaller volume of BG was found among older participants, participants with BMI below 25 and participants with WML below median value. A smaller volume of MTL was associated with older participants, participants with BMI below 25, current smokers, participants without MRI infarct-like lesions and participants with fasting glucose level below 5.6 mmol/L. Neither BG nor MTL baseline volumes were associated with blood pressure levels or APOE genotype.

Table 3: Association of BG and MTL baseline volume with vascular risk factors

Risk factors	N	Basal ganglia volume (cm^3)		MTL volume (cm^3)	
		Mean (SD)[a]	p[b]	Mean (SD)[a]	p[b]
Age continuous		−0.62 (0.14)[c]	<.0001	−0.22 (0.04)[c]	<.0001
< 75[d] years old	169	35.9 (3.1)	0.001	10.8 (1.0)	<.0001
⩾ 75 years old	199	35.0 (3.4)		10.5 (1.2)	
APOE					
33	223	35.3 (3.5)		10.6 (1.2)	
34/44	98	35.6 (3.0)	0.7	10.7 (1.1)	0.74
23/22	40	35.8 (3.0)		10.7 (1.2)	
Body mass index continuous		0.55 (0.14)[c]	<.0001	0.22 (0.04)[c]	<.0001
< 25 kg/m^2	141	34.5 (3.1)	0.003	10.3 (1.1)	0.0001
⩾ 25 kg/m^2	225	36.0 (3.3)		10.9 (1.1)	
LDL continuous		−0.01 (0.17)[c,e]	0.96[e]	0.05 (0.05)[c,e]	0.34[e]
< 4.1 mmol/L	261	35.6 (3.3)	0.56[e]	10.7 (1.2)	0.40[e]
⩾ 4.1 mmol/L	107	35.0 (3.4)		10.5 (1.1)	
HDL continuous		−0.19 (0.15)[c,e]	0.20[e]	−0.09 (0.05)[c,e]	0.06[e]
Low	23	35.4 (3.3)	0.21[e]	10.7 (1.2)	0.95[e]
High	345	35.8 (3.5)		10.6 (1.0)	
Smoking					
Never	172	35.1 (3.3)		10.6 (1.1)	
Former	163	35.8 (3.2)	0.3	10.7 (1.2)	0.006
Current	33	34.8 (3.4)		10.4 (1.0)	
Alcohol intake					
Never	78	34.7 (2.9)		10.3 (1.0)	
Former	33	36.0 (2.8)	0.54	10.9 (1.0)	0.48
Current	255	35.5 (2.8)		10.7 (1.2)	
Diabetes					
No diabetes	327	35.4 (3.3)	0.45	10.6 (1.1)	0.29
Diabetes	41	35.5 (3.0)		10.9 (1.1)	

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LDL, serum low-density lipoprotein; HDL, serum high-density lipoprotein

a raw means (unadjusted for age, sex and ICV), or beta (standard error) if stated

b *p*-value from general linear model corrected for age, sex, ICV; for continuous variables z-scores were used

c beta (standard error) from general linear model corrected for age, sex, and ICV

d cut off at median value

e additionally adjusted for use of statins

Table 3 – continued from previous page

Risk factors	N	Basal ganglia volume (cm^3)		MTL volume (cm^3)	
		Mean (SD)[a]	p[b]	Mean (SD)[a]	p[b]
Fasting glucose continuous		−0.12 (0.14)[c]	0.41	−0.002 (0.04)[c]	0.96
< 5.6 mg/dL	192	35.1 (3.1)	0.59	10.5 (1.1)	0.04
⩾ 5.6 mg/dL	176	35.7 (3.5)		10.8 (1.2)	
WML continuous		0.34 (0.15)[c]	0.02	0.06 (0.05)[c]	0.19
< 12.5[d] cm^3	184	34.8 (3.2)	0.0004	10.5 (1.1)	0.49
⩾ 12.5 cm^3	184	36.1 (3.3)		10.8 (1.2)	
MRI infarct-like lesions					
No	258	35.4 (3.2)	0.99	10.6 (1.1)	0.007
Yes	110	35.4 (3.5)		10.8 (1.2)	
Systolic BP continuous		0.05 (0.14)[c,e]	0.73[e]	−0.01 (0.05)[c,e]	0.75[e]
< 140 mmHg	171	35.2 (3.1)	0.44[e]	10.6 (1.1)	0.88[e]
⩾ 140 mmHg	197	35.6 (3.4)		10.7 (1.2)	
Diastolic BP continuous		0.28 (0.15)[c,e]	0.06[e]	−0.02 (0.05)[c,e]	0.68[e]
< 90 mmHg	343	35.3 (3.3)	0.07[e]	10.6 (1.1)	0.99[e]
⩾ 90 mmHg	25	37.2 (3.4)		11.0 (1.5)	

WML, white matter lesions; BP, blood pressure

a raw means (unadjusted for age, sex and ICV), or beta (standard error) if stated

b *p*-value from general linear model corrected for age, sex, ICV; for continuous variables *z*-scores were used

c beta (standard error) from general linear model corrected for age, sex, and ICV

d cut off at median value

e additionally adjusted for use of antihypertensive medication

Analysis of volume change over the 2.4 year period

Basal Ganglia

Annualized percent change in BG was not associated with age or any vascular risk factors except systolic blood pressure (Table 4). Participants with systolic blood pressure ⩾ 140 mmHg had a steeper decline ($\Delta = -0.23\%/yr$, $p = 0.03$). However, in the full risk factor model, none of the risk factors showed a significant association with BG percent change.

Medial Temporal Lobe

Annualized percent change in MTL was linearly associated with age (β (SE) = −0.167 (0.052), $p < 0.001$) and was steeper in participants ⩾ 75 years compared to younger

Table 4: Association of annualized percent change in BG and MTL volume with vascular risk factors

Risk factors	N	Basal ganglia Mean (SD)	p[a]	Medial temporal lobe Mean (SD)	p[a]
Age		−0.060 (0.045)[b]	0.18	−0.167 (0.052)[b]	0.001
< 75 years old (median value)	169	−0.53 (0.79)	0.65	−0.65 (1.00)	0.04
⩾ 75 years old	199	−0.59 (0.89)		−0.99 (1.03)	
Apo E genotype					
33	223	−0.54 (0.86)	0.12	−0.69 (0.88)	
34 or 44	98	−0.66 (0.80)		−1.16 (1.23)	<0.0001
23 or 22	40	−0.41 (0.88)		−0.70 (0.91)	
Body mass index		0.004 (0.046)[b]	0.93	0.061 (0.054)[b]	0.93
< 25 kg/m^2	141	−0.58 (0.79)	0.58	−0.98 (1.16)	0.27
⩾ 25 kg/m^2	225	−0.55 (0.88)		−0.72 (0.92)	
Diabetes					
No diabetes	327	−0.55 (0.83)	0.51	−0.82 (1.06)	0.67
Diabetes	41	−0.69 (0.94)		−0.89 (0.83)	
Serum low-density lipoprotein		−0.025 (0.052)[b,c]	0.63[c]	0.091 (0.059)[b,c]	0.13[c]
< 4.1 mmol/L	261	−0.57 (0.89)	0.94[c]	−0.88 (1.08)	0.34[c]
⩾ 4.1 mmol/L	107	−0.55 (0.73)		−0.67 (0.89)	
Serum high-density lipoprotein[d]		−0.012 (0.046)[b,c]	0.79[c]	−0.043 (0.052)[b,c]	0.42[c]
Low	23	−0.43 (0.80)	0.45[c]	−0.77 (1.20)	0.86[c]
High	345	−0.59 (0.85)		−0.84 (1.01)	

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a p from general linear model corrected for age, sex, ICV, baseline volume; b β (standard error) from general linear model corrected for age, sex, ICV, and baseline volume; c additionally adjusted for use of statins; d threshold for women low: HDL < 1.30 mmol/L and high: ⩾ 1.30 mmol/L, for men low: < 1.03 mmol/L and high: ⩾ 1.03 mmol/L.

Table 4 – continued from previous page

Risk factors	N	Basal ganglia Mean (SD)	p[a]	Medial temporal lobe Mean (SD)	p[a]
Smoking status					
Never	172	−0.47 (0.83)		−0.68 (0.95)	
Former	163	−0.64 (0.88)	0.36	−0.99 (1.06)	0.13
Current	33	−0.66 (0.86)		−0.87 (1.19)	
Alcohol intake					
Never	78	−0.41 (0.82)		−0.69 (1.13)	
Former	33	−0.54 (0.82)	0.41	−0.89 (0.90)	0.48
Current	255	−0.62 (0.86)		−0.86 (1.02)	
Fasting glucose		−0.081 (0.044)[b]	0.06	−0.056 (0.052)[b]	0.25
$<$ 5.6 mg/dL	192	−0.57 (0.79)	0.55	−0.91 (1.10)	0.25
$\geqslant$ 5.6 mg/dL	176	−0.56 (0.90)		−0.75 (0.95)	
White matter lesions volume					
$<$ 12.5 cm^3 (median value)	184	−0.52 (0.72)	0.88	−0.67 (0.96)	0.08
$\geqslant$ 12.5 cm^3	184	−0.61 (0.95)		−0.99 (1.08)	
MRI infarct-like lesions					
No	258	−0.52 (0.82)	0.28	−0.78 (1.01)	0.34
Yes	110	−0.68 (0.89)		−0.95 (1.09)	
Systolic blood pressure		−0.080 (0.045)[b,c]	0.08[c]	−0.155 (0.051)[b,c]	0.003[c]
$<$ 140 mmHg	171	−0.44 (0.78)	0.03[c]	−0.72 (0.98)	0.16[c]
$\geqslant$ 140 mmHg	197	−0.67 (0.88)		−0.93 (1.07)	
Diastolic blood pressure		−0.015 (0.047)[b,c]	0.74[c]	−0.143 (0.053)[b,c]	0.008[c]
$<$ 90 mmHg	343	−0.55 (0.85)	0.30[c]	−0.81 (1.03)	0.10[c]
$\geqslant$ 90 mmHg	25	−0.77 (0.83)		−1.15 (1.11)	

a p from general linear model corrected for age, sex, ICV, baseline volume; b β (standard error) from general linear model corrected for age, sex, ICV, and baseline volume; c additionally adjusted for use of antihypertensive medication.

participants ($\Delta = -0.34\%/\text{yr}$, $p = 0.04$). There was significantly more annualized decline in MTL volumes in carriers of the APOE genotype 34/44 ($\Delta = -0.47\%/\text{yr}$, $p < 0.0001$) and a steeper decline in MTL volume with increasing systolic ($p = 0.003$) and diastolic ($p = 0.008$) blood pressure. Furthermore, in the full risk factor model for MTL volume change, APOE $\varepsilon 4$ (β (SE) $= -0.47$ (0.11), $p < 0.0001$), systolic and diastolic blood pressure remained significantly associated with a steeper decrease in volume of MTL.

Interaction terms

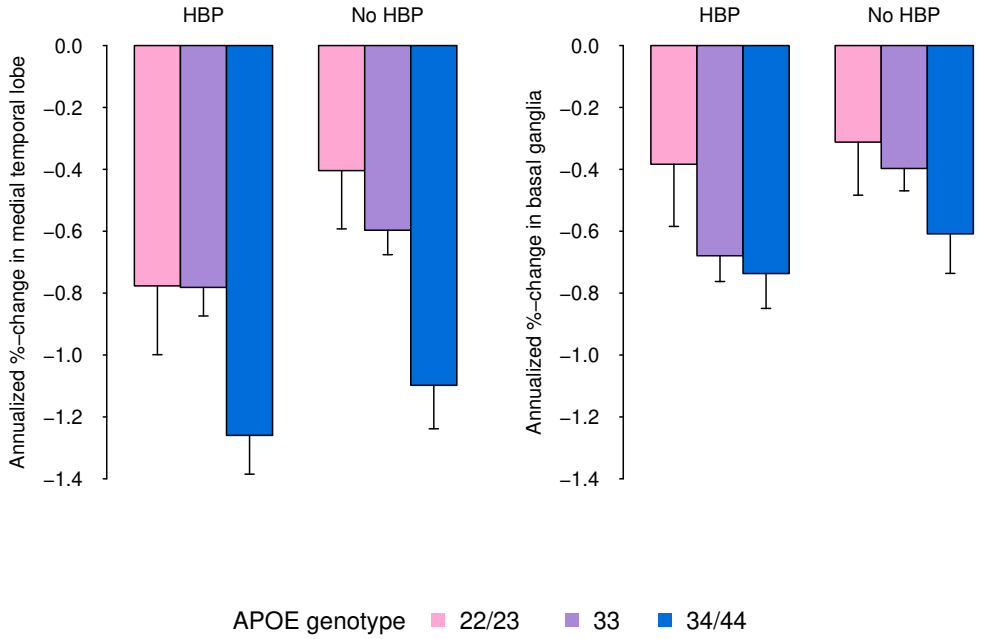
All potential relevant interaction terms, including all possible combinations between age, blood pressure and APOE genotype, were found nonsignificant (all p-values > 0.32). In figure 2 we show combined effects of high blood pressure and APOE genotype for mean values of annualized percent change in BG and MTL adjusted for age, sex, and ICV. Change in BG and MTL volumes were higher among hypertensive participants compared to non-hypertensive participants, however, we found no evidence for an interaction with APOE genotype.

DISCUSSION

In the present follow-up study we investigated the influence of late life exposure to vascular risk factors on MTL and BG atrophy rates. Neurodegeneration of MTL and BG are both associated with cognitive impairment with ageing, we therefore expected both structures to show increased atrophy rates in the presence of well-known vascular risk factors in this sample of non-demented older people. However, MTL and BG volume changes showed different susceptibility to vascular risk factors. MTL volume decline over 2.4 years was significantly steeper 1) as systolic and diastolic blood pressures increased and 2) in carriers of the APOE $\varepsilon 4$ allele. In contrast, BG volume loss was slightly higher in participants with high systolic blood pressure, but was not associated with any of the other vascular risk factors that were investigated.

The association of higher blood pressure in late life with increased MTL atrophy rates is important. MTL atrophy may form (part of) the neuropathological basis leading to cognitive decline in older people, and the results of the present study suggest controlling high blood pressure in late life may limit MTL atrophy. Additionally, we showed that systolic and diastolic blood pressure and APOE $\varepsilon 4$ independently increased MTL atrophy. Mechanisms linking high blood pressure and APOE $\varepsilon 4$ to increased MTL atrophy are under investigation. High blood pressure has been associated with decreased perfusion in the brain in men (Waldstein et al. 2010), which may play a pathogenic role in brain

Figure 2: Combined effects of hypertension and Apo E gentoype on MTL volume decline



atrophy. The APOE polymorphism in its turn is known to affect serum lipid levels, and to play a role in regeneration and re-myelinization of axons (Mahley and Rall 2000). APOE $\varepsilon 4$ carriers are assumed to be less effective in protecting neurons from excessive damage and have a reduced regenerative capacity.

Although some studies with cross-sectional design show diminished MTL volumes with high blood pressure (den Heijer, Launer, et al. 2005; Korf, Scheltens, et al. 2005; Lu et al. 2011), others failed to show this association, especially those that study late-life risk factor exposure (Gattringer et al. 2012). This discrepancy is also visible in our results. The cross-sectional analysis did not show any difference in baseline MTL volume with higher blood pressure or presence of APOE $\varepsilon 4$ compared to the rest of the sample. Possibly this discrepancy is related to study sample composition. It is known that in preclinical dementia, blood pressure tends to go down while brain atrophy is already ongoing (Qiu et al. 2004). These effects may have distorted the cross-sectional analysis since populations of non-demented subjects consist of healthy and undiagnosed individuals (Tolppanen et al. 2012). One of the strengths of the present study was therefore the availability of follow-up data.

Although several reports have been written on the susceptibility of BG to hypertension-related SVD and arteriolosclerosis, in this study no consistent associations were found between vascular risk factors and changes in volume of the BG. We did find a trend of increased loss of BG volume with higher systolic blood pressure but this was only significant when systolic blood pressure was taken as a dichotomous variable. Possibly the weak association is due to slight increased atrophy of BG secondary to global brain atrophy. Men displayed a steeper decline in BG volume than women, which has also been reported in other studies, in particular for the putamen (Coffey et al. 1998; Nunnemann et al. 2009).

What might explain the contrast in vascular risk profile between the MTL and BG? Possibly this is related to the difference in vascular anatomy of the two regions. BG are supplied by the lenticulostriate and thalamic arteries, which are branching directly from the medial and posterior cerebral artery (Cho et al. 2008; Schmahmann 2003). As a consequence, the hydrostatic pressure in the circle of Willis is directly translated into the small, thin-walled arteries and arterioles of the BG. On the one hand, this makes these vessels vulnerable for hypertension-induced arteriolosclerosis that can give rise to hemorrhages and lacunar infarcts in the BG. On the other hand, due to the relatively high hydrostatic pressure, perfusion pressure in these vessels, even if affected by arteriolosclerosis, is maintained. This is different for the MTL, which is perfused by fine leptomeningeal vessels that arise after gradual branching from the posterior cerebral artery, anterior choroidal artery (to a lesser degree), and medial cerebral artery (amygdala) (Duvernoy 2005). The hydrostatic pressure in the leptomeningeal vessels is relatively low as a consequence of the gradual branching, making them relatively immune for the development of arteriolosclerosis. Excessive central pressure, however, has been associated with micro vascular remodeling that increases resting resistance and hyperemic reserve (Mitchell et al. 2005). It may be hypothesized that high blood pressure gives rise to hypoperfusion of MTL as a consequence of this remodeling, resulting in widespread atrophy and changes of the tissue composition. Moreover, hippocampus is known for its sensitivity to ischemia (Atlas 1996) and hypoperfusion may particularly affect the volume of this structure. More studies are needed to investigate the relation between higher blood pressure and effects on perfusion of cerebral regions.

Regarding the other vascular risk factors that were studied, we observed positive associations of baseline volumes of both BG and MTL with BMI, of WML with BG, and of MRI infarct-like lesions and blood glucose with MTL. These associations are not readily explained and may require further investigation. For BMI it has been shown that obesity in midlife is a risk factor for the development of AD (M Kivipelto et al. 2005), however, later in life similar age-related volumetric changes in the brain were found similar in obese vs. nonobese (Driscoll et al. 2012). Moreover, it is known that

individuals who are CSF Aβ-positive, PiB-positive, or have an elevated tau/Aβ ratio have lower mean BMI than Aβ-negative individuals (Vidoni et al. 2011). Therefore, as with the cross-sectional analysis of blood pressure and APOE genotype, these associations may be distorted by the presence of undiagnosed preclinical dementia in this non-demented sample.

A limitation of our study was the relatively short duration of follow-up and therefore we could not determine the effects of vascular risk factors on MTL and BG atrophy over a longer term. Yet, the observed significant associations with MTL volume change suggest the duration of the study was sufficient enough to detect unmistakably different effects of vascular risk factors on BG and MTL volume decline.

CONCLUSION

Higher systolic and diastolic blood pressures, and the presence of APOE ε4, were independently associated with a steeper decline in volume of MTL over 2.4 years in older people. In contrast, atrophy rate of BG was not associated with the vascular risk factors. Although BG are a site of frequent manifestations of SVD, their distinct vascularization possibly leads to relative preservation of perfusion in the presence of vascular risk factors.

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APPENDIX

Manual segmentation protocol

The caudate nucleus, putamen, globus pallidus, and thalamus were delineated on axial T1-weighted 3-dimensional images (acquisition parameters: TR = 21.0 ms; TE = 8.0 ms; flip angle = 30°; section thickness = 1.5 mm; number of sections=110; no section gap; whole brain coverage; FOV = 240 mm; matrix = 256 × 256). Anatomical borders of the caudate were medial the lateral ventricle, lateral the internal capsule, inferior the nucleus accumbens and more posterior the internal capsule. The boundaries of the putamen were medial the internal capsule and globus pallidus, and lateral the external capsule (the claustrum was not separately labeled). The globus pallidus laterally bordered the putamen, and anteriorly and medially the internal capsule. The thalamus included the thalamus, pulvinar, subthalamic nucleus, and hypothalamus. The anterior border and lateral border were formed by the posterior limb of the internal capsule, the medial border by the lateral ventricle, and more caudally the septum pellucidum and superior colliculus, and the posterior border by the third ventricle and crus fornix. The nucleus accumbens was drawn in coronal plane as the gray matter connecting caudate nucleus and putamen. A line from the lower tip of the lateral ventricle to the lower tip of the internal capsule was considered the superior boundary. The septum pellucidum was regarded the medial border. The nucleus was delineated posteriorly until the anterior commissure was seen. The amygdala was identified in coronal plane, at the level of the anterior commissure and drawn superior to the top of the temporal horn of the lateral ventricle and hippocampus. Medial and lateral anatomical boundaries were the cerebrospinal fluid (CSF) of the uncal sulcus and white matter of the MTL. The inferior border was formed by the temporal horn of the lateral ventricle and more anteriorly by white matter of the entorhinal cortex. The hippocampus was identified on the coronal slice where the mamillary bodies were visible. Areas included were the CA-1 through CA-4 sections, dentate gyrus, and subiculum. A straight horizontal line from the top of the temporal horn of the lateral ventricle formed the superior border with amygdala and the gray-white matter junction between the subiculum and white matter of the parahippocampal gyrus formed the inferior border. CSF in the temporal horn formed the lateral border and CSF of hippocampal sulcus the medial border. Posteriorly, the structure was drawn until no longer seen, usually where the splenium and crus fornix were clearly visible. Both amygdala and hippocampus were reviewed in axial plane and modified if necessary along the described borders.