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Comparison of Normative Percentiles of Brain Volume Obtained from NeuroQuant® vs. DeepBrain® in the Korean Population: Correlation with Cranial Shape

한국 인구에서 NeuroQuant®와 DeepBrain®에서 측정된 뇌 용적의 정상규준 백분위수 비교: 두개골 형태와의 연관성

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Purpose This study aimed to compare the volume and normative percentiles of brain volumetry in the Korean population using quantitative brain volumetric MRI analysis tools NeuroQuant® (NQ) and DeepBrain® (DB), and to evaluate whether the differences in the normative percentiles of brain volumetry between the two tools is related to cranial shape.
Materials and Methods In this retrospective study, we analyzed the brain volume reports obtained from NQ and DB in 163 participants without gross structural brain abnormalities. We measured three-dimensional diameters to evaluate the cranial shape on T1-weighted images. Statistical analyses were performed using intra-class correlation coefficients and linear correlations.
Results The mean normative percentiles of the thalamus (90.8 vs. 63.3 percentile), putamen (90.0 vs. 60.0 percentile), and parietal lobe (80.1 vs. 74.1 percentile) were larger in the NQ group than in the DB group, whereas that of the occipital lobe (18.4 vs. 68.5 percentile) was smaller in the NQ group than in the DB group. We found a significant correlation between the mean normative percentiles obtained from the NQ and cranial shape: the mean normative percentile of the occipital lobe increased with the anteroposterior diameter and decreased with the craniocaudal diameter.
Conclusion The mean normative percentiles obtained from NQ and DB differed significantly for

many brain regions, and these differences may be related to cranial shape.

Index terms Brain; Magnetic Resonance Imaging; Artificial Intelligence; Software

INTRODUCTION

Reduced brain volume is associated with several diseases such as dementia, Alzheimer's disease, epilepsy, and multiple sclerosis. Early intervention for these diseases directly affects patients' quality of life; therefore, early detection is crucial (1-4). However, the diagnosis of brain atrophy in clinical practice mainly relies on visual assessment and is associated with high interobserver variability. Therefore, MRI-brain volumetry software programs are in growing demand for more objective brain atrophy assessments in aging populations.

The commercial software NeuroQuant® (NQ, Cortechs.ai; San Diego, CA, USA) and DeepBrain® (DB, VUNO Inc., Seoul, South Korea) are automated quantitative brain volumetric MRI analysis tools for detecting neurodegenerative diseases. NQ has been approved by the Food and Drug Administration of the United States and Conformité Européenne (CE) and is widely used in clinical practice. NQ's normative database is built on several thousand subjects aged 3 to 100 years with gender equivalence; however, information on race and ethnicity has not been disclosed (5-8). On the other hand, DB, wherein the database is based on the Korean population, has been approved by the Ministry of Food and Drug Safety of South Korea and CE and has recently been applied in the clinical setting (9).

Several studies have validated the accuracy of segmented volume measurement by NQ, which appears to work relatively well (10-12). However, no previous studies have compared the normative percentiles of brain volumetry in different races and only a few have compared the normative percentiles using different volumetry tools. Although Vinke et al. (13) showed that the normative data of subcortical volume from three different cohorts were highly interchangeable, all participant groups were Caucasian. In addition, the normative percentiles of various cortical brain structures were not analyzed.

Neuroanatomical differences between Asians and Caucasians have already been studied (14-16). East Asians have rounder heads, and flatter occiputs and foreheads than Caucasians. Lee et al. (17) also found that Korean standard brain templates (mean brain length, width, and height of 16.5, 14.3, and 12.1 cm, respectively) showed different shapes and sizes from Caucasian templates (18.3, 14.2, and 13.3 cm, respectively).

In addition, several studies have shown an association between brain and cranial volumes (18, 19). Therefore, we hypothesized that a discrepancy between the results of NQ and DB observed in the Korean population is related to cranial shape.

In this study, we aimed to compare the volume and normative percentiles of brain volumetry obtained from NQ developed in the United States with those obtained from DB developed based on the Korean population and to determine whether the difference is related to cranial shape.

MATERIALS AND METHODS

PARTICIPANTS

This was a retrospective study on patients who underwent brain MRI at a neurology outpatient clinic at a single tertiary care institution between June 2020 and October 2020. Brain MRI was performed along with volume measurement for 163 patients who visited the Department of Neurology with mild neurological symptoms, such as headache, dizziness, and somatic symptom disorder, and who were not diagnosed with neurodegenerative disease. They had no gross structural brain abnormalities, such as an old infarction or hemorrhage on T2-weighted imaging (T2WI) and susceptibility weighted imaging (SWI). In patients aged > 65 years, small vessel disease of Fazekas grade 1 and a global cortical atrophy score of 1 on T2 fluid-attenuated inversion recovery (FLAIR) images were considered within the normal range (20). Of the 163 patients, 76 were male and 87 were female, with a mean age of 55.6 years, ranging from ages 19–85 years.

The Institutional Review Board approved this study and waived the requirement for informed consent owing to the retrospective nature of the study (IRB No. 2022-07-015-001).

MRI ACQUISITION

Brain MRI was performed using a 3T scanner with a 20-channel head coil (MAGNETOM Vida; Siemens Healthcare, Erlangen, Germany). Three-dimensional (3D) sagittal T1 magnetization-prepared rapid gradient-echo (MPRAGE) imaging was performed in all patients for brain volumetry: repetition time (TR), 2300 ms; effective echo (TE), 2.05 ms; flip angle, 9°; field of view (FoV), 220 × 220 mm; matrix, 288 × 288; slice thickness, 0.8 mm; imaging time, 5 min 57 s. Axial T2WI was performed using the following parameters: TR, 5330 ms; TE, 90 ms; flip angle, 110°; FoV, 220 × 220 mm; matrix, 528 × 370; slice thickness, 5.0 mm. T2 FLAIR imaging was performed with the following parameters: TR, 9000 ms; TE, 95 ms; inversion time, 2500 ms; flip angle, 150°; FoV, 199 × 220 mm; matrix, 320 × 188; slice thickness, 5.0 mm. SWI was also obtained with the following parameters: TR, 37.00 ms; TE, 20 ms; flip angle, 15°; FoV, 197 × 220 mm; matrix, 384 × 206; slice thickness, 2.0 mm.

VOLUMETRIC ANALYSES

All MRI images were reviewed by a single neuroradiologist (with more than 16-year experience in neuroimaging). Using 3D T1 MPRAGE images, the volumes and normative percentiles for the whole brain and 16 brain structures were obtained using NQ and DB.

MEASUREMENT OF CRANIAL SHAPE

The 3D maximum lengths of the transverse (Trans), anteroposterior (AP), and craniocaudal (CC) cranium diameters were measured using 3D T1-weighted images. The transverse diameter is defined as a straight line through the posterior commissure (PC) terminating in the inner cortex of both temporal bones. The AP diameter is defined as a straight line from the inner table of the frontal convexity to the inner table of the occipital convexity in the plane passing through the anterior commissure and PC. The CC diameter is defined as a straight line through the PC terminating in the inner cortex of the vertex and foramen magnum (Fig. 1).

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 27 (IBM Corp., Armonk, NY, USA). The correlation between the volume and normative percentiles obtained from NQ and DB was evaluated using Pearson's correlation coefficients and intraclass correlation coefficients (ICCs) in a two-way random effects model. Linear regression analysis was used to assess the relationship between cranial shape and the normative percentile obtained using NQ.

RESULTS

The volume measurement obtained from NQ and DB showed good-to-excellent inter-method reliability in 13 regions (r = 0.837 to 0.99; ICC = 0.63–0.97) with the exception of the occipital lobe (ICC: 0.577), pallidum (ICC: 0.048), ventral diencephalon (ICC: 0.495), and cerebellum white matter (ICC: 0.598) (Table 1).

However, there was a significant difference between the mean normative percentiles obtained from NQ and DB (Table 2). Assuming that the mean normative percentile is the 50th percentile in the normal population, the mean normative percentile obtained from DB was distributed between the 46th and 74th percentiles, whereas that obtained from NQ was more widely distributed than that from DB between the 18th and 90th percentiles. The mean normative percentiles obtained from NQ and DB showed low correlation coefficients and ICC values. The mean normative percentiles of various cortical structures obtained from NQ were larger than those obtained from DB: thalamus (90.8 vs. 63.3 percentile), putamen (90.0 vs. 60.0 percentile), and parietal lobe (80.1 vs. 74.1 percentile). In contrast, the mean normative percentile of the occipital lobe was smaller in the NQ group than in the DB group (18.4 vs.

Fig. 1. 3D measurement of cranial shape.
A. On 3D T1-weighted imaging, the maximum transverse diameter is measured from the right temporal bone to the left temporal bone in the plane passing through the PC (arrow).
B. On 3D T1-weighted imaging, the maximum anteroposterior diameter is measured from the frontal convexity to the occipital convexity in the plane passing through the AC-PC line (arrow). The maximum craniocaudal diameter is measured from the vertex to the level of the foramen magnum in the plane passing through the PC (arrowhead).
AC = anterior commissure, PC = posterior commissure

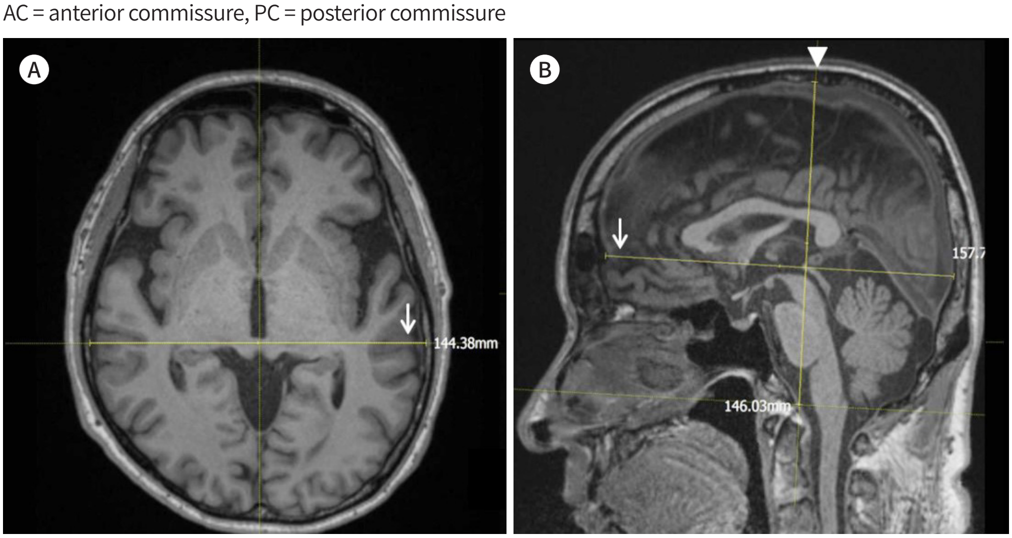

Table 1. Comparisons of Mean Volume Obtained from NeuroQuant® and DeepBrain®

	NeuroQuant® Mean Volume	DeepBrain® Mean Volume	*r*	*p*-Value	ICC	*p*-Value
Hippocampus	8.032	9.042	0.900	< 0.001	0.784	< 0.001
Temporal lobe	133.803	120.198	0.951	< 0.001	0.807	< 0.001
Frontal lobe	184.420	156.696	0.941	< 0.001	0.632	< 0.001
Parietal lobe	123.082	110.220	0.938	< 0.001	0.794	< 0.001
Occipital lobe	55.059	45.022	0.841	< 0.001	0.577	< 0.001
Cortical gray matter	506.316	456.084	0.969	< 0.001	0.805	< 0.001
Cerebral white matter	486.288	462.983	0.953	< 0.001	0.940	< 0.001
Brainstem	23.016	21.582	0.978	< 0.001	0.918	< 0.001
Thalamus	16.790	15.121	0.902	< 0.001	0.779	< 0.001
Caudate	6.189	7.167	0.892	< 0.001	0.762	< 0.001
Putamen	12.570	10.780	0.837	< 0.001	0.664	< 0.001
Pallidum	1.217	2.806	0.277	< 0.001	0.048	< 0.001
Ventral diencephalon	6.239	7.583	0.701	< 0.001	0.495	< 0.001
Ventricle	32.832	27.699	0.998	< 0.001	0.964	< 0.001
Cerebellum (cortex)	101.899	99.303	0.974	< 0.001	0.970	< 0.001
Cerebellum (white matter)	33.391	30.273	0.559	< 0.001	0.598	< 0.001
Intracranial volume	1504.146	1322.605	0.982	< 0.001	0.663	< 0.001

The units are mL. Pearson's correlation coefficients and ICCs in the two-way random effects model were used to assess the differences in volumes between NeuroQuant® and DeepBrain®.
ICC = intraclass correlation coefficient

68.5 percentile).

In the NQ results, the volumes of all brain structures were positively proportional to the Trans, AP, and CC cranium diameters, whereas the mean normative percentiles were quite varied. Table 3 compares the Trans, AP, and CC cranium diameters with the mean normative percentiles reported by the NQ. The normative percentiles of the forebrain parenchyma, cortical gray matter, and frontal lobe decreased with the CC diameter (B = -1.245, standard error [SE] = 0.405; B = -1.369, SE = 0.433; B = -1.463, SE = 0.417). The normative percentile of the occipital lobe increased with the AP but decreased with the CC diameter (B = 0.817, SE = 0.236; B = -0.721, SE = 0.324). The normative percentile of the temporal lobe increased with the Trans and decreased with CC diameter (B = 0.755, SE = 0.377; B = -1.305, SE = 0.461). The normative percentile of the brainstem increased with the CC and decreased with the Trans and AP diameters (B = 0.912, SE = 0.431; B = -0.745, SE = 0.353; B = -0.635, SE = 0.313). The normative percentiles of the cerebellum and parietal lobe decreased with the AP diameter (B = -0.619, SE = 0.312; B = -0.646, SE = 0.230).

DISCUSSION

This study evaluated the inter-method reproducibility between the NQ and DB in Korean patients. Overall, brain volumes obtained from the NQ and DB showed good-to-excellent inter-method reliability, while the mean normative percentiles were significantly different be-

Table 2. Comparisons of Mean Normative Percentiles of Brain Volumetry Obtained from NeuroQuant® and DeepBrain®

	NeuroQuant®	DeepBrain®	r	p-Value	ICC	p-Value
	Mean Percentile	Mean Percentile				
Hippocampus	71.6	54.4	0.531	< 0.001	0.615	< 0.001
Temporal lobe	46.1	70.2	0.454	< 0.001	0.486	< 0.001
Frontal lobe	40.2	66.9	0.488	< 0.001	0.483	< 0.001
Parietal lobe	80.1	74.1	0.289	< 0.001	0.436	< 0.001
Occipital lobe	18.4	68.5	0.322	< 0.001	0.174	< 0.001
Cortical gray matter	46.4	71.9	0.377	< 0.001	0.400	< 0.001
Cerebral white matter	77.6	52.3	0.328	< 0.001	0.340	< 0.001
Brainstem	51.3	50.6	0.615	< 0.001	0.762	< 0.001
Thalamus	90.8	63.3	0.290	< 0.001	0.256	< 0.001
Caudate	67.3	53.3	0.750	< 0.001	0.800	< 0.001
Putamen	90.0	60.0	0.327	< 0.001	0.248	< 0.001
Pallidum	22.4	57.8	0.118	0.133	0.114	0.069
Ventral diencephalon	28.7	53.1	0.182	0.020	0.228	0.010
Ventricle	48.0	48.3	0.924	< 0.001	0.951	< 0.001
Cerebellum (cortex)	40.7	59.5	0.641	< 0.001	0.661	< 0.001
Cerebellum (white matter)	87.6	54.7	0.031	0.698	0.025	0.362
Intracranial volume	48.1	46.6	0.953	< 0.001	0.975	< 0.001

Pearson's correlation coefficients and ICCs were used to assess statistical differences in mean normative percentiles between NeuroQuant® and DeepBrain®.
ICC = intraclass correlation coefficient

tween NQ and DB. This result could be due to the difference in normative reference data installed in NQ and DB, and the heterogeneous results of the mean normative percentiles obtained from NQ may be related to the cranial shape in Koreans.

In terms of volume, good-to-excellent inter-method reliability was observed in 13 regions, except for the occipital lobe, putamen, pallidum, ventral diencephalon, and cerebellar white matter. In particular, a weak positive correlation in the pallidum (ICC: 0.048) can be explained by the poor differentiation of the pallidum from the white matter on T1-weighted images.

The mean normative percentiles obtained from NQ ranged wider than those obtained from DB. The mean normative percentiles obtained from DB ranged between the 46th and 74th percentiles in this study, whereas those obtained from NQ ranged between the 18th and 90th percentiles. Larger normative percentiles obtained from NQ were observed in several brain structures, including the thalamus (90.8 vs. 63.3 percentile), putamen (90.0 vs. 60.0 percentile), and parietal lobe (80.1 vs. 74.1 percentile). In contrast, the mean normative percentile obtained from NQ was significantly smaller than that obtained from DB in the occipital lobe (18.4 vs. 68.5 percentile). This is presumed to be the result of the difference between the normative reference data loaded into NQ and DB.

The mean normative percentiles obtained from brain volumetry software may vary according to the demographics of the reference population, such as age, sex, and ethnicity. We assumed that the results mentioned above might be related to the difference in cranial shape

Table 3. Correlation Between Mean Percentiles Obtained from NeuroQuant® and Cranial Shape

Brain Structure	Dimension	Unstandardized Coefficient		*p*-Value
		B	Standard Error	
Forebrain parenchyme	Transverse	0.574	0.332	0.085
	Anteroposterior	0.420	0.294	0.156
	Craniocaudal	-1.245	0.405	0.002*
Cortical gray matter	Transverse	0.174	0.354	0.625
	Anteroposterior	0.166	0.314	0.599
	Craniocaudal	-1.369	0.433	0.002*
Cerebellum	Transverse	-0.680	0.352	0.055
	Anteroposterior	-0.619	0.312	0.049*
	Craniocaudal	0.309	0.430	0.474
Brainstem	Transverse	-0.745	0.353	0.036*
	Anteroposterior	-0.635	0.313	0.044*
	Craniocaudal	0.912	0.431	0.036*
Frontal lobe	Transverse	-0.015	0.341	0.966
	Anteroposterior	0.536	0.303	0.078
	Craniocaudal	-1.463	0.417	0.001*
Parietal lobes	Transverse	0.015	0.259	0.955
	Anteroposterior	-0.646	0.230	0.005*
	Craniocaudal	-0.143	0.316	0.651
Occipital lobes	Transverse	-0.224	0.266	0.400
	Anteroposterior	0.817	0.236	0.001*
	Craniocaudal	-0.721	0.324	0.028*
Temporal lobe	Transverse	0.755	0.377	0.047*
	Anteroposterior	-0.284	0.334	0.398
	Craniocaudal	-1.305	0.461	0.005*

Linear regression analysis was used to assess statistical differences in mean percentiles obtained from NeuroQuant® and cranial shape.
*Statistically significant.

between Asians and Caucasians; East Asians have rounder cranial shapes and flatter occiputs and foreheads than Caucasians. In our study, the mean normative percentiles of each brain structure were significantly correlated with the measured 3D cranial diameters. Primarily, the normative percentile of the occipital lobe increased with the AP diameter of the cranium and decreased with the cranial CC diameter.

To date, MRI volumetry software programs display the normative percentile of brain regions according to age and sex, but do not provide ethnicity-adjusted normative percentiles. Therefore, it is questionable whether the normative percentiles given by the software can be trusted when applied to patients with ethnicities different from that of the reference population used for software development. Therefore, it is necessary to develop various brain volumetry programs with normative percentiles for each ethnicity and apply a software program suitable for the appropriate ethnicity. In such cases, the universal applicability of brain volumetric software is significantly limited. Such limitations may be overcome if the normative percentiles of segmented brain regions from an MRI volumetric software program can be modified using the Trans, AP, and CC diameters measured on an individual's brain MRI. Thus, it may be closer to the actual normative percentile, regardless of the reference dataset installed in the software programs.

Finkelsztejn et al. (21) compared the measured brain volumes of healthy patients from Brazil using MSmetrix, a brain volumetric MRI analysis tool, based on a reference dataset consisting mainly of Europeans. They showed that in terms of the whole brain volume, 2% of healthy adult patients from Brazil were below the 5th percentile, and in terms of gray matter, 3% of the patients were below the 5th percentile of the MSmetrix standards. This suggests that the ethnicity of the reference population could influence brain volumetry, which is consistent with the findings of our study.

Currently, there are many available MRI-based volumetric and segmentation software packages: FSL (22), Voxel-Based Morphometry (23), FreeSurfer (24), Statistical Parametric Mapping (25), NeuroQunat® (10, 11, 26), DeepBrain® (9, 27), Neuroreader® (12), MSmetrix (28, 29), and Inbrain® (30, 31). Several studies have compared brain volumetric softwares, and most studies have shown good-to-excellent inter-method reliability for brain regions except for the pallidum; our study also showed similar results (8, 10, 32-34). However, Song et al. (35) recently reported that NQ and DB were significantly different in demonstrating brain volume and normal percentiles for most brain regions. Overall, the volumes obtained from NQ tended to be larger than those obtained from DB in our study. This observation has also been reported in several studies comparing NQ with FreeSurfer, volBrain, and DB (32, 35-37). Koussis et al. (37) showed that NQ and volBrain could qualitatively detect the relative size of each brain segment by applying a least-squares regression linear equation. This means that although NQ seems to show a tendency to measure slightly larger than other software packages, both software packages can distinguish the relatively smaller or larger volume of a structure.

Our study has several limitations. First, it was not conducted in healthy volunteers. We enrolled study participants who visited the outpatient department of neurology with mild neurological symptoms, such as headache, dizziness, and somatic symptom disorder, and were not diagnosed with a neurodegenerative disease. The mean normative percentiles of the total intracranial volume measured in our study using NQ and DB were 48.1 and 46.6, respectively, which were close to the average. These results support the fact that our study participants were close to a normal healthy cohort (38, 39). In addition, the mean normative percentiles of brain volumetry in our participants obtained using DB were close to the average for many brain regions. Although the participants in our study were not healthy volunteers, they were considered to have demographics that could reflect the brain volume characteristics of Koreans. Second, the study was retrospective, and a selection bias may have been present because only subjects without gross structural brain abnormalities were included. In addition, this study included a small sample of participants from a single tertiary referral hospital. Further studies are necessary to ensure that the results are applicable to multicenter and multinational settings. Third, the NQ and DB provide volumetric data, including absolute volume, volume percentage of intracranial volume, and normative percentile. However, the percentage of intracranial volume was not included in this study. Therefore, further studies on the correlation between the volume percentage of intracranial volume and cranial shape are required. Finally, we did not consider the reproducibility of the other MR scanners. The measured volume may differ in other MRI scanners because technical factors influence the volumetric brain software.

In conclusion, we compared the volume and normative percentile of brain volumetry in the Korean population in the NQ and DB, which were developed based on different reference populations. Although NQ and DB showed excellent inter-method reliability in volume measurement, they showed significantly different mean normative percentiles in many brain regions. In addition, there was a significant association between the discrepancy in the mean normative percentiles and cranial shapes, especially in the occipital lobe. This suggests the necessity of correcting normative percentiles using the trans, AP, and CC diameters on brain MRI to reflect an individual's cranial shapes.

Author Contributions

Conceptualization, Y.M.H., K.E.H.; data curation, all authors; formal analysis, all authors; investigation, Y.M.H., K.E.H.; methodology, Y.M.H., K.E.H.; project administration, Y.M.H., K.E.H.; resources, all authors; software, Y.M.H., K.E.H.; supervision, Y.M.H., K.E.H.; validation, Y.M.H., K.E.H.; visualization, Y.M.H., K.E.H., C.E.S.; writing—original draft, Y.M.H., K.E.H.; and writing—review & editing, all authors.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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한국 인구에서 NeuroQuant®와 DeepBrain®에서 측정된 뇌 용적의 정상규준 백분위수 비교: 두개골 형태와의 연관성

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목적 이 연구의 목적은 한국 인구에서 NeuroQuant (이하 NQ)와 DeepBrain (이하 DB)에서 측정된 뇌 용적과 정상규준 백분위수를 비교하고, 두개골 형태와의 연관성을 확인하는 것이다.
대상과 방법 이 연구는 구조적 뇌 이상이 없는 163명의 한국인을 대상으로 NQ와 DB에서 측정된 뇌 용적과 정상규준 백분위수를 비교하고, 두개골 형태와의 연관성을 확인한 후향적 연구이다. 급내상관계수분석과 선형분석의 통계학적 분석을 시행하였다.
결과 정상규준 백분위수는 시상(90.8 vs. 63.3 percentile), 피각(90.0 vs. 60.0 percentile), 그리고 두정엽(80.1 vs. 74.1 percentile)에서 NQ가 DB보다 더 큰 것으로 나타났고, 후두엽(18.4 vs. 68.5 percentile)은 DB가 NQ보다 큰 것으로 나타났으며, 특히 후두엽의 경우 두개골 형태와의 비교 연구에서 유의미한 연관성을 보였고, 두개골의 전후 방향의 길이와 비례하고 상하방향의 길이와는 반비례했다.
결론 NQ와 DB에서 얻은 정상규준 백분위는 각 뇌 영역마다 유의미한 차이를 보였고, 그 차이는 한국 인구의 두개골 형태와 유의미한 관계가 있었다.

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