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

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CHAPTER 7

Bigger brains atrophy faster in later life

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ABSTRACT

Previous literature suggests that in various clinical groups, those with larger ICV cope better facing the (relative) same amount of neurodegenerative changes when compared to those with smaller ICV. Therefore, ICV is often regarded as a proxy for brain reserve. However, whether larger ICV attenuates the amount of neurodegenerative changes or attenuates the effects of neurodegenerative changes has not been sufficiently studied. In the present study, we studied the relation of ICV to several MRI markers of neurodegeneration, i.e., brain atrophy, ventricular dilatation and white matter lesions (WML) load. Furthermore, we studied the relation of ICV to change in cognitive speed measured over 5 year. Our study population consisted of cross-sectional ($N = 4507$) and follow-up samples ($N = 1852$) from the well-described community-based Age, Gene, Environment, and Susceptibility - Reykjavik Study (AGES-RS) and included older adults spanning the spectrum from healthy cognition (HC) to mild cognitive impairment (MCI) and dementia. Automatically segmented brain MRI was used to estimate ICV and neurodegenerative markers. In HC, larger ICV was associated with lower fraction of total brain volume (TBV) and larger fractions of ventricular (vCSF) and WML volume. These relations were slightly more pronounced in MCI and dementia. Furthermore, after a five year follow-up, larger ICV was significantly associated with a larger yearly increase in vCSF and WML. In HC and MCI, larger ICV was also associated with a larger decrease in cognitive speed, which could partially be explained by the larger change in TBV, vCSF, and WML in larger ICV. Thus, contrarily to expectations, larger ICV was associated with higher levels of MRI markers for neurodegeneration and a larger decrease in cognitive speed.

INTRODUCTION

Previous epidemiological and clinical research suggests that those with a larger intracranial volume (ICV) cope better with neurodegenerative changes compared to those with a smaller ICV. Larger ICV and head circumference have been associated with better cognitive functioning in non-demented older adults (Farias et al. 2012; Gupta et al. 2015; Perneczky et al. 2012; Royle et al. 2013; Wolf et al. 2004). Larger ICV has also been associated with an attenuation of the negative impact of neurodegenerative changes, as represented by brain atrophy and having an APOE $\varepsilon 4$ allele, on clinical disease progression in persons with MCI (Guo et al. 2013; Perneczky et al. 2012). Additionally, smaller ICV and head circumference have been associated with an increased risk for mild cognitive impairment (MCI) and Alzheimer's disease (AD) (Schofield et al. 1997; Wolf et al. 2004).

These findings are theoretically encapsulated in the concept of brain reserve. Brain reserve has been defined by Barulli and Stern (2013) as differences in brain size and other quantitative aspects of the brain that explain differential susceptibility to functional impairment in the presence of pathology or other neurological insults (Barulli and Stern 2013). ICV is considered to reflect prior maximal brain size (Sgouros et al. 1999) and often regarded as a proxy for brain reserve. The larger the ICV, the larger the "reserve" is at the start of the neurodegenerative process. The concept of brain reserve has provided a theoretical basis to describe discrepancies in the relation of ICV and function in various clinical groups. For instance, brain reserve was proposed as an explanation of the association of larger ICV with a lower risk of progression in multiple sclerosis independent from disease burden (Sumowski et al. 2016). Or for example, Guo et al (2013) showed that older people with large ICV and severe atrophy (defined as a brain parenchymal fraction (PF) of $\leqslant 0.66$) experienced slower cognitive deterioration when compared with older people with small ICV and mild atrophy. Furthermore, they found that the impact of brain atrophy and the presence of the APOE $\varepsilon 4$ allele on cognition was less in MCI cases with large ICV compared to small ICV. They proposed their findings supported the theory of a compensatory role of brain reserve.

Although the concept of brain reserve describes a similar phenomenon in various clinical groups, it is not well understood why larger ICV is beneficial to cognitive performance when facing neurodegeneration. Hypothetically, ICV may influence the amount of neurodegeneration and be associated with a resistance to neurodegenerative changes. The effect of ICV would then manifest itself as less neurodegenerative changes in those with larger ICV compared to peers with smaller ICV (Arenaza-Urquijo and Vemuri 2018). Among studies that propagate such an explanation are population cohorts studies that hypothesize that factors in early life favoring brain growth, contribute to enhanced re-

sistance to neurodegenerative changes and lead to a decreased incidence of dementia (Prince et al. 2011). However, most authors support the hypothesis that larger ICV is associated with an increased resilience (i.e., better than expected performance in face of neurodegenerative burden) to neurodegenerative changes, as in the examples given above. The nature of the compensatory mechanisms leading up to his effect is, however, not well understood. Larger brains are considered to have larger cell counts and/or larger amount of synaptic connections and therefore may withstand more neurodegenerative changes before clinical deficits appear because of a buffering effect. An important difference between the two theories of brain reserve is that the theory of resistance considers ICV to attenuate the amount of neurodegeneration, whereas the theory of resilience considers ICV to attenuate the effect of neurodegenerative changes. Whether or not a dependency exists between ICV and neurodegenerative burden and whether or not ICV attenuates the effect of neurodegenerative changes on cognition are verifiable scientific questions that have not been studied sufficiently.

As part of the efforts to further define the concept of brain reserve, here, we studied whether ICV was associated with an increased resistance or resilience to neurodegenerative changes in a large well-described population-based cohort of older people spanning the spectrum from normal cognition to dementia. Brain atrophy, ventricular dilatation, and WML load are considered markers of neurodegeneration that can be evaluated well by structural MRI. First, we studied the relation of ICV to these markers of neurodegeneration in HC, to determine whether ICV was associated with a resistance to neurodegenerative changes. Second, we studied the relation of ICV to the amount of brain atrophy, ventricular dilatation, and WML load in MCI and dementia and compared that to HC. And lastly, we studied whether ICV was related to the change in cognitive speed over five years and whether this relation was mediated by the change in the markers of neurodegeneration.

METHODS

Study design

Our study sample was extracted from the population-based cohort of the Age, Gene, Environment/Susceptibility – Reykjavik study (AGES-Reykjavik) consisting of 5764 men and women, born between 1907–1935. The general design and demographics of the AGES-Reykjavik have been described elsewhere (Harris et al. 2007). Participants underwent extensive clinical and cognitive evaluation and brain MRI between 2002–2006 and surviving participants were invited for a follow-up examination on after five years. All participants signed an informed consent. The AGES-Reykjavik study was approved

by the Intra-mural 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 automated segmentation of MRI

Brain MRI was performed on a 1.5-T GE Signa Twinspeed system MRI scanner at the Icelandic Heart Association. The image protocol included a 3D axial T1-weighted acquisition, a fluid-attenuated inversion recovery (FLAIR) sequence, and a fast spin echo proton density (PD)/T2-weighted (de Jong, Wang, et al. 2012; Sigurdsson et al. 2012; Sveinbjornsdottir et al. 2008). A fully automated segmentation pipeline was developed based on the Montreal Neurological Institute processing pipeline (Sigurdsson et al. 2012; Zijdenbos, Forghani, and Evans 2002). The pipeline used a multispectral approach to segment voxels into global tissue classes [cerebrospinal fluid (CSF), GM, WM and white matter hyperintensities (WMH)], of which the methods and validation were described previously (Sigurdsson et al. 2012). Cerebral spinal fluid (CSF), gray matter (GM), white matter (WM) and white matter lesions (WML) were separately segmented. WML included periventricular, deep and juxtacortical WMH. CSF was divided into ventricular CSF (lateral, third and fourth ventricle) and peripheral CSF (surrounding brain tissue in the sulci and basal cisterns), using the AGES atlas for regional segmentation (Forsberg et al. 2017). Total brain volume (TBV) was the sum of the GM, WM, and WML. ICV was the sum of TBV and CSF. Percentage TBV of ICV was considered a measure of global brain atrophy. Percentage vCSF of ICV was considered a marker for ventricular dilatation. Percentage WML of ICV was considered a measure for WML burden. Volume measurements of follow-up brain MRI were acquired the same way as measurements at baseline. Absolute change per year in TBV, vCSF, and WML, was calculated as (value at baseline – value at follow-up) / interval in years between scans. Yearly change per mill ICV in TBV, and per myriad vCSF and pCSF, were calculated as annualized absolute change $\times$ 1000 or $10,000$ / ICV.

Educational level, cognitive test score, and other covariates

Sample demographics and characteristics were chosen based on studies of their association with cognitive functioning in older age. Educational level (primary, secondary, college and university education), smoking history (never, ever), and alcohol intake history (never, ever) 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 (SD = 4.2) years earlier. Diabetes was defined as a history of physician diagnosed diabetes, use of glucose-modifying medication, or a fasting blood glucose $\geqslant$ 7.0 mmol/L. Hypertension was defined as measured systolic blood pressure $\geqslant$ 140 mmHg or diastolic blood pressure $\geqslant$ 90 mmHg, or self-reported doctor's diagnosis of hypertension, or use of antihypertensive medications. Speed of processing score was calculated as a composite of the following standardized tests: Figure Comparison Test (Salthouse and Babcock 1991), the Digit Symbol Substitution Test (Wechsler 1955), and the Stroop Test part 1 and 2 (Saczynski et al. 2008; Stroop 1935).

Diagnosis of dementia and MCI were ascertained in a three-step process, as described previously (Harris et al. 2007). In summary, every subject screened positive on the Mini-Mental State Examination and the Digit Symbol Substitution Test, were administered (underwent) extensive diagnostic neuropsychological test battery, a neurological examination, and one of their proxies was interviewed. A panel including a geriatrician, neurologist, neuropsychologist, and neuroradiologist reviewed all the data and made a consensus diagnosis of dementia and MCI. Dementia was classified according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria (American Psychiatric Association 1994). MCI was defined as having a borderline score ($<$ 1.5 standard deviations below a score determined according to the distribution of scores in a cohort subsample) in memory or two other domains, not severe enough to be classified as dementia.

Analytical sample

Brain MR scanning was performed on consenting MR eligible subjects. From the total AGES-RS sample of 5764 participants, 4726 underwent successful MRI. Tissue segmentation was successful in 4613 MR scans. Cases for whom cognitive status (either healthy cognition, MCI or dementia) was not determined (N = 106) were excluded. Our final study sample consisted of 4507 people with successful brain MRI and segmentation of the images, of whom 3883 had healthy cognition, 422 were diagnosed with MCI, and 202 with dementia.

The follow-up sample (N = 3316) consisted of all invited surviving participants from the baseline cohort. Part of this sample underwent successful follow-up brain scanning between 2007–2011, with an average interval of 5.19 (SD = 0.25) years from the first scan (n = 2641). From this sample, we excluded those with missing MRI at baseline (N = 87) and missing cognitive status assessment (N = 20). Our analysis was focused on the relation between ICV to change MRI based markers of neurodegeneration (i.e., brain atrophy, ventricular dilatation, and WML load), which constitute relatively small numbers over the course of 5 years. To ensure our results would not be distorted by

drift of the ICV measurements, for instance due to the update of the MRI scanner software, we excluded participants with more than 1% change in ICV between the two time points ($N = 682$). There were 40 individuals who had received MCI diagnosis at baseline, but who were scored HC at follow-up. In the follow-up sample they were considered HC. Our final follow-up sample consisted of 1586 non-demented participants, 176 participants with a diagnosis of MCI, and 90 with a diagnosis of dementia at time point 2, with successful brain MR segmentation at both time points.

Statistical analysis

All statistical analysis and graphs were computed with R v 3.4.3 (R Core Team 2014).

Comparison of study samples

Regarding the baseline sample, general characteristics and covariates were compared between groups of HC, MCI and dementia. Regarding the follow-up sample, general characteristics and covariates were compared between the group of participants who were included to those who were excluded based on a $\geqslant 1\%$ difference in ICV between baseline and follow-up measurements.

Analysis of the relation of ICV and markers of neurodegeneration

The relation of ICV to brain atrophy, ventricular dilatation, and WML load was first examined cross-sectionally in the baseline sample of HC. Quartiles of distribution of ICV were calculated in the HC sample among men and women separately. Threshold of the quartiles of ICV (in cm^3) were 1347, 1418, and 1486 for women, and 1536, 1615, and 1692 for men. Mean values of sample characteristics and fractions of TBV, vCSF, and WML over ICV were calculated per quartile of ICV. Associations of ICV to sample characteristics and fractions of TBV, vCSF, and WML were analyzed using a logistic regression model for categorical variables as dependent variable and a linear regression model for continuous variables as dependent variable. In both types of models, ICV was entered as independent continuous variable and adjustments were made for age and sex. Models for the relation of ICV to fractions of TBV, vCSF, and WML were further adjusted for educational level, smoking and drinking history, and diagnosis of diabetes and hypertension. A p-value < 0.05 was considered significant.

Second, the relation of ICV to brain atrophy, ventricular dilatation, and WML load, was visualized and analyzed in different age groups. Deciles of ICV were computed separately for each quartile of age with thresholds 66–71, 72–75, 76–79, and 80–95. The mean fractions of TBV, vCSF and WML over ICV were plotted for each decile of

ICV and for each quartile of age separately. For each quartile of age, a separate linear model was created with fraction of TBV, vCSF, or WML as dependent variable and ICV as independent variable, together with corrections for sex, educational level, smoking and drinking history, and diagnosis of diabetes and hypertension. The regression lines of each quartile of age were displayed in the same graph. The relation of ICV to fractions of TBV, vCSF, and WML was compared between the quartiles of age by testing the interaction term for ICV and quartile of age in the whole sample of baseline HC (also corrected for sex, educational level, smoking and drinking history, and diagnosis of diabetes and hypertension). A $p < 0.05$ was considered significant.

Third, the relation of ICV to the change in fractions of TBV, vCSF, and WML, over a period of on average five years was examined. Change in fraction of TBV was expressed as yearly change per mill of ICV and change in fractions of vCSF and WML were expressed as yearly change per myriad of ICV. The change in these markers was entered in a linear model as dependent variable, with baseline ICV measurement as independent continuous variable with adjustments for age, educational level, sex, smoking and drinking history, and diagnosis of diabetes and hypertension. The relation of ICV to change in fractions of TBV, vCSF, and WML after five-year follow-up was also visualized. Again, deciles of ICV were computed for the follow-up sample of HC. Mean values of annualized change per year in fractions of TBV, vCSF, and WML over ICV were plotted for each decile of ICV. The regression lines from the linear models were drawn in the same graph.

ICV and markers of neurodegeneration in MCI and dementia

The relation of ICV to fractions of TBV, vCSF, and WML was visualized and compared between groups of HC, MCI, and dementia. Deciles of ICV were computed separately for HC, MCI, and dementia. Mean values of fractions of TBV, vCSF and WML over ICV were plotted for each decile of ICV and for HC, MCI, and dementia groups separately. A linear model was created separately for HC, MCI, and dementia, with fraction of TBV, vCSF, or WML as the dependent variable and baseline ICV measurement as the independent variable. Corrections were made for age, sex, educational level, smoking and drinking history, and diagnosis of diabetes and hypertension. The relation of ICV to fractions of TBV, vCSF, and WML was compared among groups of HC, MCI, and dementia by testing the interaction term for ICV and group status (also corrected for sex, educational level, smoking and drinking history, and diagnosis of diabetes and hypertension). A $p < 0.05$ was considered significant.

Analysis of the relation of ICV and change in cognitive speed

Whether ICV was related to the change in cognitive speed over five years was assessed separately in HC, MCI, and dementia. First, mean cognitive speed scores at baseline and follow-up between the quartiles of ICV of HC were compared. Second, the relation was assessed in a linear model with change in cognitive speed entered as dependent variable and baseline ICV measurement entered as independent variable together with age, sex, and speed score at baseline. To assess whether the relation of ICV to change in cognitive speed was mediated through change in neurodegenerative markers, a second linear model was made with further addition of change in TBV, vCSF, and WML.

RESULTS

Sample characteristics

Mean age of our sample was 76.3 (5.4) years, and 58.1% ($N = 2619$) of the sample were women. ICV was on average 1502 (148) cm^3 and TBV was on average 1039 (99) cm^3. Twenty four percent of the women ($N = 629$) and 32% of the men ($N = 605$) had a college or university education. Compared to HC, MCI and dementia groups were on average older, had a lower percentage of women, lower educational level, lower speed of processing, lower BMI, lower percentage of alcohol consumers and higher prevalence of hypertension (Table 1). There was no difference in mean ICV between the different cognitive status groups. Sample characteristics of the included participants versus the excluded participants of the follow-up sample did not differ (Table 2).

The relation of ICV and markers of neurodegeneration

In the baseline sample of HC, when ICV was taken as a continuous variable, those with larger ICV were on average younger, had a higher educational level, a faster speed of processing, smoked and drank more, and a lower prevalence of diabetes and hypertension (Table 3). Fraction of TBV over ICV was significantly lower in those with larger ICV and fractions of vCSF and WML over ICV were significantly larger in those with larger ICV. These relations did not change after correction for age, sex, educational level, smoking and drinking history, and diagnosis of diabetes or hypertension.

Figure 1 displays the relations of ICV with fractions of TBV, vCSF and WML per quartile of age. Mean fraction TBV declined with each consecutive older quartile of age. Yet, in all age groups, mean fraction TBV also declined with each consecutive larger decile of ICV. Also, mean fractions of vCSF and WML increased with each consecutive

Table 1: Sample characteristics of baseline study samples

Sample characteristics, %(N)	HC	MCI	Dementia	p^a
	$N = 3883$	$N = 422$	$N = 202$	
Age (years), M (SD)	75.7 (5.2)	79.7 (5.4)	80.9 (4.9)	<.0001
Women	59.4 (2307)	50.5 (213)	49.0 (99)	<.0001
ICV (in cm^3), M (SD)	1502 (147)	1494 (156)	1510 (154)	0.39
Higher education	29.9 (1160)	10.9 (46)	13.9 (28)	<.0001
Speed of processing, M (SD)	0.223 (0.634)	−0.888 (0.869)	−1.53 (1.20)	<.0001
BMI (kg/m^2), M (SD)	27.0 (4.3)	26.8 (4.4)	25.8 (4.2)	0.0004
Never smoked	40.5 (1573)	41.7 (176)	41.1 (83)	0.89
Never drank alcohol	21.4 (826)	28.9 (121)	28.6 (57)	0.0003
Diabetes	11.1 (430)	10.2 (43)	11.5 (23)	0.85
Hypertension	79.6 (3089)	86.0 (363)	84.7 (171)	0.002

a p-value from ANOVA for continuous variables and χ^2 test for class variables.

% (N), percentage (number); M (SD), mean (standard deviation); HC, healthy cognition; MCI, mild cognitive impairment; ICV, intracranial volume; Higher education, college or university education; BMI, body mass index.

older quartile of age and in all age groups mean fractions of vCSF and WML increased with each consecutive larger decile of ICV. Thus, slopes of ICV fractions of TBV, vCSF, and WML in the different age groups had a different intercept but ran parallel. The interaction term ICV x quartile of age were non-significant, being 0.33 for TBV, 0.89 for vCSF, and 0.44 for WML.

Figure 2 and table 4 display the influence of ICV on change in neurodegenerative markers according to ICV. Measured over a 5 year period, yearly increase in vCSF and WML (expressed in per myriad ICV) was significantly larger in those with larger ICV, with 7.55 (4.88) in the lowest quartile of ICV compared to 9.49 (5.85) in the highest quartile of ICV for vCSF and with 6.80 (7.13) in the lowest quartile compared to 9.15 (10.14) in the highest quartile for WML (both $p < 0.001$). Figure 2 also shows the relation between ICV and change in TBV per mill ICV, and change in vCSF and WML per myriad ICV. Although, visually the change in per mill TBV was larger in those with larger ICV, this trend did not reach significance ($p = 0.34$).

ICV and markers of neurodegeneration in MCI and dementia

Figure 3 displays the relations of ICV and fractions of TBV, vCSF, and WML in groups of HC, MCI, and dementia. Mean fraction of TBV was lower in MCI and dementia

Figure 1: ICV and markers of neurodegeneration in different age groups

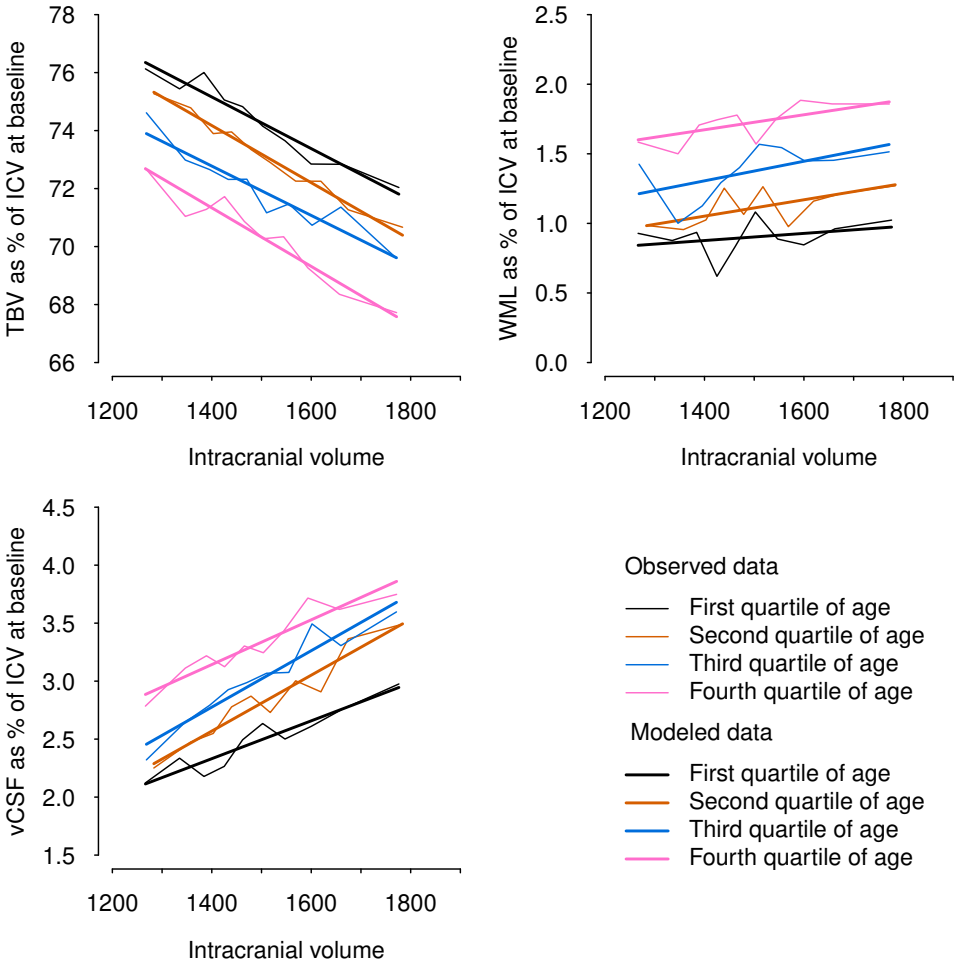

Figure 2: ICV and change in markers of neurodegeneration over 5 years in HC

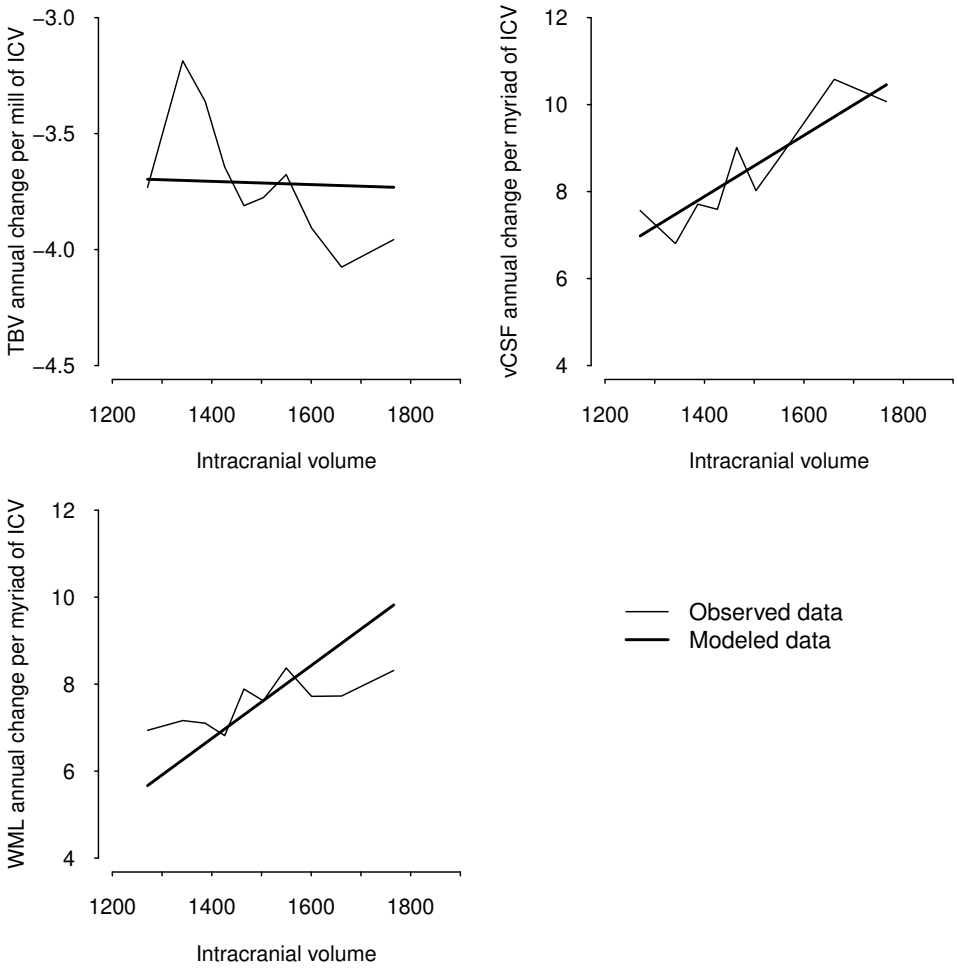

Figure 3: Association of ICV with neurodegeneration in HC, MCI and dementia

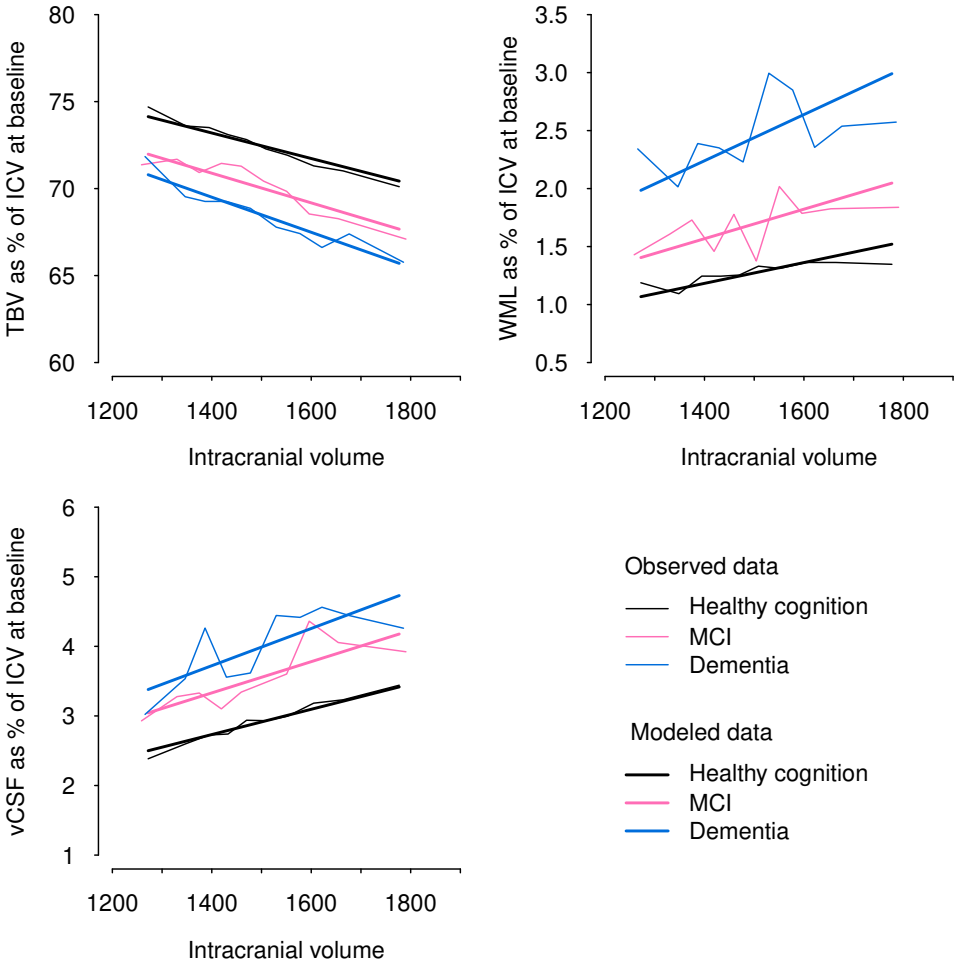

Table 2: Comparison of included versus excluded participants of the follow-up sample

Sample characteristics, % (N)	Included subjects ICV change < 1% $N = 1852$	Excluded subjects ICV change ⩾ 1% $N = 682$	p^a
Age (years), M (SD)	74.6 (4.6)	74.7 (5.2)	0.69
Women	59.0 (1093)	58.4 (398)	0.80
Higher education	27.1 (502)	30.2 (206)	0.14
Speed of processing	0.070 (0.780)	0.013 (0.776)	0.11
BMI (kg/m^2), M (SD)	25.0 (3.3)	24.9 (3.4)	0.62
Never smoked	43.5 (806)	43.8 (299)	0.92
Never drank alcohol	20.6 (379)	20.9 (140)	0.92
Diabetes	9.62 (178)	8.52 2 (58)	0.44
Hypertension	77.6 (1438)	77.6 (529)	0.99

a p-value from t-test for continuous variables and χ^2 test for class variables.

ICV, intra cranial volume; M (SD), mean (standard deviation); Higher education, college or university education; BMI, body mass index

compared to HC, yet in all groups, fraction of TBV also declined in each consecutive larger decile of ICV. Also, mean fractions of vCSF and WML were higher in MCI and dementia compared to HC, yet in all groups, mean fractions of vCSF and WML increased in each consecutive larger decile of ICV. A subtle divergence of slopes of relation of ICV and fractions of TBV, vCSF and WML can be observed, with slopes in MCI and dementia being slightly steeper compared to the slopes in HC. The$p$-value for the interaction term with cognitive status did not reach significance but indicated a trend, being 0.12 for TBV, 0.18 for vCSF, and 0.16 for WML.

The relation of ICV and change in cognitive speed

In the follow-up sample, mean cognitive speed had decreased more in those with larger ICV. Cognitive speed had changed from 0.044 (0.71) to −0.17 (0.77) in quartile 1, from 0.22 (0.67) to 0.015 (0.74) in quartile 2, from 0.27 (0.65) to 0.046 (0.67) in quartile 3, and from 0.27 (0.62) to −0.010 (0.73) in quartile 4. Table 5 shows the relation of ICV to change in cognitive speed. ICV was significantly negatively associated with change in cognitive speed in HC ($p = 0.006$) and in MCI ($p < 0.001$) but not in dementia ($p = 0.12$). Thus, in HC and MCI, those with larger ICV had decreased more in cognitive speed compared to those with smaller ICV. After adding change in TBV, vCSF, and WML, to the model, the association of ICV to change in cognitive speed was attenuated, but continued to be significant in MCI ($p = 0.004$).

Table 3: Sample characteristics and neurodegeneration per quartile of ICV in HC at baseline

Sample characteristics markers of neurodegeneration, % (N)	Quartile of ICV (sex specific) Q1 $N = 1127$	Q2 $N = 1127$	Q3 $N = 1126$	Q4 $N = 1127$	p^a	p^b
Age (years), M (SD)	76.6 (5.6)	76.5 (5.5)	76.2 (5.3)	75.8 (5.3)	<.0001	
Women	58.1 (655)	58.1 (655)	58.1 (654)	58.1 (655)	-	
Higher education	19.1 (215)	25.7 (290)	30.2 (340)	34.5 (389)	<.0001	
Speed of processing, M (SD)	−0.071 (0.814)	0.029 (0.818)	0.139 (0.779)	0.120 (0.869)	<.0001	
BMI (kg/m^2), M (SD)	25.0 (3.5)	24.9 (3.2)	25.0 (3.3)	24.9 (3.3)	0.96	
Never smoked	46.4 (523)	40.2 (453)	38.6 (435)	37.4 (421)	0.002	
Never drank alcohol	46.4 (523)	40.2 (453)	38.6 (435)	37.4 (421)	0.0006	
Diabetes	12.7 (143)	11.6 (130)	8.36 (94)	11.4 (129)	0.01	
Hypertension	82.8 (933)	81.5 (919)	78.2 (880)	79.1 (891)	0.004	
As % of ICV, M (SD)						
TBV	72.9 (3.7)	72.3 (3.8)	71.9 (3.8)	71.1 (4.2)	<.0001	<.0001
vCSF	2.76 (1.11)	3.01 (1.30)	3.09 (1.30)	3.23 (1.32)	<.0001	<.0001
WML	1.28 (1.35)	1.30 (1.28)	1.39 (1.35)	1.50 (1.46)	<.0001	<.0001

a p-value from general linear model with ICV as continuous variable adjusted for age and sex.

b model additionally adjusted for smoking history, drinking history, diagnosis of diabetes and diagnosis of hypertension.

% (N), percentage (number); M (SD), mean (standard deviation); Higher education, college or university education; BMI, body mass index; ICV, intracranial volume; TBV, total brain volume; vCSF, ventricular cerebrospinal fluid volume; WML, white matter lesion volume.

Table 4: ICV and neurodegenerative markers over 5 years in HC

Annualized change, M (SD)	Quartile of ICV (sex specific) Q1 $N = 397$	Q2 $N = 396$	Q3 $N = 396$	Q4 $N = 397$	p^a
TBV ‰ ICV	−3.79 (1.93)	−3.56 (2.00)	−3.76 (1.91)	−3.74 (1.97)	0.43
vCSF ‰ ICV	7.55 (4.88)	8.23 (5.17)	9.00 (5.93)	9.49 (5.85)	<.0001
WML ‰ ICV	6.80 (7.13)	7.20 (7.77)	7.11 (7.83)	9.15 (10.1)	0.02

a *p*-value from general linear model with change in TBV, vCSF or WML as dependent variable and ICV as continuous independent variable adjusted for age, sex, smoking history, drinking history, diagnosis of diabetes and diagnosis of hypertension.

M (SD), mean (standard deviation); ICV, intracranial volume; TBV, total brain volume; vCSF, ventricular cerebrospinal fluid volume, WML, white matter lesion volume.

DISCUSSION

Main findings

In a large sample of older individuals, larger ICV was associated with a lower fraction of TBV and larger fractions of vCSF and WML. These relations were similar in different age groups, slightly more pronounced in MCI and dementia, and independent from other sample characteristics associated with larger ICV (sex, educational level, smoking history, alcohol history, diagnosis of diabetes or hypertension). Furthermore, after a five year follow-up, larger ICV was significantly associated with a larger yearly increase in vCSF and WML. In HC and MCI, larger ICV was also associated with a larger decrease in cognitive speed, which could partially be explained by the larger increase in ventricular dilatation and WML in larger ICV.

General discussion

We investigated in a large sample of older people whether ICV was associated with either a higher resistance or higher resilience to neurodegenerative changes. ICV is often regarded as a proxy for brain reserve, because previously it was shown that in various clinical groups those with larger ICV seemed to cope better with the (relatively) same amount of neurodegenerative changes compared to those with smaller ICV (Hedges and Woon 2010; Kesler et al. 2003; Skoog et al. 2012; Sumowski et al. 2016; Tate et al. 2011). The notion of resistance implies that among people without overt neurodegenerative disease, those with larger ICV have fewer neurodegenerative changes, as measured by brain atrophy and WML load. However, our study showed that in a general popula-

Table 5: ICV and change in cognitive speed over 5 years

	HC $N = 1586$		MCI $N = 176$		Dementia $N = 90$	
Model 1	β (SD)	p^a	β (SD)	p^a	β (SD)	p^a
Age	−0.021 (0.002)	<.0001	−0.010 (0.010)	0.30	0.021 (0.029)	0.47
Sex	0.004 (0.027)	0.88	−0.019 (0.116)	0.87	0.23 (0.36)	0.53
Cognitive speed at baseline	−0.11 (0.02)	<.0001	−0.37 (0.05)	<.0001	−0.24 (0.17)	0.17
ICV at baseline	−0.026 (0.009)	0.006	−0.13 (0.04)	0.0009	−0.23 (0.14)	0.10
Model 2						
Age	−0.020 (0.002)	<.0001	−0.011 (0.009)	0.21	0.015 (0.030)	0.63
Sex	−0.013 (0.026)	0.62	−0.016 (0.109)	0.88	0.12 (0.37)	0.76
Cognitive speed at baseline	−0.12 (0.01)	<.0001	−0.33 (0.05)	<.0001	−0.21 (0.17)	0.23
Change in TBV	0.36 (0.05)	<.0001	0.19 (0.22)	0.39	0.57 (0.66)	0.39
Change in vCSF	−0.56 (0.21)	0.006	−2.08 (0.82)	0.01	−1.36 (2.50)	0.59
Change in WML	−0.44 (0.12)	0.0004	-0.40 (0.48)	0.40	−0.44 (1.23)	0.73
ICV at baseline	−0.017 (0.009)	0.05	−0.11 (0.04)	0.004	−0.20 (0.14)	0.17

a p-value from general linear model with change in cognitive speed score as dependent variable and independent variables listed in the 1st column.
HC, healthy cognition; MCI, mild cognitive impairment; ICV, intracranial volume; TBV, total brain volume; vCSF, ventricular cerebrospinal fluid volume; WML, white matter lesion volume.

tion, larger ICV was associated with more neurodegenerative changes, both in terms of absolute and relative volumes. This finding was supported by the result of the follow-up analyses taken 5 years from baseline that showed a disproportionately faster increase in vCSF and WML in those with larger ICV. The relation between larger ICV and higher levels of markers of neurodegeneration is intriguing. Although, those with larger ICV had a higher prevalence of lifestyle traits unfavorable for health, i.e., they had smoked and drank more, these factors did not exert an influence on the relation of ICV and neurodegenerative markers and therefore could not explain the phenomenon. Why then would a brain that was favored to grow larger during early life, loose its volume quicker in later life and contain relatively more WML? The present study did not enable us to find an explanation, but we put forward two hypotheses. First, it may be that a larger brain is more difficult to maintain and therefore may be more vulnerable to neurodegenerative changes. Such a proposition could also explain for instance why those with larger ICV have been found to have an accelerated conversion to dementia (An et al. 2016). Our second hypothesis is that the brain atrophies in an allometric fashion, i.e., the larger the ICV, the proportionally larger the decrease in brain parenchymal volume per unit of time. Although, there is some familiarity with allometric geometrical scaling of brain structures to ICV (de Jong, Vidal, et al. 2017; Im et al. 2008), there are no reports on size-dependent non-linearity in age-related brain atrophy.

Furthermore, we investigated whether ICV was associated with an increased resilience to neurodegenerative changes. First, we compared the relation of ICV with neurodegenerative markers in HC to groups of MCI and dementia. In all groups larger ICV was associated with proportionately more neurodegenerative changes. A non-significant trend indicated that the effect of ICV on the amount of neurodegenerative changes was slightly more pronounced in MCI and dementia. Thus, finding more neurodegenerative changes in those with larger ICV in MCI or dementia seems not to be related to a later expression of a neurodegenerative disease due to a buffer effect in people with larger ICV. Rather, our study showed the relation of ICV to neurodegenerative markers was independent of the presence of a neurodegenerative disease. Second, we also studied whether ICV was related to change in cognitive speed in HC. At baseline those in quartile 4 had the fastest mean cognitive speed, but at follow-up the mean cognitive speed score of quartile 4 had dropped below the mean score of those in quartile 2. Also, after controlling for age, sex, and baseline speed score, cognitive speed had decreased significantly more in those with larger ICV. Since larger ICV was related to larger ventricular dilatation and larger increase in WML, it seems plausible that this could explain the faster decrease in cognitive speed. Indeed, when ICV together with change in TBV, vCSF, and WML were entered in the same model to explain change in cognitive speed, the effect of ICV on change in cognitive speed was largely attenuated, indicating that, in HC, the larger

decrease in cognitive speed in those with larger ICV was mediated through the presence of more brain atrophy and a higher increase in WML. In the MCI group, like in HC, larger ICV was also significantly associated with larger decrease in cognitive speed. However, this effect was only partially mediated through the change in vCSF. We do not have an explanation for the association of ICV with change in cognitive speed that seemed independent from the markers of neurodegeneration we controlled for. Possibly, brain atrophy and ventricular dilatation did not reflect the full extent of neurodegeneration in MCI. All together, regarding cognitive speed, we found no support for the notion that a larger ICV would be associated with a greater resilience in face of neurodegenerative changes.

The results of this study are important for our understanding of brain ageing in several ways. First, we found no supporting evidence that ICV was associated with either a raised resistance or resilience to neurodegenerative changes in older people. On the contrary, we found that larger ICV was associated with a higher degree of neurodegenerative changes and a larger decrease in cognitive speed. This can become clinically apparent as a faster conversion to dementia or as a faster clinical deterioration in those with a larger ICV, as previously described (An et al. 2016; Mungas et al. 2018). Second, if atrophy occurs in a non-linear fashion according to ICV, the interpretation of volumetric differences between groups will depend on the ICVs of the two groups. Furthermore, in our sample there was a substantial difference of 3.17% in mean fraction of TBV between the lowest and the highest decile of ICV. Whereas the difference in mean fraction of TBV between cognitively healthy and demented people was only 2.51%. Thus, the magnitude of the effect of ICV on fraction of TBV variation exceeded that of diagnosis of dementia, which indicates that the size-dependent non-linear brain atrophy could obscure pathological patterns of brain ageing.

Strengths and limitations

Strength of the current study was the availability of information on demographics, relevant risk factors, clinical parameters, and brain MRI for a large sample of older people spanning the range from HC, to MCI and dementia. We could therefore study the relation of ICV and markers of neurodegeneration not only in clinical groups but also in healthy cognitive ageing. Furthermore, the availability of follow-up data of a large part of the sample for further analysis supported and strengthened our findings in the cross-sectional data. However, the follow-up data did not show a faster decline in yearly change in TBV after 5 years and therefore we cannot be entirely certain whether the cross-sectional association of larger ICV with lower fraction TBV is based on faster atrophy of the brain in larger ICV. Theoretically, it is also possible that larger ICV is as-

sociated with smaller fraction TBV throughout the life span. A longer follow-up duration could make the relation between ICV and brain atrophy more clear. Another potential limitation of the current study was that all measures of neurodegenerative markers were based on estimations of the automated MRI segmentation pipeline. Automated segmentation of MRI into different tissue classes forms a very robust method compared to visual qualitative assessment scores. Even so, it is possible that the segmentation pipeline introduces errors into the tissue segmentation. However, we could not identify an error that could have affected all three different MRI markers of neurodegeneration in the same manner. Another potential problem may be a systematic error in estimation of ICV by the segmentation pipeline. A previous study compared the ICV estimation of Statistical Parametric Mapping (SPM, version 8) and Freesurfer (FS, version 5.1.0) to reference estimations of ICV based on manual segmentation and found that both automated methods overestimated ICV (Nordenskjold et al. 2013). Interestingly, they found that the overestimation of ICV by FS was related to the reference ICV estimation. FS did not explicitly segment ICV, but estimated it based on the determinant of the affine transform matrix used to align the image with an atlas. Affine transform only crudely approximates head shape. However, the automated segmentation pipeline used in the current study has two advantages over the segmentation software that was tested before. First, it made use of a probabilistic tissue atlas that was developed based on a sample of MRI from the AGES-RS cohort, and thus the atlas was age appropriate. And second, the tissue segmentation made use of non-linear transformation to warp the atlas from standard space to native space and therefore if present would be able to allow allometry in brain geometry.

CONCLUSION

In a large sample of older individuals spanning the range from normal cognition to dementia, larger ICV was associated with a relatively smaller brain volume and larger volumes of vCSF and WML. Larger ICV was also associated with a faster increase in vCSF and WML over five years. Moreover, larger ICV was significantly associated with a larger decline in cognitive speed, which was partially mediated through the change in TBV, vCSF, and WML. Thus, contrarily to what is often proposed in literature, we found no evidence for the notion that ICV is associated with a higher resistance or resilience to neurodegenerative changes. Rather, a larger ICV was associated with relatively more brain atrophy, a higher WML load, and a faster decline in cognitive speed.

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