https://doi.org/10.17221/33/2019-VETMED

The volume fraction values of the brain compartments using the Cavalieri principle and a 3T MRI in brachycephalic and mesocephalic dogs

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Citation: Bakici C, Akgun RO, Ozen D, Algin O, Oto C (2019): The volume fraction values of the brain compartments using the Cavalieri principle and a 3T MRI in brachycephalic and mesocephalic dogs. Veterinarni Medicina 64, 482–489.

Abstract: This study was aimed at: 1) estimating the volume and the volume fraction values of brain ventricles, grey matter and white matter with the Cavalieri principle and 2) creating three-dimensional reconstruction models of the brain ventricles by using magnetic resonance imaging. The brain structures of dogs were scanned with a 3T magnetic resonance system. The volumes of the total brain, the grey matter, the white matter, the lateral ventricle, the third ventricle, the cerebral aqueduct and the fourth ventricle of both sides were estimated separately by using a combination of the Cavalieri principle and the point-counting method. In addition to that, magnetic resonance images of dog brains were uploaded to the 3D slicer software to design the three-dimensional reconstruction models. The mean volume fraction values of the left and right lateral ventricle, third ventricle, cerebral aqueduct, and fourth ventricle were 1.83 ± 0.14%, 1.75 ± 0.1%, 0.7 ± 0.07%, 0.2 ± 0.04%, and 1 ± 0.32% for the brachycephalic dogs and 1.69 ± 0.04%, 1.66 ± 0.03%, 0.91 ± 0.03%, 0.27 ± 0.05%, and 0.71 ± 0.15% for the mesocephalic dogs, respectively. There was no statistically significant difference between the brachycephalic and mesocephalic dogs in all the volume fraction values ($P > 0.05$). This study showed the volume and the volume fraction values of the brain ventricles and the structures in the different types of the dogs' head shapes. These volume fraction values can be essential data for determining some diseases. Magnetic resonance imaging can be used for precise volume estimations in combination with the Cavalieri principle and the point-counting method.

Keywords: brain; magnetic resonance imaging; three-dimensional reconstruction; volume

The volumes of the brain ventricles are used to determine many diseases in medicine (Calmon and Roberts 2000; Tang et al. 2001; Furlong et al. 2013; Mayer et al. 2016) and veterinary medicine (Vite et al. 1997; Akdogan et al. 2010; Woo et al. 2010; Schmidt et al. 2015). Hydrocephalus, cerebral atrophy, epilepsy, dementia, schizophrenia and Alzheimer's are the leading diseases determined by the counting volume, the volume ratio and the area measurements of the brain and the ventricles (Calmon and Roberts 2000; Kimotsuki et al. 2005; Acer et al. 2010; Akdogan et al. 2010; Woo et al. 2010). Although the differences in the dog skulls affect the size of the ventricles, it is noted that the asymmetry and enlargement of the ventricles in the diseases are often shaped independently

https://doi.org/10.17221/33/2019-VETMED

of the shape of the skull (Woo et al. 2010). Magnetic resonance imaging (MRI) provides clearer and more accurate images due to the high tissue contrast than computerised tomography (CT) images (Acer et al. 2010). An MRI presents detailed information on the soft tissue especially for brain structures *in vivo* (Mayer et al. 2016). 3T MR systems are preferred in psychiatric disorders and neurological research due to its fine image quality in thin thickness (Furlong et al. 2013). It is frequently used for the early diagnosis of diseases related to the central nervous system in both human medicine and veterinary medicine (Woo et al. 2010; Mayer et al. 2016). It is also known that these types of diseases are easily measured by MRI (Acer et al. 2010).

The combination of MRI and computer-based image analysis provides the possibilities for non-invasive measurements such as the volume, ratio or length on the brain structures. These computer-based image analyses are varied (Calmon and Roberts 2000; Schmidt et al. 2015). Previously, the volume of the brain and ventricles were estimated by using measurements such as water displacement or weight. In addition to that, it has been possible to obtain the most accurate estimates of these measurements with the new methods that have recently begun to be implemented (Vite et al. 1997). The Cavalieri principle provides an unbiased estimation of the volume or the volume ratios of the irregular tissues. It is an established principle combining the point-counting method for the volumetric stereological estimations (Pilegaard et al. 2017). These measurements can be estimated with the Cavalieri principle on both the microscopic sections and the MRI or CT images of the nervous system (Tang et al. 2001; Akdogan et al. 2010; Keller et al. 2012; Furlong et al. 2013). However, the tissue or organ must be divided into sections entirely, these sections must be parallel to each other, these cross-sectional intervals must be certain, and the starting point must be selected randomly due to the requirements for the application of the Cavalieri principle (Gunderson and Jensen 1987).

In this study, we estimated the volume and the volume fraction values of the grey matter, the white matter, the lateral ventricle, the third ventricle, the cerebral aqueduct, and the fourth ventricle on both sides separately using the Cavalieri principle in two different types of dog head shape. In addition, we composed the three-dimensional (3D) reconstruction model of the brain ventricles.

MATERIAL AND METHODS

The material of this study consisted of eight dogs with different types of head shape. Four clinically healthy brachycephalic (three Pitbull Terriers and one Dogo Argentino) and four mesocephalic (Golden Retriever) dogs were used for this study. All the experimental procedures were approved by the Bilkent University Animal Experiments Local Ethics Committee (2016/43).

The animals were anaesthetised by administration of xylazine (2 mg/kg, *i.m.*) and ketamine hydrochloride (10 mg/kg, *i.v.*). Thereafter, they were placed in the prone position and scanned using a 32-channel human head coil with a 3 Tesla MR (Trio, Siemens, Erlangen, Germany). The images taken with the T1-weighted and T2-weighted space sequences on the dorsal, sagittal and transversal planes were examined by Leonardo Workstation software (Siemens Medical Solutions, Erlangen, Germany). The scan parameters for the T1-weighted images had an echo delay time (TE) of 12 ms, a repetition time (TR) of 600 ms, a slice thickness = 1 mm, an FOV: 230 × 230 mm, the total number of slices = 125 and the total scanning time was around 8 minutes. The scan parameters for the T2-weighted images were a TE of 404 ms, a TR of 3000 ms, a slice thickness = 1 mm, an FOV: 230 × 230 mm, the total number of slices = 125 and the total scanning time was around 11 minutes. The 3D reconstructed images of the entire ventricle system were created using a 3D Slicer software (3D slicer, 4.7.0 version, GitHub, San Francisco) through DICOM files. The 3D images were obtained by volume rendering using the "Threshold" function. The resulting selections were adjusted manually with a paint tool on every slice. The "Make model" function was used to create the 3D model.

The skull shape classification was determined by the LW-index (LWI) (Koch et al. 2014). The LWI calculation was carried out by the following formula:

$$\text{LWI} = \frac{\text{cranial length}}{\text{cranial width}} \quad (1)$$

where:

LWI – skull shape index;

cranial length – distance between the rostral border of the incisive bone to the dorsal border of the foramen magnum;

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cranial width – greatest distance between the outer borders of the zygomatic arches.

These estimations were measured from the sagittal (cranial length) and the transverse (cranial width) plane MRI images. The brachycephalic dogs were considered to have an LWI < 1.44.

The volume estimations were performed using the Cavalieri probe of the Stereo Investigator Software (Version 10.50, MBF Bioscience, USA) with the help of a computerised light microscope (Leica DM 4000 B, Germany) and a digital camera (CX 9000, MBF Bioscience, USA). The compartments referred to as the "grey matter" (GM) were; the cerebral and the cerebellar grey matter, the uncus, the hippocampus, the dentate gyrus, the subiculum, the hippocampal gyrus, the cingulate gyrus, the subcallosal area, and the amygdala. The compartments referred to as the "white matter" (WM) were; the white matter (excluding the cerebral and the cerebellar ventricle system), the basal ganglia (the caudate nucleus, the putamen, the globus pallidus, the substantia nigra, and the subthalamic nucleus), the brainstem nuclei (the red nucleus and the cerebral nerve nuclei), and the cerebellar nuclei (the dentate nucleus, the globose nucleus, the emboliform nucleus, and the fastigial nucleus). The compartments of the ventricle system were referred to as the lateral ventricle (LV), the third ventricle (TdV), the cerebral aqueduct (CA), and the fourth ventricle (FV). In accordance with the systematic random sampling, one of the two images were selected for each dog's individuals. The distance between the two points assigned by the point counting grid for each image was determined as 4000 μm. The volume calculations were carried out by the following formula:

$$V = Ap \times m \times t \times (\Sigma P) \quad (2)$$

where:

- V – volume of the focused sample;
- m – section evaluation range;
- Ap – area of each point on the point counting grid;
- t – cross section thickness;
- P – number of the points at the desired region in the section (Gundersen and Jensen 1987; Garcia-Finana et al. 2003).

The volume fraction is defined as the volumetric ratio of a specified structure to the whole structure as indicated below. This volume fraction value should be between 0 and 1. The volume fractions of the GM, WM, LV, TrV, CA, and FV were estimated using the following equation (Howard and Reed 2005):

$$V(X,Y) = \frac{\text{volume of } X \text{ phase in } Y \text{ reference space}}{\text{volume of } Y \text{ reference space}} \quad (3)$$

The coefficient of error (CE) for the obtained data was estimated by a stereo investigator program in order to see the reliability of the Cavalieri principle (Gundersen and Jensen 1987).

The Mann-Whitney U test was used to analyse the differences between the groups. A probability value of less than 0.05 was considered significant unless otherwise noted. SPSS 14.01 (License No.: 9869264) was used for the statistical analysis.

RESULTS

Four brachycephalic and four mesocephalic normal dogs were evaluated in this study. The volume estimations of the brain compartments (GM and WM) and the ventricular system components (LV, TrV, CA and FV) of the dogs were measured by the Cavalieri principle as shown in Figure 1 and these results are given in Table 1 and Table 2. The LW index showed that three Pitbull Terriers and one Dogo Argentino were classified as the brachycephalic dogs and four Golden Retrievers were categorised as mesocephalic. The values of the LWI of the brachycephalic dogs and the mesocephalic dogs were estimated as 1.32 ± 0.02 and 1.54 ± 0.03, respectively (Table 2). The mean (± SEM) volume fraction values of the left GM, right GM, left WM, right WM, left LV, right LV, TdV, CA, and FV to the total brain volume (TBV) of the brachycephalic dogs and the mesocephalic dogs are given in Table 2. There was no statistically significant difference between the brachycephalic and mesocephalic dogs in all the volume fraction values ($P > 0.05$).

The mean volumes (± SEM) of the ventricular system of the brachycephalic dogs and the mesocephalic dogs using the Cavalieri principle are given in Table 1 for the left LV, right LV, TdV, CA, and FV. In addition to that, the left GM, right GM, left WM, and right WM volumes are given in Table 1 with all the CE values of these estimations. The left

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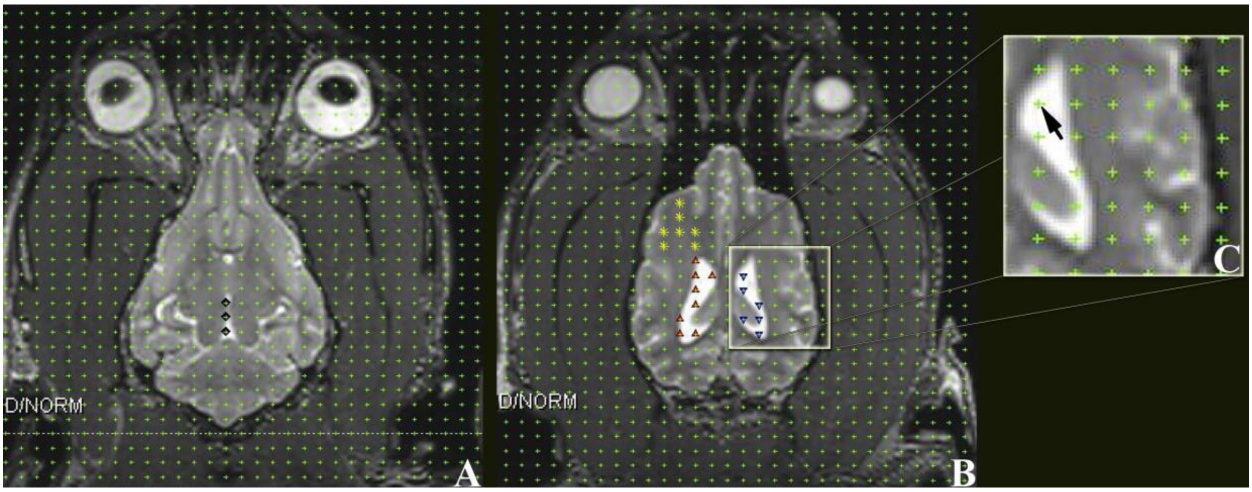

Figure 1. The frontal T2-weighted image sections at the cerebral aqueduct level (**A**) and the lateral ventricle level (**B**) with a point counting grid. The right corners were counted on the point counting grid of the desired regions (**C**) – black arrow

Table 1. The volume, CE and P-values of the left GM, right GM, left WM, right WM, left LV, right LV, TdV, CA, FV of the brachycephalic and mesocephalic dogs

	Structure	Classification	*N*	Mean ± Standard Error of the Mean	Median (Min–Max)	CE	*P*
Volume (mm^3)	Left grey matter	brachycephalic	4	35 691 ± 3188.39	33 862 (30 186–44 854)	0.007	0.021
		mesocephalic		20 464.5 ± 357.44	20 665 (19 440–21 088)	0.011	
	Right grey matter	brachycephalic	4	36 322.25 ± 2142.08	34 832.5 (33 008–42 616)	0.007	0.021
		mesocephalic		20 314.5 ± 276.6	20 124 (19 888–21 122)	0.011	
	Left white matter	brachycephalic	4	20 187.5 ± 2340.16	19 280.5 (16 262–25 927)	0.009	0.043
		mesocephalic		13 131.5 ± 1099.99	12 183 (11 744–16 416)	0.011	
	Right white matter	brachycephalic	4	18 922.25 ± 2742.11	18 181.5 (14 125–25 201)	0.009	0.083
		mesocephalic		12 827.5 ± 982.4	12 287 (11 120–15 616)	0.011	
	Left ventricle	brachycephalic	4	2057.25 ± 135.08	2062.5 (1733–2371)	0.041	0.021
		mesocephalic		1149 ± 42.5	1130 (1072–1264)	0.07	
	Right ventricle	brachycephalic	4	2002 ± 255.75	1767 (1706–2768)	0.043	0.02
		mesocephalic		1132 ± 18.11	1122 (1104–1180)	0.07	
	Third ventricle	brachycephalic	4	709.75 ± 77.11	768.5 (483–819)	0.085	0.248
		mesocephalic		612 ± 16.51	608 (576–656)	0.113	
	Cerebral aqueduct	brachycephalic	4	175.5 ± 26.65	170.5 (120–241)	0.238	0.773
		mesocephalic		166.5 ± 11.18	165 (144–192)	0.247	
	Fourth ventricle	brachycephalic	4	1051.25 ± 279.18	880 (591–1854)	0.069	0.043
		mesocephalic		455 ± 91.98	462 (224–672)	0.107	

CA = cerebral aqueduct; FV = fourth ventricle; GM = grey matter; LV = left ventricle; TdV = third ventricle; WM = white matter

https://doi.org/10.17221/33/2019-VETMED

Table 2. The volume fractions, and *P*-values of the left GM, right GM, left WM, right WM, left LV, right LV, TdV, CA, FV and LW index of the brachycephalic and mesocephalic dogs

	Structure	Classification	N	Mean ± Standard Error of the Mean	Median (Min–Max)	*P*
Volume Fraction (mm³)	Left grey matter	brachycephalic	4	30.3 ± 0.55	30.15 (29.2–31.7)	0.191
		mesocephalic		29.06 ± 0.59	29.35 (27.4–30.14)	
	Right grey matter	brachycephalic	4	31.05 ± 1.02	30.9 (29.2–33.2)	0.564
		mesocephalic		28.88 ± 0.96	29.74 (26–30.02)	
	Left white matter	brachycephalic	4	17.2 ± 0.64	17.2 (15.8–18.6)	0.468
		mesocephalic		18.64 ± 0.96	17.83 (17.4–21.5)	
	Right white matter	brachycephalic	4	16 ± 1.11	15.95 (13.7–18.4)	0.248
		mesocephalic		18.21 ± 0.72	17.72 (17.1–20.3)	
	Left ventricle	brachycephalic	4	1.83 ± 0.14	1.85 (1.5–2.1)	0.468
		mesocephalic		1.69 ± 0.04	1.68 (1.61–1.8)	
	Right ventricle	brachycephalic	4	1.75 ± 0.1	1.75 (1.5–2)	0.468
		mesocephalic		1.66 ± 0.03	1.66 (1.6–1.73)	
	Third ventricle	brachycephalic	4	0.7 ± 0.07	0.65 (0.6–0.9)	0.108
		mesocephalic		0.91 ± 0.03	0.9 (0.86–1)	
	Cerebral aqueduct	brachycephalic	4	0.2 ± 0.04	0.2 (0.1–0.3)	0.237
		mesocephalic		0.27 ± 0.05	0.24 (0.2–0.4)	
	Fourth ventricle	brachycephalic	4	1 ± 0.32	0.8 (0.5–1.9)	0.773
		mesocephalic		0.71 ± 0.15	0.67 (0.4–1.1)	
	LW index	brachycephalic	4	1.32 ± 0.02	1.33 (1.26–1.35)	0.021
		mesocephalic		1.54 ± 0.03	1.52 (1.5–1.61)	

CA = cerebral aqueduct; FV = fourth ventricle; GM = grey matter; LV = left ventricle; TdV = third ventricle; WM = white matter

GM, right GM, left WM, left LV, right LV, and FV volume values were significantly different between the brachycephalic and the mesocephalic dogs ($P < 0.05$) but the right WM, TdV, and CA values were not statistically significant ($P > 0.05$).

DISCUSSION

Magnetic resonance is the best and most commonly used imaging technique for visualising the compartments of the brain *in vivo* (Woo et al. 2010; Furlong et al. 2013). However, in order to prevent bias due to some factors inherent in the imaging processes, the values must be estimated carefully on the MR images. On the other hand, volume estimations also had some difficulties and limitations in the past. Due to the lack of facilities provided by the technology, problems were encountered in *post-mortem* measurements. The fixation process applied to the brain tissue also causes shrinkage. As a result, the estimated values may not meet its true data (Vite et al. 1997; Tang et al. 2001; Furlong et al. 2013). For this very reason, the stereological method, the Cavalieri principle, is used to overcome these estimation problems and obtain the quantitative data concerning the volume and volume fraction values of the compartments of the brain by using a 3T MRI, which was investigated in this study. Our data and previous studies (Keshavan et al. 1995; Acer et al. 2010; Akdogan et al. 2010) suggested that the Cavalieri principle with the combined application of the point counting stereology was simple, swift, and time efficient methods to apply the estimation on the MR or CT images without any other procedures.

https://doi.org/10.17221/33/2019-VETMED

Different breeds of dogs have different types of skull shapes, thus creating problems during the classification. In some studies, measurements without any classification are composed problems, in fact, there are several methods used for this classification (Vite et al. 1997; Koch et al. 2014; Pilegaard et al. 2017). In this study, the LW index was used for the classification of brachycephalic and mesocephalic dog breeds. Brachycephalic dogs were considered to have an LWI < 1.44.

The Cavalieri principle has been used for the effect of the skull type on the estimation of the cortex and the lateral ventricle size in dogs (Pilegaard et al. 2017). This method has also been used in the estimation of a *post-mortem* brain surface area using a 3T MRI (Furlong et al. 2013). It has also been used in a study on ageing in Beagle dogs (Kimotsuki et al. 2005). The Cavalieri principle with a combination of unbiased and accurate sampling and counting methods gives an almost precise result on the estimation. This stereological method makes a statistical estimate of the reliability of the values obtained as a result of the measurements. This CE depends on the sampling procedure, the point counting grid, and the complexity of the object (Akdogan et al. 2010; Pilegaard et al. 2017). Our results of the GM, WM, LV, TV, and FV were seen as acceptable CE values, but the CA had a higher a CE value because of it being small volume and performing estimations on only a few MR slices. The Cavalieri principle generally requires about a maximum 200 points to be counted on 10–15 sections for the complex 3D shape to have an approximately 5–10% CE value (Howard and Reed 2005).

Woo et al. (2010) evaluated the hydrocephalic ventricular changes on the volumes of the ventricles and brain by multiplying the area of the selected region and slice thickness using an MRI. The MR images were acquired on a 0.2T and 4–6 mm thickness which had lower tesla values and a larger thickness than the present study. The mean volume of the right ventricle, left ventricle, and brain were 967.86 mm^3, 887.72 mm^3, and 44 679.80 mm^3 for the normal dogs and 4509.62 mm^3, 4064.94 mm^3, and 40 121.62 mm^3 for dogs with the hydrocephalus, respectively. Vite et al. (1997) measured the total ventricle volume by multiplying the area of the selected region and slice thickness using an MRI. The MR images were achieved on a 1.5T and 5 mm thickness which had lower tesla values and a larger thickness than the present study. The mean total ventricle volumes were 14 800 mm^3 in English bulldogs and 2200 mm^3 (a range of 700–3700 mm^3) in Beagles. Kimotsuki et al. (2005) compared the lateral ventricle volumes with the age-associated changes by a hand-drawing manner using an MRI. The MR images were obtained on a 4.7T and 3 mm thickness which had a higher tesla value and thickness than the present study. The volume of the lateral ventricle space was found to be 1700 mm^3 (a range of 149–5960 mm^3) in the dogs. Pilegaard et al. (2017) evaluated the cortex and the lateral ventricle volume by the Cavalieri principle and point counting method using a 0.2T MRI. The volume of the lateral ventricle ranged from 200 mm^3 to 4600 mm^3 in the dogs. Reinitz et al. (2017) measured the distribution of the cerebrospinal fluid volume among the compartments by automatic 3D segmentation using an MRI. The MR images were acquired on a 1.5T and a 1 mm thickness. The range of the volume of the left ventricle, right ventricle, third ventricle, cerebral aqueduct, and fourth ventricle was found to be 260–1360 mm^3, 220–1170 mm^3, 210–380 mm^3, 60–130 mm^3 and 140–370 mm^3, respectively. Schmidt et al. (2015) compared the cerebral white matter and grey matter volume with the normal and lateral ventricle enlargement in dogs using an MRI. The MR images were obtained on a 1T and a 2–3 mm thickness. The ratio of the white matter to the grey matter were 0.232 and 0.1736 in the normal dogs and in the dogs with the lateral ventricle enlargement, respectively. In this study, the volume and volume fraction of all the compartments of the brain were estimated by the Cavalieri principle and point counting method using a 3T MRI and a 1 mm thickness with no gap. The MR images were distinct and clear in the Tesla machine with a higher value. The lateral ventricle volumes of the brachycephalic and mesocephalic dogs in our study were similar to those obtained by Kimotsuki et al. (2005), Woo et al. (2010), Pilegaard et al. (2017) and Reinitz et al. (2017). The fourth ventricle volumes of the mesocephalic dogs in our study were similar to those obtained by Reinitz et al. (2017). The total volumes of the mesocephalic dogs in our study were like those obtained by Pilegaard et al. (2017). The difference in the volume of the brain ventricles found may be attributable to the differences in the methodology used in these studies. In some previous studies, the volumetric measure-

https://doi.org/10.17221/33/2019-VETMED

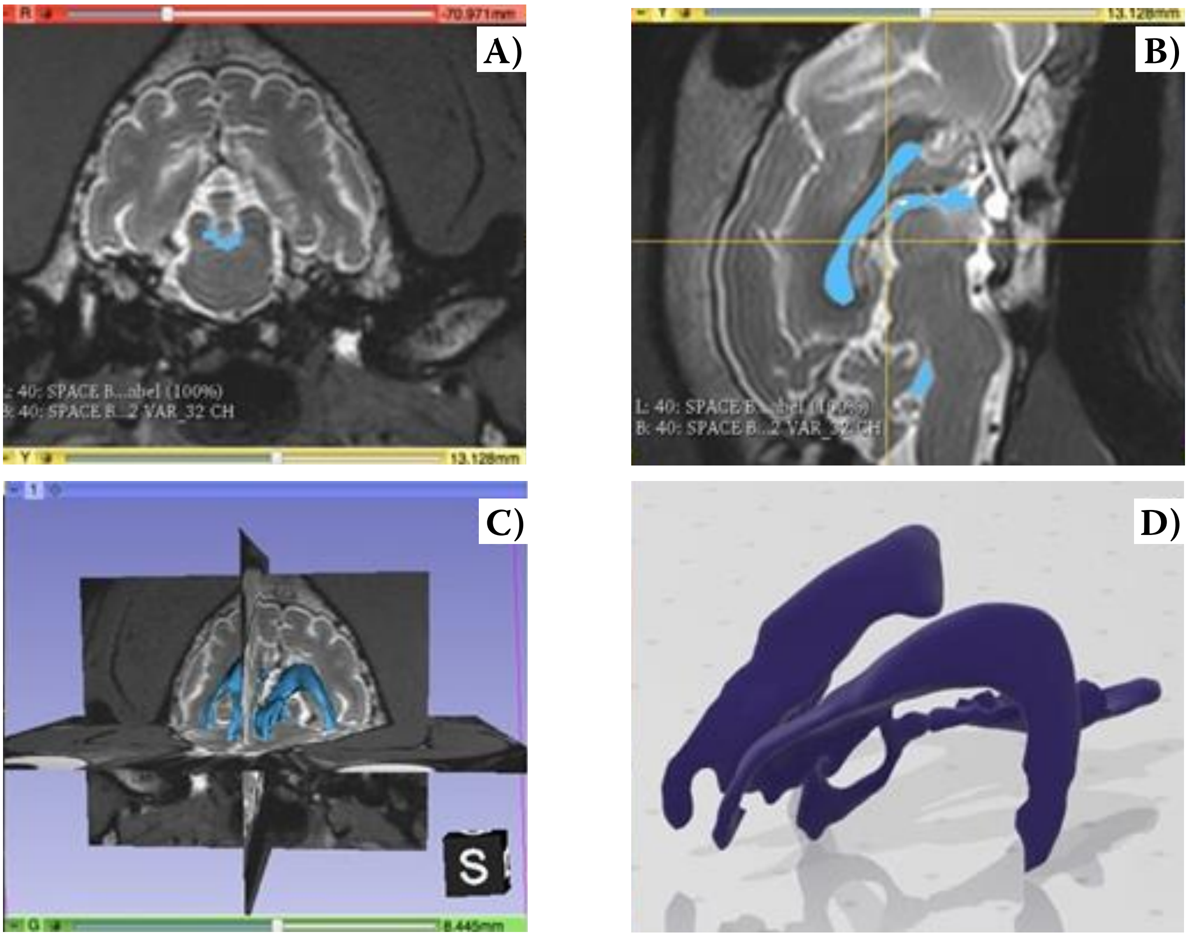

Figure 2. The transversal (**A**) and sagittal (**B**) T2-weighted images of the mesocephalic dog. The 3D reconstruction viewer mode of the ventricle sys-tem with all the planes of the MR image (**C**) and the 3D reconstructed ventricle system model of the brain (**D**)

ments of the brain structures were compared and examined with body weight formulations (Woo et al. 2010; Schmidt et al. 2015; Reinitz et al. 2017). Importantly, the ratios between the volumes of the neural structures may have a constant value, which is independent of the body size (Acer et al. 2010). Therefore, we estimated the volume and the volume fraction values of the brain compartments independently from the body weight. Only the LW index was used to classify the dogs.

Advancing technological innovations improve veterinary anatomy education. 3D reconstruction images obtained by imaging techniques have been a leading source of these materials. Thus, the position, shape, and relationship of the structures are understood more easily with an approach to the structure from the desired angle (Lee et al. 2010). In this study, the 3D reconstruction images of the ventricles in the brain were obtained from 3T MR images. These 3D reconstruction images might be useful and helpful for both students and lecturers in veterinary anatomy education (Figure 2).

In conclusion, we have evaluated the volume and the volume fraction values of the brain structures in brachycephalic and mesocephalic dogs using a combination of a 3T MRI and the Cavalieri principle. In addition, the 3D reconstructed models of the ventricular system have been created for the better understanding the relationship of the related structures. These findings can be helpful to examine, compare, and estimate the anatomical and pathological problems of the brain structures in the different breeds of dogs.

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Received: March 4, 2019
Accepted after corrections: August 16, 2019