

Research report

# The relationship between head size and intracranial volume in elderly subjects

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## Abstract

**Objective:** To study the relationship between parenchymal head volume (PHV) and intracranial volume (ICV), and to compare the ability of these two measurements to reflect the association between maximum mature brain volume and late-life cognition. **Methods:** An elderly sample of humans with a range of cognitive functions from normality, via mild cognitive impairment (MCI) to dementia (mean age 78.6, S.D. 2.8; mean MMSE 25.4, S.D. 4.2) was examined. Head-to-head measurements of ICV and parenchymal head volume (PHV) were obtained from three-dimensional T1 weighted magnetic resonance images using automated procedures. Analyses of cognitive functions were based on continuous and categorical variables. **Results:** PHV explained 55% of the variance in ICV. The ratio between PHV and ICV remained constant with increasing age and cognitive impairment. Measurements of PHV and ICV yielded comparable correlations with global cognitive performance. Group differences over gender and cognitive states were equally present in ICV and PHV. The relative risks of cognitive impairment that were associated with either small ICV or PHV were comparable. **Conclusions:** Measures of PHV can be considered as useful estimates of ICV and cerebral volume reserve.

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**Theme:** Disorders of the nervous system

**Topic:** Degenerative disease: Alzheimer's - cognitive function

**Keywords:** Cognition; Alzheimer's disease; Mild cognitive impairment; Intracranial volume; Head size; Brain reserve

## 1. Introduction

Brain growth is the main determinant of the size of the cranial vault, which normally ceases to grow at ~7 years of age. In the 20s, the volume of the brain starts to decrease, while it is presumed that the intracranial volume (ICV) remains constant [30].

Larger brains may be better protected against the clinical expression of aging and disease-related structural changes [18,23]. Presuming that head size reflects the maximum

mature brain volume (MMBV), a number of epidemiological studies confirmed the assumption of brain volume reserve effects by finding a significant relationship between head circumference and cognitive performance [11,26,34] and/or risk of dementia [2,32].

The intracranial volume is generally considered to be a more accurate indicator of MMBV than head size. However, neuroimaging studies did not always support an association between ICV and cognition [6,16].

To date, little is known about the relationship between ICV and parenchymal head volume (PHV). Estimates of the correlations between brain and skull sizes lie between 0.2 and 0.8 [17,36]. Skull thickness may differ by gender and ethnicity [1,29], as could also the correlation between ICV and PHV. Furthermore, ageing and effects associated with dementia disorders, such as estrogen deficiency and

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weight loss, could differentially influence the scalp and bone parenchyma of the head.

In accordance with some other studies [4,5,8,21,22,31], we previously found significant cross-sectional ICV differences over cognitive states in a sample of elderly subjects examined with MRI [38]. Based on this sample, this study aimed to explore the relationship between ICV and PHV and its ability to reflect a possible association with late-life cognitive functions.

## 2. Material and methods

### 2.1. Subjects

Informed written consent was obtained from all subjects and/or their legal caregivers. The study received approval from the local Ethics Committee.

A total of 99 subjects (34 males, 65 females) within a relatively narrow age range of 75–85 years (mean age 78.6, S.D. 2.8; mean MMSE 25.4, S.D. 4.2), representing the birth years 1913–1923, were examined. The sample included 68 non-demented participants (mean age 79.2, S.D. 2.8; mean MMSE 27.9, S.D. 1.5) from the Leipzig Longitudinal Study of the Aged (LEILA 75+) [27] who were consecutively recruited to represent a cognitive continuum based on MMSE strata, and a reference group of 31 demented patients who were recruited from patients of the Memory Clinic of the University Department of Psychiatry.

Three clinical groups were formed based on clinical dementia rating [15] and standard diagnostic criteria for dementia disorders [39]. A total of 34 (15 male) had a clinical dementia rating (CDR) of 0 and were regarded as the cognitively normal control group (NC). All normal subjects had MMSE scores above 28 and SIDAM scores above 48. None of these showed any considerable cognitive decline during a 2.4-year follow-up period. A total of 34 subjects (ten male) had a CDR of 0.5 (questionable dementia), but were not demented according to ICD-10 research criteria, i.e. they had normal activities of daily living. They were regarded as ‘mildly impaired’ (MCI). The mean CDR sum of boxes score of  $0.9 \pm 0.8$  in this group indicates a very mild degree of cognitive impairment. Psychometrically, MCI subjects in this study performed at least 1 S.D. below age- and education adjusted means [3] in one or more cognitive domains. Of these subjects 20 had relatively isolated short-term memory impairment. The others showed both short-term memory impairment and additional difficulties in performing visuo-spatial or calculation tasks. Hence, these subjects would fulfil modified criteria for aging-associated cognitive decline (AACD) [3,20]. Only a minority would meet the Mayo Clinic criteria for amnesic MCI [25].

The patients’ group (‘demented’, De) included 31 patients (nine male) with dementia of mild to moderate

severity (CDR 0.5–2). All received a diagnosis of pure or mixed Alzheimer type dementia according to ICD-10 research criteria [39].

### 2.2. Methods

#### 2.2.1. Clinical assessment

All subjects, including those from LEILA 75+ were clinically investigated in the Memory Clinic of the University Department of Psychiatry, Leipzig. The clinical assessments included thorough neurological and psychiatric examinations, and an informant interview, as previously described [37].

#### 2.2.2. Clinical dementia rating

The CDR [15] comprises the six sub-categories ‘memory’, ‘orientation’, ‘judgement and problem solving’, ‘community affairs’, ‘home and hobbies’ and ‘personal care’. A rating of 0.5 is consistent with ‘questionable impairment’. The ratings in each sub-category can be summed to yield the ‘sum of boxes’ score. The global CDR score is derived by a standard algorithm.

#### 2.2.3. The Structured Interview for the diagnosis of Dementia of Alzheimer type, Multi-infarct dementia and dementias of other aetiologies according to ICD-10 and DSM-III-R (SIDAM)

All subjects underwent the cognitive test battery of the SIDAM [40]. The SIDAM is a diagnostic screening instrument that has been deliberately constructed to service each element of the DSM-III-R and ICD-10 criteria for dementia. It contains a cognitive test battery which includes all MMSE items [7] and a number of additional items. The 55 tasks can be summed up to give the SIDAM score (SISCO), which ranges from 0 (the worst cognitive impairment) to 55 (no cognitive impairment). The SISCO covers a broader range of cognitive functions than the MMSE and is also sensitive to mild degrees of cognitive decline. It can be divided into eight sub-scores which describe the following subtypes of intellectual functioning: orientation, immediate recall, delayed recall, long term memory, verbal abilities/calculation, visuo-spatial function, intellectual function, and aphasia/apraxia. Recently established age- and education-specific norms for the SISCO sub-scores [3] allow us to estimate the prevalence of various types of MCI with operationalised criteria, such as ‘amnesic MCI’ [24,25] or ‘ageing-associated cognitive decline’ (AACD) [20].

#### 2.2.4. MRI acquisition

Three-dimensional T1-weighted MR data sets were obtained from all subjects (Siemens Vision 1.5T, MPRAGE sequence, TR 11.4 ms, TE 4.4 ms, 128 slices, matrix  $256 \times 256$ , voxel size  $0.9 \times 0.9 \times 1.5$  mm).

### 2.2.5. Analysis of MR data sets

Collected data sets were analysed with the BRIAN system [19]. Analyses were performed blind to knowledge of the cognitive state or other clinical data of the subjects. The data sets were aligned with the stereotactical coordinate system and interpolated to an isotropic voxel size of 1 mm using fourth-order b-spline interpolation.

**2.2.5.1. Segmentation of ICV.** A boundary guided region growing segmentation procedure was used to segment brain and cerebrospinal fluid (CSF) compartments, as described previously [14,37]. The region growing method allows a fully automated, operator-independent segmentation of the cerebral compartments white matter, grey matter, and inner and outer cerebrospinal fluid spaces. The ICV was defined as the sum of the three compartments.

The method starts from a seed point and absorbs the highest grey level point in its boundary to expand the region. The segmented region in the first step, called ‘the mask’, is used to prevent the growing process from joining the non-brain parts of the head. The intensity change between dura mater and bone is used to detect the boundary of ICV (Fig. 1).

**2.2.5.2. Segmentation of PHV.** The parenchymal head volume (PHV) estimate was defined as the tissue components (including brain, CSF, skull and scalp) above a caudal cut-off plane which was defined as the level parallel to and 20 mm below the line between anterior and posterior commissure. To segment the PHV, tissue was separated from background using an automated thresholding procedure (k-means algorithm). After morphological opening with a 3-mm kernel, the largest connected component was determined in the volume. Tissue voxels 20 mm below the AC–PC plane were removed, and the remaining voxels counted as the PHV (Fig. 1).

**2.2.5.3. Validity, reliability and longitudinal stability.** Subjective assessment of the results demonstrated a high performance and face validity of the method. Further validation studies of the method were carried out by comparing the automatically derived volumetric measurements of ICV with manual intracranial area (ICA) measurements on the same scans which were performed on T1-weighted images in the frame of another study [13].

The correlation between ICV and ICA in 83 subjects was  $r=0.815$  ( $P<0.0005$ ). Correlation coefficients in subgroups with normal cognition, MCI and dementia were 0.84, 0.86, and 0.81, respectively.

To assess the reliability of the measurements, ICV and PHV were segmented from serial MR data sets in a sub-sample. A total of 12 subjects (four with NC, five with MCI and three with dementia) received a second MR scan which was acquired at a mean of 20.3 months (10–29 months) after the first MR image. The intra-class correlation coefficients between the first and second measurements were 0.99 (95% CI 0.95–1.0,  $P<0.0005$ ) and 0.98 (95% CI 0.92–0.99,  $P<0.0005$ ) for ICV and PHV, respectively, indicating a high re-scan and re-measurement reliability. The mean difference between the first and second measurements was 3.5% in ICV (S.D. 2.2) and 2.2% (S.D. 2.1) in PHV. The ratio between ICV and PHV did not differ between the first and second measurements (mean change 1%, S.D. 2.7%,  $P=0.14$ ). Measurement variations in both ICV and PHV were independent of cognitive state (and hence the presumed rate of brain atrophy) (Kruskal–Wallis,  $P>0.2$ ).

### 2.2.6. ApoE genotyping

The apolipoprotein E (ApoE) genotype, the main genetic susceptibility factor in Alzheimer’s disease, was assessed from blood leukocytes (30  $\mu$ l whole blood) in a sub-sample of 58 patients as described previously [33].

### 2.2.7. Statistical analyses

Statistical analyses were carried out using SPSS for Windows (Release 9.0.1).

To assess the reliability and longitudinal stability of ICV and PHV measurements, intra-class correlation coefficients were calculated based on a one-way random effect model. Pearson and/or partial correlation coefficients were computed to analyse the relationship between continuous measures.

Correlation comparisons and aggregated correlation coefficients were computed for gender subgroups where appropriate. Correlation coefficients in subgroups were tested for homogeneity and aggregated by standard methods for parametric meta-analysis [35], using Fisher’s  $z$ -transforms of the Pearson coefficients.

Two different linear regression models were calculated.



Fig. 1. Automated segmentation of ICV and PHV. (A) 3D T1-weighted MR dataset of a 80-year-old woman with normal cognition (MMSE 28, SISCO 50). (B) Segmentation result based on boundary-guided region growing in the same brain dataset. ICV was defined as the sum of CSF plus brain volume. (C) An estimate of the parenchymal head volume was derived by an automated thresholding procedure which separated the head volume, i.e. the parenchymal tissue of the head, from background. Tissue voxels 20 mm below the AC–PC plane were removed, and the remaining voxels counted as the PHV.

The first evaluated the predictive power of PHV alone, the second model included possible confounds of the relationship between PHV and ICV (age, gender, education).

To assess possible group differences over the three cognitive states, one-way ANOVA with Tukey post-hoc analyses were used after testing for variance homogeneity (Levene statistics,  $P>0.4$ ). The level of statistical significance was defined as  $P<0.05$ . For the analysis of within-group gender differences, the  $t$ -test for independent samples was applied.

To explore the risk associated with small MMBV, we used a categorical approach and transformed the continuous measurements of ICV and PHV into approximate quartiles separately for each gender. To calculate differences and trends in the frequency of cognitive impairment,  $\chi^2$  statistics for linear trends were calculated. Relative risks and confidence intervals were calculated according to standard procedures.

### 3. Results

#### 3.1. Characteristics of the sample

The characteristics of the study groups are shown in Table 1. The preponderance of females in this sample reflects the gender proportion in this age group in the general population. Because the gender proportion is not equal across cognitive states, gender effects were taken into consideration in all subsequent analyses.

Table 3 shows the measurements in ICV and PHV for the whole sample and subgroups.

#### 3.2. The relationship between ICV and PHV

Pearson correlation coefficients between ICV and PHV were 0.562 ( $P=0.001$ ) in males and 0.682 ( $P<0.0005$ ) in females. This difference was not statistically significant ( $P=0.37$ ) (Fig. 2). The aggregated correlation coefficient for males and females was  $r=0.645$  (95% CI 0.511; 0.749).

The ratio between ICV and PHV differed between 0.56 and 0.77 (mean 0.68). No significant differences were present over cognitive states ( $F(2, 96)=1.48$ ,  $P=0.232$ ).

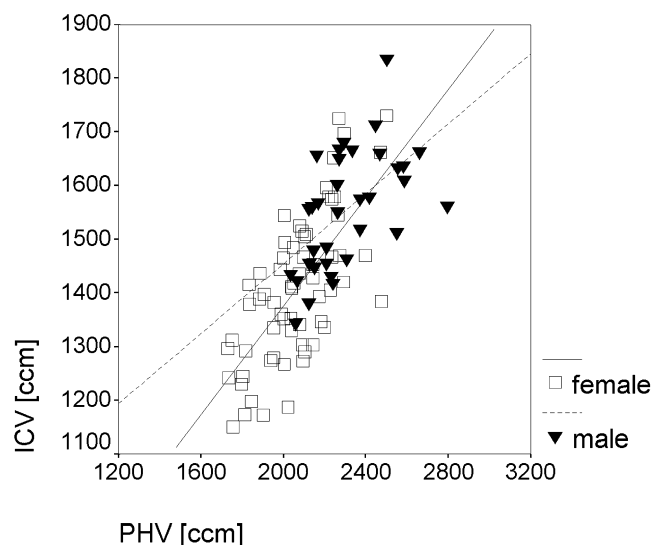


Fig. 2. The relationship between ICV and PHV. Scatterplot of ICV versus PHV in 99 elderly subjects with a continuum of cognitive functions. Correlation coefficients were 0.682 ( $P<0.0005$ ) in 65 females and 0.562 ( $P=0.001$ ) in 34 males. The difference between the correlation coefficients is not significant ( $P$  for comparison=0.37). The aggregated correlation coefficient is  $r=0.645$  (95% CI 0.511; 0.749).

No gender differences were found ( $F(1, 97)=0.0009$ ,  $P=0.532$ ).

To determine, whether there might be age- and/or cognition-related changes in the ability of PHV to reflect ICV (which could for example occur if lower estrogen levels or weight loss accelerated shrinkage of the head parenchyma), we correlated the ICV-PHV ratio with age and global cognitive performance. The ratio between PHV and ICV remained constant with increasing age ( $r=0.071$ ,  $P=0.485$ ) and cognitive performance ( $r=0.086$ ,  $P=0.398$ ) without significant differences between men and women.

Table 2 shows the results of regression analyses examining the predictability of ICV from PHV and possible confounds. The single most important contribution in both models was from PHV (Table 2).

The ApoE 4 allele status was known in a sub-sample of 58 subjects. The frequencies of the ApoE e4 allele were 1/20 (5%) in NC, 11/23 (47.8%) in MCI, and 4/15 (26.7%) in De. Neither ICV nor PHV differed between subjects with and without an ApoE 4 allele. Neither ICV

Table 1  
Characteristics of the sample

	Normal cognition (NC) (CDR 0)	Mildly impaired (MCI) (CDR 0.5)	Demented (De) (CDR 0.5–2)
Male/female, $n$	15/19	10/24	9/22
MMSE <sup>#</sup> , mean (S.D.)	28.9 (0.7)	26.6 (1.5)	20.9 (3.7)
Years of education <sup>§</sup> , mean (S.D.)	12.4 (2.9)	10.5 (1.6)	11.1 (1.9)
Age, mean (S.D.)	78.7 (2.4)	78.7 (2.4)	78.2 (2.6)

S.D., standard deviation.

<sup>#</sup>Significant difference over all groups (ANOVA, Tamhane post-hoc,  $P<0.0005$ ).

<sup>§</sup>Significant difference between NC and MCI (ANOVA, Tamhane post-hoc,  $P=0.008$ ).

Table 2  
Regression models predicting ICV from PHV and possible confounds

Predictor variables	Unstandardized coefficients <i>B</i>	Standardized coefficients $\beta$	<i>T</i>	<i>P</i> -value
Regression model 1 ( $F=117.98$ , $P<0.001$ , $r^2=0.554$ )				
Constant	455.091		4.895	0.000
PHV	0.466	0.741	10.862	0.000
Regression model 2 ( $F=33.19$ , $P<0.001$ , $r^2=0.573$ )				
Constant	550.618		1.630	0.107
PHV	0.408	0.653	8.341	0.000
Age	0.097	0.002	0.026	0.979
Education	7.712	0.124	1.784	0.078
Gender	-40.854	-0.133	-1.724	0.088

nor PHV correlated with the ApoE 4 allele status in either gender (Spearman  $r=0.172$ ,  $P=0.5$  in males,  $r=-0.102$ ,  $P=0.5$  in females).

### 3.3. Association of ICV and PHV with late-life cognition

Moderate correlations between two parameters do not necessarily imply that they equally reflect the association with a third factor, such as cognition or education. Based on our previously reported results in this sample [38], an association between ICV and cognitive performance as well as education was to be expected in the subgroup of women, but not in men. We were therefore interested to know whether PHV reflects the significant correlations and group differences over cognitive states that were present in ICV.

PHV yielded group differences over cognitive states and gender comparable to ICV (Table 3). Table 4 shows that PHV yielded correlations with SISCO and education comparable to ICV. The statistically significant negative correlation between PHV and age in women presumably reflects secular trends. The correlation coefficient of ICV and age in women was weaker, but in the same direction.

Finally, we performed a quartile analysis to demonstrate the association between small head size and small ICV in the subgroup of 67 females. Table 5 shows that both parameters yielded similar results. Women having an intracranial volume in the lowest quartile had an increased risk of being cognitively impaired (relative risk 1.48; 95% CI 1.15; 1.89) as compared to those in the three higher

Table 4  
Pearson correlation coefficients

		SISCO	Education	Age
Women	ICV	0.35**	0.34**	-0.13
	PHV	0.26*	0.2	-0.25*
Men	ICV	0.03	0.04	-0.04
	PHV	-0.01	0.14	0.06

\* $P<0.05$ .

\*\* $P<0.01$ .

Table 5  
Percentage of female subjects ( $n=65$ ) with normal cognition in each quartile of ICV and PHV, respectively

Quartile	First	Second	Third	Fourth
Of ICV, %	5.3	21.1	31.6	42.1
Of PHV, %	12.5	21.1	26.3	42.1

quartiles. Having a PHV within the lowest quartile also increased the risk in a similar fashion (relative risk 1.33, 95% CI 1.01; 1.76). Having ICV or PHV in the highest quartile decreased the risk of cognitive impairment as compared to the three lower quartiles (ICV and PHV: relative risk 0.64, 95% CI 0.39; 1.07) (Table 5).

There were significant linear trends for both ICV ( $\chi^2=8.5$ ,  $df$  1,  $P=0.003$ ) and PHV ( $\chi^2=6.8$ ,  $df$  1,  $P=0.009$ ) towards a decreased prevalence of cognitive impairment with increased volumes.

Table 3  
Mean values and standard deviations in ICV and PHV over cognitive states and gender

Group		Total	NC	MCI	De	One-way ANOVA			
						<i>F</i>	<i>df</i>	<i>P</i> -value	Tukey test
ICV (cm <sup>3</sup> )	Women, mean (S.D.)	1408 (131)	1495 (140)	1399 (119)	1344 (122)	7.3	2,62	0.001	NC>MCI, De
	Men, mean (S.D.)	1555 (110)	1549 (103)	1575 (129)*	1544 (109)*	0.229	2,31	0.797	
PHV (cm <sup>3</sup> )	Women, mean (S.D.)	2071 (112)	2187 (257)	2033 (173)	2012 (173)	6.2	2,62	0.004	NC>MCI, De
	Men, mean (S.D.)	2310 (190)	2302 (180)	2317 (232)*	2313 (177)*	0.008	2,31	0.992	

De, dementia; ICV, intracranial volume; MCI, mild cognitive impairment; NC, normal cognition.

\*Significant gender difference, *T* test,  $P\leq 0.001$ .

#### 4. Discussion

In this cross-sectional study, head-to-head comparisons of PHV and ICV were conducted. The study sample included elderly subjects in a narrow range of 75–85 years. Even though our conclusions may be limited to this age group, this represents a steadily increasing part of the population in Western societies with a considerable prevalence of cognitive impairment and dementia. Our sample included subjects with mild cognitive impairment. This group of subjects was defined using broad clinical criteria. The majority of these subjects had very mild cognitive deficits consistent with the supposedly benign category of aging-associated cognitive decline [20]. Hence, our MCI group most likely represents a heterogeneous group of subjects. Therefore, etiological assumptions with regard to this group have to be made with extreme caution. Pathological studies reported a considerable prevalence of Alzheimer pathology even in non-demented elderly subjects [10], but also a high variation of cognitive performance beyond the severity of AD pathology [28].

Measurements of ICV were based on a sophisticated operator-independent segmentation technique. Visualisation of the dural margins is known to be difficult on T1-weighted images. In comparison, segmentation of head parenchyma against background is relatively simple. Since a precise quantitative validation for our segmentation method is not yet available, we carefully considered the possibility of measurement error, especially with regard to non-systematic errors. High correlations between manually outlined intracranial area measurements and automatically achieved ICV in all cognitive states, as well as the absence of an effect of cognitive state on re-scan–re-measurement variation in both ICV and PHV make non-systematic errors unlikely. The quantitative results of ICV measurements in this study are in the range of results reported by a number of previous studies [6,16,22].

With regard to the relationship between ICV and PHV, our study demonstrates a moderate correlation between these two measures. The correlation was weaker in men, but not significantly so. On the other hand, there was a lack of correlation between cognitive measures and both ICV and PHV in men. Therefore, it appears unlikely that the somewhat weaker correlation between PHV and ICV in men can be used to explain gender differences in the association between head circumference and late-life cognitive functions as suggested by a previous study [32].

Our study did not address the possible error introduced by measuring only head circumference as an estimate of volume. In a post-mortem study which assessed correlations between head size and cranial capacity, a correlation of  $r=0.64$  was reported for head circumference and ICV [9]. In this study, the head circumference accounted for 41% of the variance in ICV. This is a somewhat weaker association than the one we found between PHV and ICV, as one would expect.

Neither ICV nor PHV seemed to be influenced by the ApoE 4 allele status. This is in agreement with previous findings [32]. A recent study reported that the combination of low head circumference and ApoE epsilon 4 strongly predicted an earlier onset of Alzheimer's disease [2]. However, due to the limited sub-sample in which ApoE genotyping data was available, we felt unable to analyse such complex interactions with confidence. The search for other genetic and developmental factors that may determine the relationship between MMBV and late-life cognitive disorders continues [12].

Despite 'only' moderate correlations between ICV and PHV, both measurements yielded comparable associations between small head size, and, respectively, ICV and late-life cognitive functions as well as education. This supports the idea that both measures reflect the same factor that may be referred to as 'brain reserve'.

#### 5. Conclusions

This study supports the notion that measurements of PHV may be reliable estimates of the intracranial volume, even in advanced age and in the presence of dementia disorders. It is incumbent on epidemiologists to use relatively easy-to-obtain measurements of head circumference to further elucidate the complex life-long interactions between maximum mature brain volume and cognition.

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