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Body Height Effect on Brain Volumes in Youth Decreases in Old Age in Koreans

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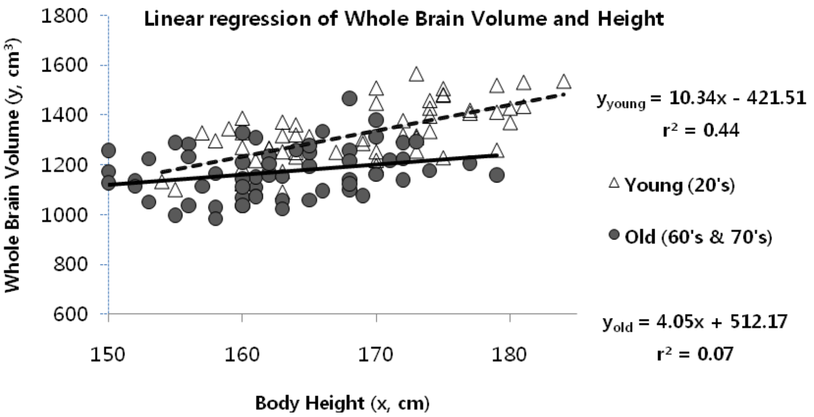
SYNOPSIS

The MRI (magnetic resonance imaging) volumetric analysis of the brain was performed in 59 healthy elderly Koreans (aged 62-76 years; 34 male, 25 female) to investigate whether the previously reported significant correlations between body height and brain volumes in the young aged Koreans (20's) still exist in the old aged Koreans (60's and 70's). Unlike previously reported significant correlations in the young aged Koreans, neither the correlation between whole brain volume and body height in male nor the correlation between cerebellar volume and body height in female show any significance in the old aged Koreans. The significant correlation between body height and whole brain volume was still observed when both male and female data were combined (r=0.27, P<0.05), but the correlation coefficient and the level of significance markedly decreased from those of previously reported Korean youth data (r=0.67, P<0.01). Simple linear regression analysis shows decrease of explanatory power of height (measured in r^2) from 44% in the youth group to 7% in the old age group on the variance of whole brain volume. Multiple linear regression analysis shows that age and sex, rather than height, are major explanatory variables for whole brain volume in the old aged Koreans. The loss of correlations in the aged group is suspected to be mainly due to age related brain volume changes.



Keywords: body height, brain volume, Korean, magnetic resonance imaging, age, sex

Introduction

The effect of body size on the brain size (weight or volume) in human has been controversial. In 1892, Marshall[1] suggested that body size parameters are important when comparing brain sizes in humans, and correction of brain size by means of body size is recommended within sexes. Pakkenberg and Voigt[2] and Passingham[3] reported some significant relationship between brain size and body height with brains aged over 18 years. Ho et al.[4] found that the brain weight correlated best with the body surface area, followed by the body height and body weight, with brains aged 25-80 years. On the contrary, Jerison[5] found no significant correlation between body height and brain size, when analyzing the same data set of Pakkenberg and Voigt[2] with limited age range (28-41 years). Jerison argued that association between height and brain volume was false positive and probably due to the secular trend toward increased height during the 20th century, which resulted in younger individuals tending to be taller and to have larger brains. Peters et al.[6] showed that the difference in the conclusions of Passingham[3] and Jerison[5] about the association between brain weight and body height resulted from difference in age range which they used to select their samples from the original Pakkenberg and Voigt[2] samples. These controversial results suggest the importance of considering the effect of brain maturation and aging during brain size analysis. This controversy may partly come from potential errors in postmortem brain preparation[7].

With the recent development of high resolution MRI (magnetic resonance imaging) techniques, brain volume has become a more useful parameter to study brain size than brain weight. Egan et al.[8] reported positive correlation (r=0.32) between body height and brain volume by MRI, with a group of subjects mainly composed of male, but Wickett et al.[9] reported very low correlation with a group of female subjects (r=0.05). It is suggested from these two studies that the body height effect on the brain volume would be differentially expressed by sex, and these results agree with the report of Pakkenberg and Voigt[2] (male: r=0.35, female: r=0.14) between body height and brain weight in postmortem brains. Koh et al.[10] performed MRI volumetry in the young aged Koreans to understand the relationship between body height and brain volumes (whole brain, cerebellum, and lateral ventricle). Some significant correlations between regional brain volumes and body height in the young aged Koreans were reported in 2005 (Table 1). They found the positive correlations between whole brain volume and body height in male as well as between cerebellar volume and body height in female. This result also supports differential expression of brain volumes by sex.

The aim of this research is to investigate whether the significant positive correlations between body height and regional brain volumes in the young aged Koreans (20's) still exist in the old aged Koreans (60's and 70's). In this study, the MRI volumetric analysis of the brains was performed in 59 healthy elderly Koreans (aged 62-76 years; 34 male, 25 female). Statistical analysis was done with the Korean data, and the results were compared with previously reported Korean youth data[10].

Results and Discussion

Table 1 shows the results of the correlation analysis of the old age group data as well as the previously published youth group data[10]. In the youth group, whole brain volume and body height in male (r=0.37, P<0.05), and cerebellar volume and body height in female (r=0.43, P<0.05) show significant positive correlations (Table 1-a). In the old age group, however, neither whole brain volume and body height in male, nor cerebellar volume and body height in female shows significant correlation any more (Table 1-b). The significant positive correlation between body height and whole brain volume was still observed when both male and female data were combined (r=0.27, P<0.05), but the correlation coefficient and the degree of significance is markedly reduced from those of youth data (r=0.67, P<0.01). Figure 1 shows the results of simple linear regression analysis between whole brain volume and body height in each age group. Explanatory power of height (measured in r^2) on the whole brain volume is markedly reduced from 44% in the youth group to 7% in the old age group. Table 2 shows the results of correlation analysis of age and brain volumes in the old age group. Whole brain volume (r=-0.48) as well as cerebellar volume (r=-0.58) show significant negative correlations with age respectively in male, but not in female. When the male and female data were combined, the only cerebellar volume shows significant negative correlation with age (r=-0.34, P<0.01), whereas lateral ventricle shows significant positive correlation with age (r=0.38, P<0.01). It is suggested from Table 2 that age effect probably masks height effect on the whole brain volume because of decrease in brain volumes and increase in ventricle volumes with aging. The sex difference in this correlation analysis results also suggests that sex might be another important variable on brain volumes in the old age group.

Table 1. Correlations between body size and brain volume (Pearson correlation coefficient)

a) in young aged Koreans (20's) (modified from Koh et al., 2005[10] with permission)												
	Male (n=30)				Female (n=30)				Male & Female (n=60)			
	HT	WB	CBL	LV	HT	WB	CBL	LV	HT	WB	CBL	LV
HT	1.00	**0.37$^+$**	0.06	0.02	1.00	0.24	**0.43$^+$**	0.13	1.00	**0.67***	**0.47***	**0.37***
WB		1.00	**0.42$^+$**	0.01		1.00	**0.59***	**0.46$^+$**		1.00	**0.61***	**0.37***
CBL			1.00	-0.12			1.00	0.17			1.00	0.15
LV				1.00				1.00				1.00
b) in old aged Koreans (60's & 70's)												
	Male (n=34)				Female (n=25)				Male & Female (n=59)			
	HT	WB	CBL	LV	HT	WB	CBL	LV	HT	WB	CBL	LV
HT	1.00	0.33	0.33	0.24	1.00	-0.21	-0.28	-0.24	1.00	**0.27$^+$**	*0.18*	**0.33$^+$**
WB		1.00	**0.88***	0.03		1.00	**0.67***	*0.15*		1.00	**0.82***	*0.14*
CBL			1.00	0.10			1.00	0.00			1.00	1.00
LV				1.00				1.00				1.00

HT, body height; WB, whole brain; CBL, cerebellum; LV, lateral ventricle.
*P<0.01. $^+$P<0.05.. Significant values are shaded and bolded.

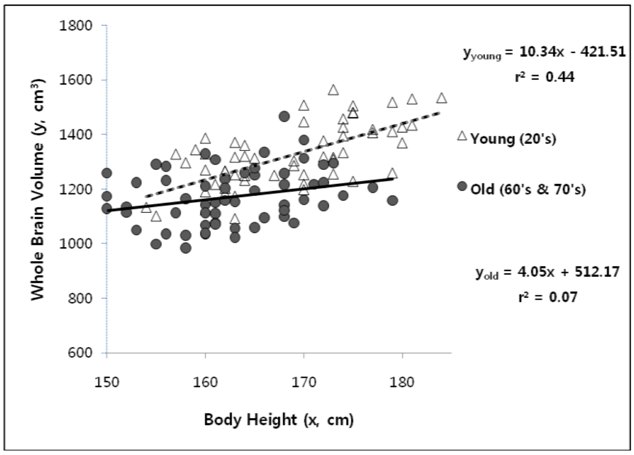


Figure 1. Simple linear regression analysis shows marked decrease in correlation between whole brain volume and body height in old group: whole brain volume is plotted against body height for each group, and the best fit line is plotted. old group (filled circle, solid line, r=0.27, P<0.05), young group (triangle, dotted line, r=0.67, P<0.01)

Table 2. Correlations between age, height and brain volume (Pearson's coefficient)

In old aged Koreans (60's & 70's)						
	Male (n=34)		Female (n=25)		Male & Female (n=59)	
	Age	HT	Age	HT	Age	HT
Age	1.00		1.00		1.00	
HT	-0.17	1.00	-0.12	1.00	0.24	1.00
WB	**-0.48***	0.33	-0.21	-0.21	-0.21	**0.27⁺**
CBL	**-0.58***	0.33	-0.19	-0.28	**-0.34***	0.18
LV	0.32	0.24	-0.02	-0.24	**0.38***	**0.33⁺**

HT, body height; WB, whole brain; CBL, cerebellum; LV, lateral ventricle. *P< 0.01, +P<0.05.
*P<0.01, ⁺P<0.05., Significant values are shaded and bolded.

In order to determine major explanatory variables on brain volumes in the old aged Koreans, multiple linear regression analysis was performed with combinations of explanatory variables [i.e. age (year), sex (female=0, male=1), height (cm)] on the response variable [i.e. whole brain volume (cm^3)]. The analysis of variance in Table 3-b indicates that at least one of the explanatory variables is related to whole brain volume (P<0.01) in each of the four different models. Coefficient of determination (r^2) is adjusted so that models with different numbers of explanatory variables can be compared. The adjusted r^2 represents the proportion of the variability of whole brain volume which can be explained by its relationship with the explanatory variables.

If age is added to the simple regression model with height only, the adjusted r^2 value increases to 0.125 (Table 3-a). Thus, multiple linear regression model with age and height provides a better fit to the data than the simple linear regression model (adjusted r^2=0.058, Table 3-a; Figure 1). Height still seems to be a significant explanatory variable (P<0.01), but not really meaningful because the confidence interval of the height parameter ranges from negative to positive values (-1.33 to 8.89). If sex is added to the above two variable model, the adjusted r^2 value increases to 0.172 (Table 3-a) indicating that 17.2% of the variability in whole brain volume can be explained by the three variable model (i.e. whole brain volume (cm^3) = 1624+76×sex-12×age+2×height). Height is no longer a significant explanatory variable in the three variable model (Table 3-d), with the confidence interval of the height parameter ranging from negative to positive values (-2.83 to 6.78). The stepwise regression analysis (by SPSS 17.0) excluded body height as an explanatory variable to estimate the whole brain volume in the old aged Koreans (Table 3).

When height is removed from the three variable model, the adjusted r^2 value slightly increases to 0.176 (Table 3-a). Thus, multiple linear regression model with sex and age provides the best fit (adjusted r^2=0.176) to the data among the four linear regression models. Thus, only sex and age variables rather than height are necessary to best estimate whole brain volume in the old aged Koreans. Multiple linear regression analysis with male only data (Table 4) also shows that height is no longer significant explanatory variable, with the confidence interval of the height parameter ranging from negative to positive values (-1.02 to 11.25). The adjusted r^2 value of the two variable model (age, height) is 0.253, implying better fit than simple linear regression model with age only (adjusted r^2=0.209, P<0.01) in Table 4.

Several previous studies have shown that the body size effect on brain size differed depending on the age distribution within the same-sex group[3,5,6]. It is suggested from these results that the loss of body height effect on brain volumes in the present study probably results from aging effect on brain volume. The present study

Table 3. Multiple linear regression analysis in elderly Koreans (60's & 70's, male & female): Response variable=whole brain volume, Significant values are shaded and bolded.

Male & Female (n=59)	a) Regression analysis statistics			b) Analysis of variance	
models	multiple correlation coefficient	coefficient of determination (r^2)	adjusted r^2	F ratio	significant F (P-value)
height	0.272	0.074	0.058	4.55	**0.037**
age, height	0.394	0.155	0.125	5.15	**0.009**
sex, age, height	0.463	0.214	0.172	5.00	**0.004**
sex, age	0.452	0.205	0.176	7.21	**0.002**
c) Parameter estimates (age, height)					
Variables	Parameter estimate	SE	t statistics	P-value	95% CI for parameter
Y intercept	894.178	340.380	2.627	0.011	(212.31 to 1576.04)
age	-8.052	3.463	-2.325	**0.024**	(-14.99 to -1.11)
height	5.111	1.886	2.710	**0.009**	(-1.33 to 8.89)
d) Parameter estimates (sex, age, height)					
Variables	Parameter estimate	SE	t statistics	P-value	95% CI for parameter
Y intercept	1624.229	488.568	3.324	0.002	(645.12 to 2603.34)
sex	76.452	37.609	2.033	**0.047**	(1.08 to 151.82)
age	-11.882	3.861	-3.077	**0.003**	(-19.62 to -4.14)
height	1.976	2.397	0.824	0.413	(-2.83 to 6.78)
e) Parameter estimates (sex, age)					
Variables	Parameter estimate	SE	t statistics	P-value	95% CI for parameter
Y intercept	1967.646	254.266	7.739	0.000	(1458.29 to 2477.00)
sex	96.390	28.711	3.357	**0.001**	(38.87 to 153.90)
age	-12.367	3.805	-3.250	**0.002**	(-20.00 to -4.74)

demonstrated no significant correlation between whole brain volume and body height in the male or female group in the old aged Koreans. Simple linear regression analysis shows only 5.8~7.4% of the variability in whole brain volume can be explained by the differences in the heights in the old age group (Table 3-a, Figure 1). The result disagrees with other reports supporting the height effect on brain volumes, in which young and middle aged subjects were included[3,6,10,11]. However, Witelson et al.[12] reported similar result with mostly old aged brains, i.e. 1~4% of height's contribution on the

Table 4. Multiple linear regression analysis in elderly Koreans (60's & 70's male only): Response variable=whole brain volume, Significant values are shaded and bolded.

Male (n=34)	regression analysis statistics			analysis of variance	
models	multiple correlation coefficient	coefficient of determination (r^2)	adjusted r^2	F ratio	significant F (P-value)
age	0.483	0.233	0.209	9.73	**0.004**
age, height	0.547	0.299	0.253	6.60	**0.004**
Parameter estimates (age, height)					
Variables	Parameter estimate	SE	t statistics	P-value	95% CI for parameter
Y intercept	1316.803	651.821	2.020	0.052	(-12.59 to 2646.20)
age	-13.852	4.819	-2.874	**0.007**	(-23.68 to -4.02)
height	5.113	3.007	1.700	0.099	(-1.02 to 11.25)

variability in brain size. Both post mortem and MRI volumetry studies have reported that brain volume decreases and ventricular volume increases with age[13,14]. In this study, the lateral ventricle volume is positively associated with age (Table 2, r=0.38, P<0.01) as previously reported by others[15-18].

Many cross-sectional studies have suggested that brain aging process may be different between the sexes with more apparent changing in male than in female[15,19-21], while some studies have shown the contrary results[22,23]. The reasons for gender difference in the age effect on whole brain volume are still uncertain, but might be differences in sex hormones or in life styles such as smoking and drinking. Table 2 shows that the whole brain volume is negatively correlated with age in male (r=-0.48, P<0.01) but not in female, and this result agrees with Condon et al.'s report[24]. These discrepant results on the human brain volume with respect to age and sex might partly come from the racial differences of the study subjects. Several studies reported racial differences in skull shape, body height, and brain volumes[6,14,25-27], and some studies suggested that racial differences probably come from differences in environmental and social factors such as malnutrition, sanitary conditions, and so on[28-30]. In this study as well as in the Korean youth study of Koh et al.[10], only homogeneous Koreans were recruited to minimize possible racial effects.

Conclusion and Prospects

In conclusion, the body height effect on brain volumes observed in the young aged Koreans decreases in the old aged Koreans. There still exist significant correlations of whole brain volume and lateral ventricular volume respectively with body height in the old aged Koreans, but the correlations become no more significant when male and female groups are analyzed separately. While height is the major explanatory variable for whole brain volume in the young aged Koreans[10], age and sex are the major explanatory variables for whole brain volume in the old aged Koreans. The loss of correlations in the aged group is suspected to be mainly due to age related brain volume changes.

It is very difficult to compare the results of many brain volume studies because of differences in sample size, distributions of race, sex, and age, health status of subjects, data acquisition protocols, method of segmentation of brain regions, and statistical methods. It would be much more informative to design a cross sectional study with larger samples which constitutes even sex distribution and continuous age distribution of young, middle, and old aged subjects to investigate changes in age, sex, and height effect. Ideally, longitudinal studies of larger samples of different races and meta-analysis of multiple cross sectional studies are desired to clearly understand the regional brain volume differences according to age, gender, race and other variables.

Materials and Methods

Subject recruitment and MRI volumetry methods were described in detail in the previous publications[10,17]. Fifty nine healthy elderly Koreans (aged 62–76 years, male 34, female 25) were recruited through advertisements on an internet web page and in local newspapers. The purpose of research and procedures were fully explained to the subjects and they were asked to sign a consent form approved by the Institutional Review Board. History-taking, physical and neurologic examinations were carried out by a neurologist. Any individuals with possible neurologic abnormalities were excluded from this study. Body height of each participant was measured prior to MRI scanning.

MRI was performed on a 1.5-Tesla Magnetom Vision instrument (Siemens, Erlangen, Germany) using T1-weighted magnetization prepared rapid acquisition gradient echo sequence (repetition time = 9.7 ms, echo time = 4 ms, flip angle = 12 degree, slice thickness = continuous 1.5 mm, number of slices = 118 and matrix 256×256). After the acquisition of MR images, the DICOM (Digital Imaging and Communications in Medicine) files were imported to the V-works 3.5 program (Cybermed Ltd, Seoul, Korea) installed in a high end Windows XP PC. The ROIs (region of interests) were segmented and measured with V-works 3.5 as in the previous study[10]. An automatic threshold tool was used to identify the brain region from the cerebrospinal fluid and additional manual tracing was used to measure the volume of each ROI. All segmented ROIs were carefully checked from horizontal, sagittal, and coronal views to ensure correct segmentation, and the volumes of each ROIs were calculated on the basis of three-dimensional models based on voxels (0.85 mm×0.85 mm×1.5 mm). The volumes of whole brain (WB), cerebellum (CBL) and lateral ventricle (LV) were segmented as in the previous study[10]. WB was segmented manually from skull, scalp and meninges[31,32]. CBL was separated manually from the brainstem, cerebellar peduncles, tentorium and remaining meninges[31,32]. LV included the entire lateral ventricle including the temporal horn. All the statistical analyses were two-tailed (P<0.05 as significant) and were done by SPSS version 17.0 (IBM, USA) and Microsoft Excel 2007 with the built-in statistical analysis module.

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