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Subcortical and white matter alterations in canine ventriculomegaly: an observational volumetric and voxel-based-morphometry study

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Abstract

Objective Ventriculomegaly and hydrocephalus are frequently found during routine clinical imaging, and hydrocephalus in dogs has been shown to alter brain tissue. Although approaches exist to differentiate canine hydrocephalus from ventriculomegaly, information about brain tissue alterations in dogs with ventriculomegaly is lacking. In this observational study, we focused on ventriculomegaly and examined the cerebral anatomical adaptations that accommodate the increased ventricular volume.

Methods 95 neuroradiological normal diagnosed dogs of different breeds were divided into the two groups, ventriculomegaly and control, according to morphological criteria and ventricle-brain-indices as determined by ratio of brain and lateral ventricle wide. Brain volumetry and voxel-based-morphometry (VBM) were conducted using automatic procedures employing the Statistical Parametric Mapping software and a canine brain atlas.

Results Significant alterations in cingulate cortex, caudate nucleus, thalamus, hippocampus, geniculate body as well as corpus callosum were observed in dogs of the ventriculomegaly group by both volumetry and VBM. Interestingly, ventriculomegaly affected only lateral ventricles, the 3rd ventricle, and the mesencephalic aqueduct but not the 4th ventricle.

Discussion A clear distinction between canine hydrocephalus and ventriculomegaly remains difficult and recent research suggests parallels between both. Advances in automated segmentation methods and voxel-based morphometry applicable to canine magnetic resonance imaging offer the opportunity to comprehensively assess structural abnormalities. In addition, clinical assessments are required to investigate the impact of ventriculomegaly on cognitive function and behavior in further studies.

Conclusion We propose the use of a lower ventricle-brain-index threshold of ≥ 0.5 to include all ventricle-associated tissue alterations with potential clinical manifestation.

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Keywords Brain, Dog, Hydrocephalus, Magnetic resonance imaging, Subcortical structures, Ventriculomegaly, Voxel-based-morphometry

Introduction

Enlarged ventricle volumes are routinely seen in dogs and could be descriptively classified as hydrocephalus or ventriculomegaly. Ventriculomegaly is among the most frequent neuroradiological diagnoses in small dog breeds, particularly in brachycephalic ones [1, 2]. It has been widely accepted that the increase in ventricular volume is not necessarily associated with clinical symptoms and dogs with ventriculomegaly are not truly considered hydrocephalic [1, 3, 4]. This applies equally to isolated occurrences as it does to ventriculomegaly as part of multifactorial pathologies like the Chiari-like malformation [5]. The ventricle-brain-index (VBI) was recently introduced and represents a reliable grading system of the lateral ventricle distention in relation to the brain tissue [6]. A VBI over 0.6 indicates an increase in intracranial pressure that manifests clinically, thereby classifying as hydrocephalus [7]. Clinical manifestation as epilepsy is questionable as a recent study failed to validate the historical correlation [8–10]. Hydrocephalus could indicate surgical intervention in the form of ventriculoperitoneal-shunting with the associated risks to reduce the high ICP and thus resolve symptoms, thus making the distinction between the two entities ventriculomegaly and hydrocephalus crucial [9–12]. Moreover, morphological investigations revealed that ventriculomegaly in dogs are associated with periventricular white matter (WM) loss similar to that observed in internal hydrocephalus [1]. Perfusion-weighted magnetic resonance imaging (MRI) studies showed that cerebral blood flow can be reduced in the periventricular WM of dogs with ventriculomegaly, as well as in clinically relevant hydrocephalus. This implies that dilatation of the cerebral ventricles can cause compression of periventricular blood vessels [13, 14]. A recent study showed that skull morphology, particularly a smaller cranial fossa volume, has a profound influence on cerebrospinal fluid (CSF) flow dynamics in the mesencephalic aqueduct [2]. Hyperdynamic CSF flow was found in both, dogs with internal hydrocephalus and with ventriculomegaly, suggesting that hyperdynamic CSF flow may serve as an indicator for impaired CSF efflux from the lateral and 3rd cerebral ventricles [15, 16]. Hence, evidence accumulates that ventriculomegaly may be a precursor to or an incompletely developed form of internal hydrocephalus [1]. It was also hypothesised that ventriculomegaly may result in subtle clinical signs that are not recognised in standard neurological examinations. In humans with normal pressure hydrocephalus, which shows parallels to canine ventriculomegaly [13], cognitive decline is associated with volume reduction in subcortical structures, including diminished volume of the basal nuclei [17] and hippocampi [18, 19]. We hypothesised that ventriculomegaly in dogs is associated with subcortical volume reductions. Thus, we conducted a volumetric assessment of the canine brain using automated segmentation methods to investigate the effects of ventriculomegaly on the brain parenchyma.

Materials and methods

Animals

The images for this observational analysis were obtained from MR studies of canine patients performed between 2016 and 2023 at University of Veterinary Medicine Vienna. Dogs with obvious structural brain alterations (e.g., due to neoplasia, post-traumatic or ischaemic lesions) were excluded to avoid including cases with compensatory CSF space enlargement. We also included dogs with hydrocephalus. Data sets of 95 neuroradiologically normal dogs of different breeds were reviewed by two independent veterinarians (TCC, BN). Fifteen MRI data sets of individuals with ventriculomegaly were identified, defined as a ventricle-brain-index (VBI) larger than 0.5 when assessing the data using FisImageJ (Version 1.53 h, RRID: SCR_002285) [20]. The VBI was calculated as the maximum continuous distance between the internal borders of the ventricles divided by the maximum width of the brain parenchyma in the same image [7]. The mean VBI was 0.44 ± 0.05 (CI95%: 0.43/0.45, Fig. 1B). The VBI was 0.42 ± 0.02 in the control group ($n = 80$) and 0.55 ± 0.03 in the ventriculomegaly group ($n = 15$, Fig. 1B).

Ethics statement

All MRI data were originally obtained for diagnostic purposes and analysed retrospectively. Therefore, ethical approval was not required because the respective authorities waive ethical review for studies based on previously obtained clinical imaging for diagnostic purposes.

Image technique

A 1.5 Tesla scanner (Magnetom Espree, Siemens Healthineers, Germany) equipped with a 15-channel Tx/Rx knee coil was used for image acquisition. Sagittal T2-weighted images of the entire brain were acquired (T2-Turbospin Echo SPACE 3D, TE/TR: 378/3200ms, echo numbers: 1, flip angle: 120, number of phase encoding steps: 196, number of averages: 1, percent phase field of view: 87.5, slice thickness 1.0 mm, acquisition matrix: $0 \times 256 \times 226 \times 0$; flip angle: variable; voxel size: $1.0 \times 1.0 \times 1.0$ mm).

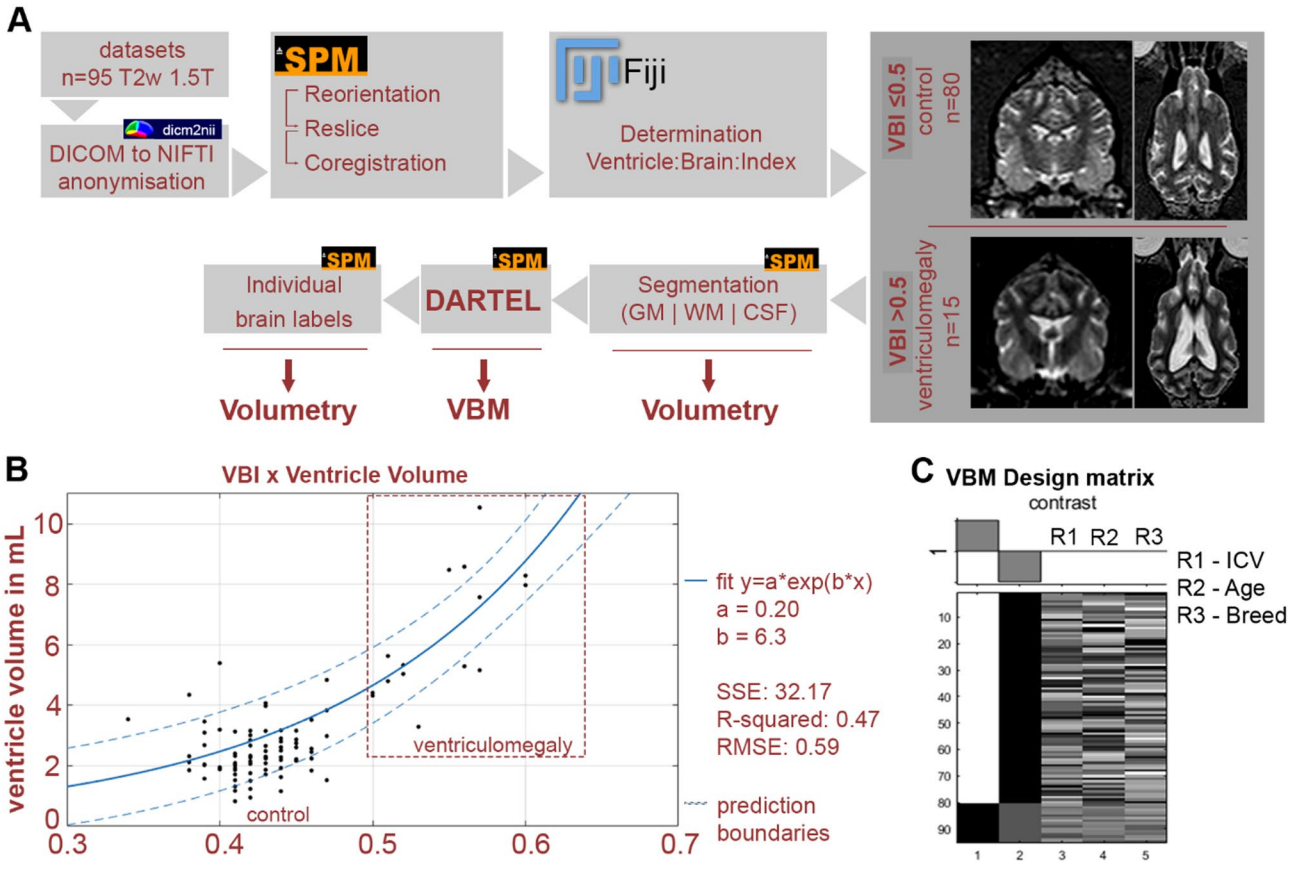


Fig. 1 Image processing procedure. (**A**) A ventricle-to-brain index (VBI) larger than 0.5 was used to identify ventriculomegaly. (**B**) Fitting the correlation of VBI and ventricle volume showed an exponential curve. (**C**) The VBM Design matrix included the covariates intracranial volume (ICV), age, and breed. GM, grey matter; WM, white matter; CSF, cerebrospinal fluid (only ventricles); DARTEL, Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra

Image processing and analysis

Image processing and analysisImage processing, as described elsewhere [21], was performed by a researcher blinded to the groups. The workflow is shown in Fig. 1A. Briefly, all DICOM datasets were anonymised and stored in NIFTI-1 format by using dcm2nii (v1.0.20211006, RRID: SCR_014099). Data were reoriented according to the canine stereotactic space (as provided in https://www.fil.ion.ucl.ac.uk/spm/ext/#templates), resliced to 0.5 mm isometric voxel size (6th order B-spline-interpolation), and rigidly co-registered (6th degree of freedom) to the canine T2w breed-averaged template using SPM12 (Version 7771, Wellcome Trust Centre, RRID: SCR_007037) [22] in Matlab 2021b (Version 9.11.0.1769968, The MathWorks, Inc., Natick, US, RRID: SCR_001622). All data were automatically segmented into grey matter (GM) and WM as well as ventricular CSF by the SPM12 routine using canine tissue probability maps [21] followed by a Markov Random Field cleanup (Markov Random field cleanup: 2). Individual GM, WM, and ventricular tissue masks were affinely co-registered using the 'Normalize' function (sampling distance: 2 mm). Subsequently, the co-registered masks were non-linearly co-registered to the canine brain template by Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) [23] using a canine DARTEL template strictly aligned with the T2w template (http://www.animal-brain-mapping.com/) followed by applying a 2 × 2 × 2 mm smoothing kernel. For volumetry, the calculated individual deformation matrices were used to map the modified canine brain atlas into the individual space [21]. The absolute (in mL) and relative (in percentages) tissue volumes were calculated from the following brain structures and labels: GM, WM, ventricle, temporal and parietal lobes, cingulate gyrus, occipital and frontal lobes, lateral ventricle, 3rd ventricle, 4th ventricle, mesencephalic aqueduct, olfactory lobe, caudate nucleus, thalamus, hippocampus, geniculate body, corpus callosum, olfactory tract, cerebellar hemisphere, vermis, and cerebellar WM. The relative volume was calculated in relation to the intracranial volume (ICV).

Statistical analysis

Statistical analysis of absolute and relative volumes was performed using Matlab 2019 and presented as mean ± standard deviation. The normality of the data distribution was evaluated by the Kolmogorov-Smirnov test. Since mask and label volumes were not normally distributed, non-parametric tests (Wilcoxon-Mann-Whitney U test, exact mode) were chosen for group comparisons. All data are presented as box plots with median, interquartile range, and 95% confidence intervals. Outliers were determined as being beyond the 95% confidence interval (CI) and are indicated by ^{x}. Levels of statistical significance are given as follows: $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Cohen's d was used to calculate effect sizes.

VBM was performed on DARTEL-registered GM, WM, and CSF masks, considering ICV, age and breed as a covariate using t-tests with a family-wise statistical significance level of 0.05 using SPM12 (Fig. 1C).

Results

Demography

The control group included 80 healthy dogs (39 females, age 6.2 ± 3.4 years, weight 19.9 ± 11.5 kg) and the ventriculomegaly group included 15 dogs (3 females, age 7.7 ± 2.7 years, weight 21.1 ± 13,3 kg). There were no statistically significant differences regarding age ($p = 0.063$) and weight ($p = 0.976$) between both groups. A total of 46 different breeds were identified, but brachycephalic breeds were equally represented in both groups (control = 11.3%; ventriculomegaly group = 13.3%, $p = 0.817$). Breed details can be found in the supplementary material.

Absolute brain volumes

The ICVs were indifferent between the control (83.5 ± 20.6 mL) and ventriculomegaly groups (92.4 ± 23.8 mL, $p = 0.133$). There were no statistically significant differences in absolute GM or WM volumes between the control group (GM: 54.1 ± 13.8mL, WM: 27.0 ± 6.0 mL; $p = 0.469$) and the ventriculomegaly group (GM: 56.7 ± 15.9 mL, WM: 29.4 ± 18.6 mL; $p = 0.743$). Not surprisingly, ventricular volumes were significantly different between the two groups (control: 2.4 ± 0.8 mL, ventriculomegaly: 6.3 ± 2.1mL; $p < 0.001$).

Relative volumes of brain structures

When normalising to ICV, relative GM and WM volumes were significantly decreased in the ventriculomegaly group (GM: $p = 0.029$; WM: $p = 0.011$), whereas the relative CSF volume was significantly increased in the ventriculomegaly group ($p = 0.001$, Fig. 2).

There were no statistically significant differences between the control and ventriculomegaly group regarding relative volumes of the neocortical lobes (temporal lobe: 17.4 ± 2.3/17.7 ± 3.0, $p = 0.453$; parietal

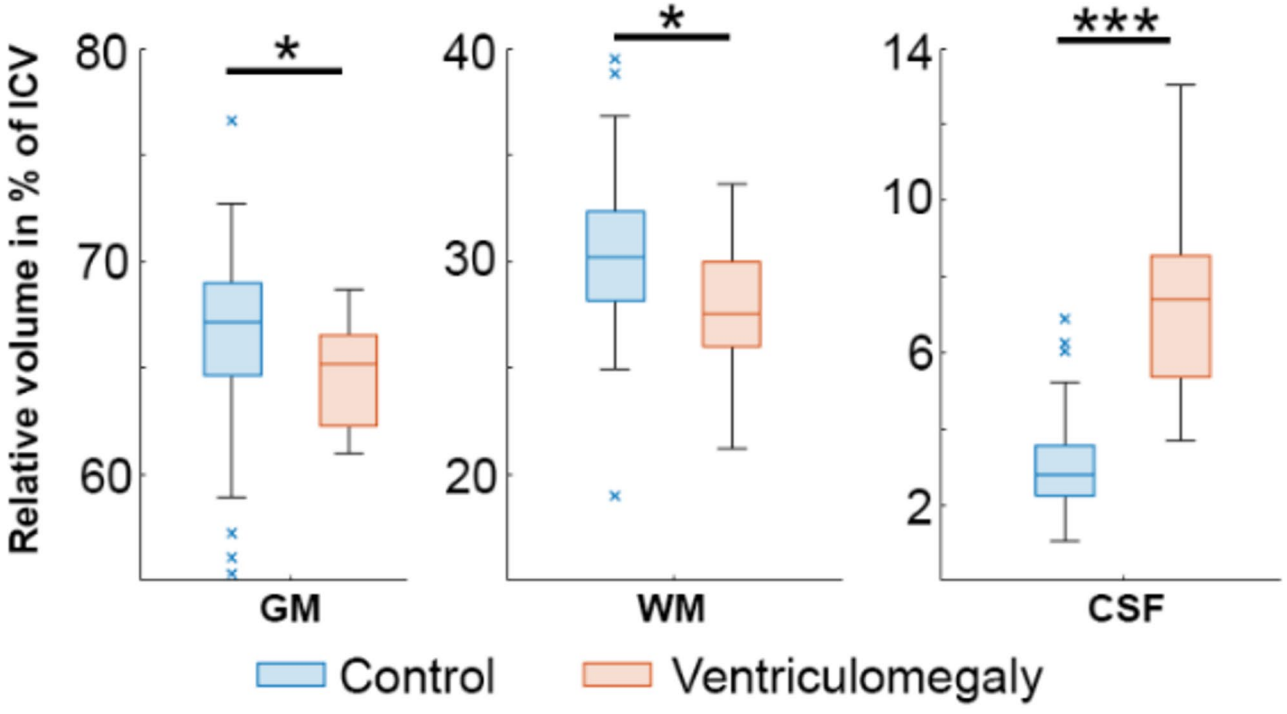


Fig. 2 Relative grey matter (GM), white matter (WM), and ventricular cerebrospinal fluid (CSF) volumes. Volumes were normalised to the intracranial volume (ICV). Boxplots represent median, interquartile and 95% confidence. Outliers are indicated by ^{x}. Significance levels are indicated by $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$

lobe: 7.1 ± 1.2/7.3 ± 1.5, $p = 0.223$; occipital lobe: 6.6 ± 1.0/6.8 ± 1.4, $p = 0.238$; frontal lobe: 9.7 ± 1.5/9.8 ± 2.6, $p = 0.771$; control/ventriculomegaly group, respectively). The olfactory lobes were significantly smaller in the ventriculomegaly group (4.0 ± 0.6/3.7 ± 0.9 mL, $p = 0.038$, Fig. 3).

Interestingly, the relative volumes of the cingulate cortices (2.6 ± 0.4/2.9 ± 0.8, $p = 0.038$, control/ventriculomegaly respectively) were significantly increased in the ventriculomegaly group. Moreover, the relative volumes of caudate nuclei (1.4 ± 0.2/1.2 ± 0.6, $p = 0.001$), geniculate bodies (0.13 ± 0.03/0.11 ± 0.06, $p = 0.043$; control/ventriculomegaly respectively), thalami (1.2 ± 0.3/1.0 ± 0.3, $p = 0.002$) as well as relative hippocampal volumes (2.3 ± 0.5/2.0 ± 0.5, $p = 0.004$) were significantly decreased in dogs with ventriculomegaly (Fig. 3). The relative volume of the corpus callosum was significantly reduced in the ventriculomegaly group (0.9 ± 0.2/0.7 ± 0.3, $p = 0.001$, Fig. 3). However, olfactory tract volumes were indifferent between groups (0.41 ± 0.1/0.43 ± 0.13, $p = 0.335$, control/ventriculomegaly respectively).

When comparing the relative volumes of cerebellar structures, the vermis (2.7 ± 0.4/2.7 ± 0.5, $p = 0.810$), cerebellar hemispheres (3.7 ± 0.9/3.6 ± 0.8, $p = 0.592$) and cerebellar WM (1.3 ± 0.4/1.3 ± 0.4, $p = 0.679$) did not differ significantly between the two groups (Fig. 3).

The lateral ventricles (2.7 ± 0.5/3.4 ± 1.0, $p = 0.002$), the 3rd ventricle (0.4 ± 0.1/0.5 ± 0.1, $p < 0.001$) and the mesencephalic aqueduct (0.08 ± 0.02/0.09 ± 0.02, $p = 0.013$) were significantly increased in the ventriculomegaly group. However, the 4th ventricle (0.09 ± 0.02/0.08 ± 0.02, $p = 0.400$) did not differ significantly between both groups (Fig. 3).

Effect sizes with Cohen's D were large for lateral ventricle, olfactory tract and corpus callosum. Medium effects were observed for the 3rd ventricle, temporal lobe and caudate nucleus. Effect sizes for mesencephalic aqueduct, occipital lobe, olfactory lobe, thalamus, hippocampus and cerebellar WM were small. The effect sizes for frontal and parietal lobe, cingulate cortices, vermis, geniculate body were very small (Fig. 4).

Voxel-based-morphometry

Clusters of significance indicating a reduced volume in the ventriculomegaly group were identified in the interthalamic adhesion, predominantly the left caudate nucleus, bilaterally in the frontal lobe dorsal to the olfactory recess of the lateral ventricles, and in the middle of both lobes cranioventrally to the genu of the corpus callosum. Additionally, a significant cluster was detected in the caudal corpus callosum (Fig. 5).

Interestingly, clusters of significance indicating an increased volume in ventriculomegaly dogs were detected in the cranial cingulate gyrus and the ventral hippocampus, the caudodorsal GM of the lateral subventricular zone, the rostral corpus callosum, bilaterally in the WM dorsal of the subventricular zone, the lateral internal capsule, and the WM ventral to the mesencephalic tectum (Fig. 5).

The lateral and 3rd ventricles including their respective recesses, especially the olfactory recesses, as well as the mesencephalic aqueduct were increased in the ventriculomegaly group (Fig. 5). However, the size of the 4th ventricle did not differ significantly between the two groups.

Discussion

The clinical diagnosis of hydrocephalus remains challenging, particularly in brachycephalic dog breeds. The VBI [7] is a feasible parameter to identify clinically relevant ventricular dilatation under elevated intracranial pressure. Unfortunately, the regular size of ventricles in different dog's breed is not determined yet. However, a reduced rostral cranial fossa volume detected in small and brachycephalic dog breeds may contribute to an enlargement of ventricle but the impact on brain parenchyma is unclear [2]. Thus, we chose a very conservative approach for identifying ventriculomegaly relevant VBI considering the confidence interval in our population with different facial skull morphology. Recent studies had shown that brachycephalic dogs with enlarged lateral cerebral ventricles include reduced relative global white matter volume [1]. Here, we demonstrate local alterations in subcortical nuclei and local WM in a population with mixture of cranio-morphological features.

Subcortical and cortical structures so far were not extensively investigated using quantitative MRI techniques in dogs with ventriculomegaly. Our data suggest that canine ventriculomegaly can also alter brain structure. Tissue volume changes observed in animals with ventriculomegaly mirror those reported in studies involving dogs with hydrocephalus [7, 15]. Specifically, smaller-than-average volumes were found in the interthalamic adhesion, the caudate nucleus as well as the corpus callosum, whereas larger-than-average volumes were found in the ventral hippocampus, the amygdala, the caudodorsal GM and WM of the lateral subventricular zone, the lateral internal capsule, and the WM at the tectum.

Deep brain structures adjacent to the expanding lateral ventricles, such as the caudate nucleus, hippocampus and thalamus and in particular the interthalamic adhesion, showed reduced volumes, as reported in hydrocephalus models and hydrocephalic patients, including humans [24]. The underlying cause may be a gradual adaptation to the space filled by the ventricular system. The reasons for the reduced volume of the corpus callosum (especially its middle part) which have been reported in hydrocephalic humans [25–27] as well as dogs with experimental induced hydrocephalus [28], are not well understood.

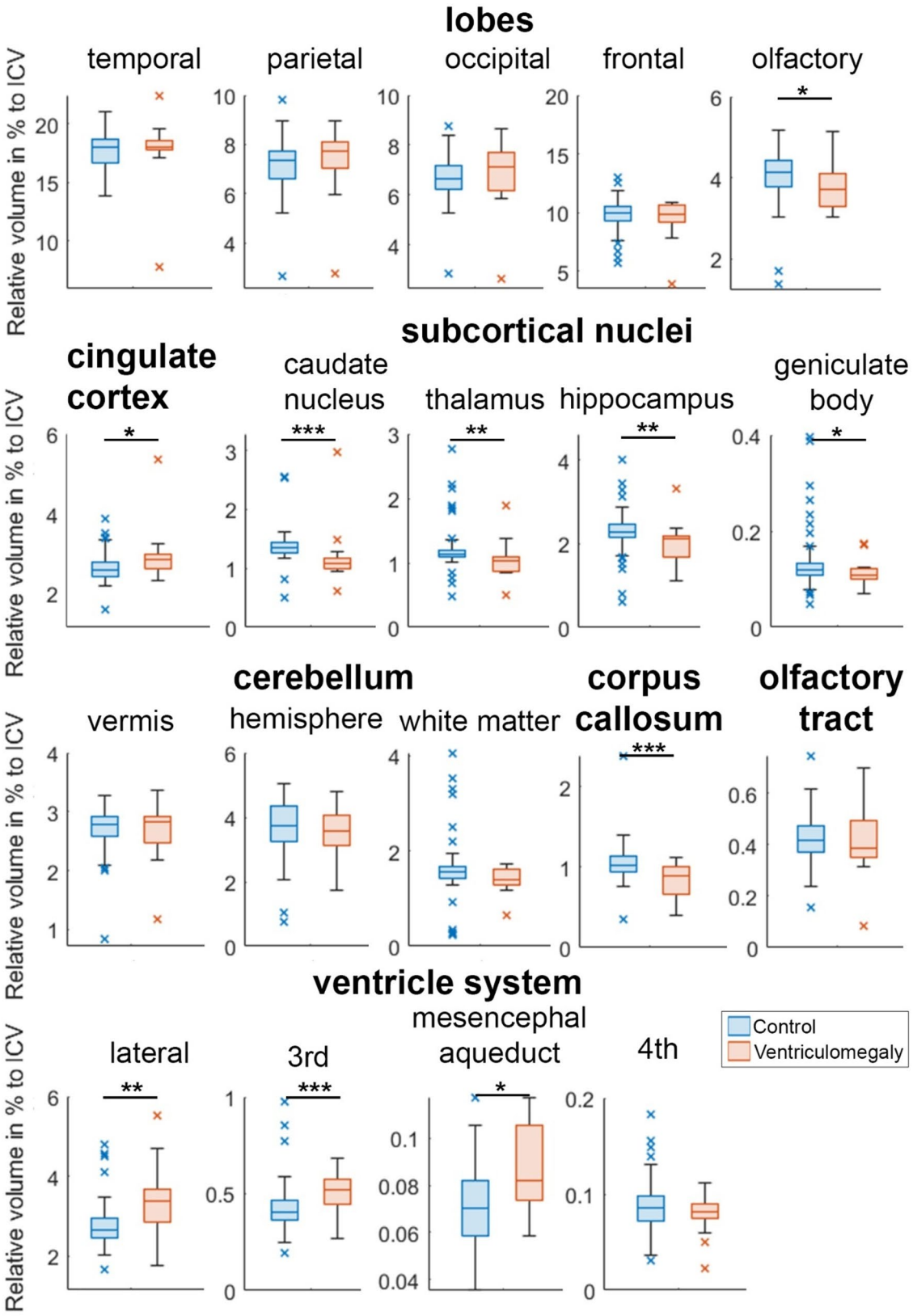


Fig. 3 Descriptive statistics of relative volume differences between control and ventriculomegaly groups. Boxplots represent median, interquartile and 95% confidence. Outliers are indicated by ˣ. Significance levels are indicated by *$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$

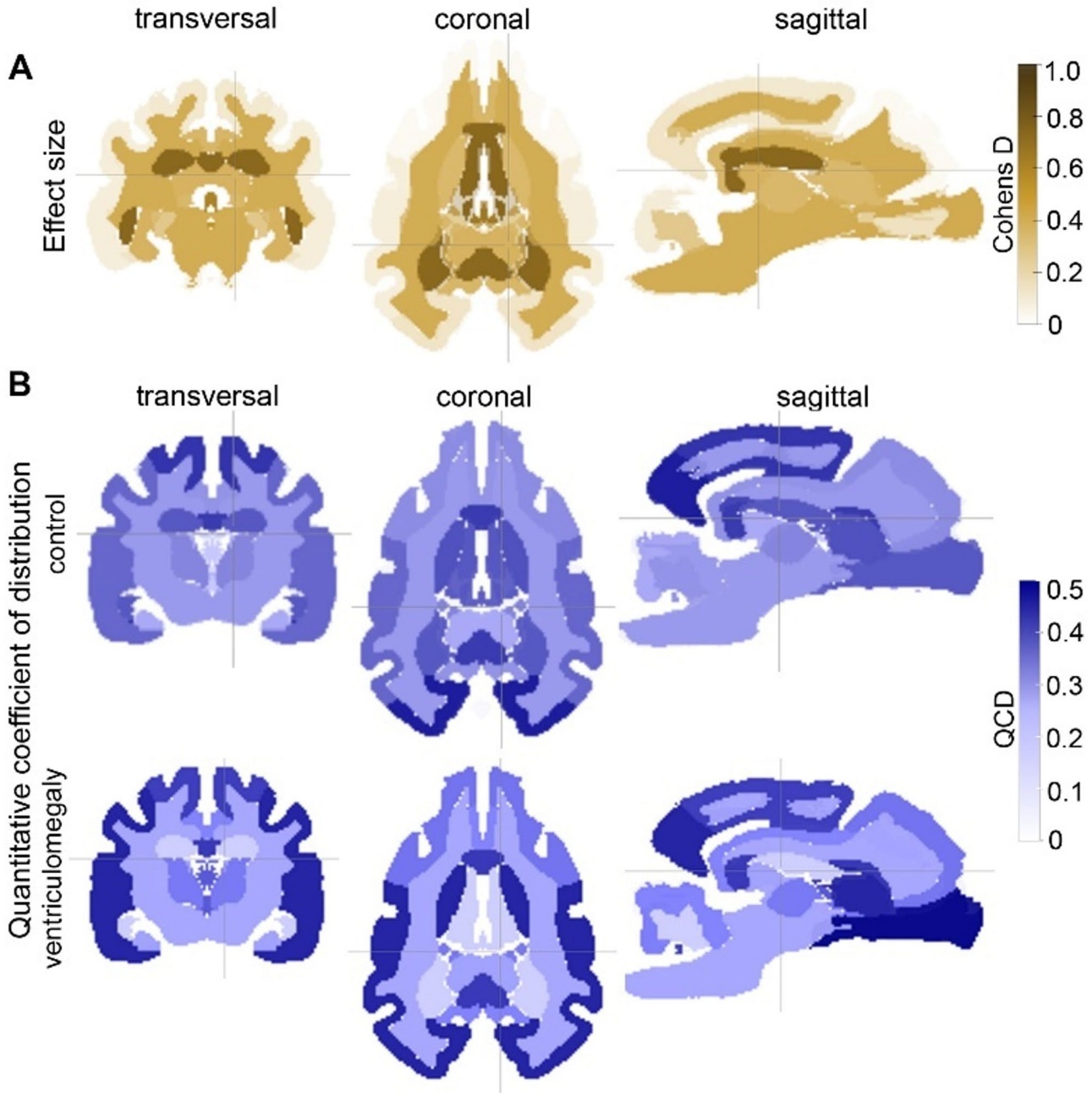


Fig. 4 (**A**) Effect size with Cohen's D and (**B**) Quantitative Coefficient of Distribution (QCD) projected on the canine brain labels

However, demyelination of the callosal axons has been suggested as a contributing pathological mechanism [29]. Previously described structural alterations associated with normal pressure hydrocephalus in humans, such as an increased dorsal convexity of the corpus callosum, have also been identified in dogs [30].

The rostral part of the corpus callosum showed a larger volume in our study, indicating a rostral volume shift with subsequent tissue loss. In contrast, the rostral cingulate gyrus volume was increased in ventriculomegaly dogs, as were the dorsal subventricular GM and WM volume. Both may be due to an emerging periventricular oedema as reported in other canine studies [7] and in human patients [31, 32]. In principle, extravasation of ventricular CSF into the periventricular WM or transependymal CSF absorption have been discussed as possible causes [33, 34]. A reduced subventricular cerebral blood flow with subsequent hypoxia and tissue oedema was reported in dogs [13], but other factors such as local gliosis due to chronic tissue stress should also be considered [35, 36].

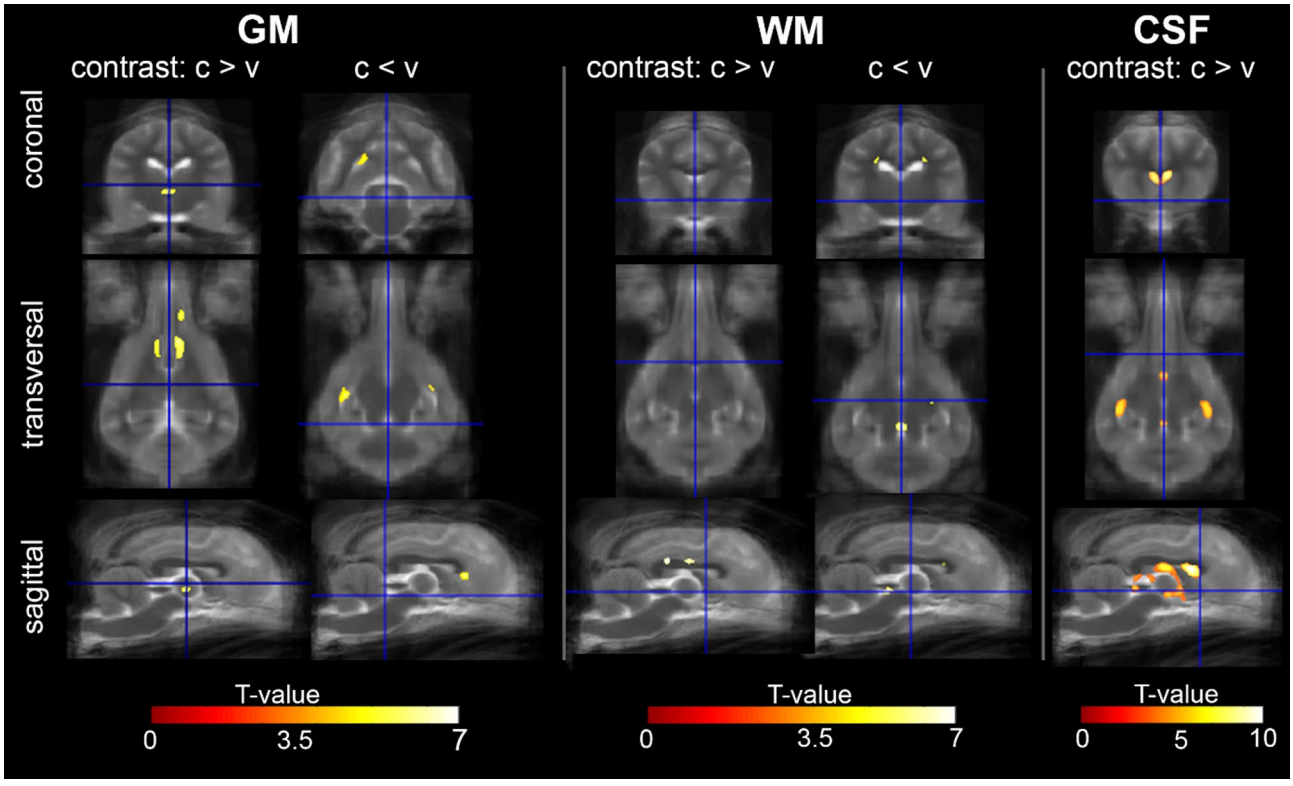


Fig. 5 Results of VBM. Cluster of significance in GM and WM as well as CSF after t-test with the contrasts c < v and c > v for each tissue class were projected onto the canine T2w template. T-values of the clusters are given below each projection. c, control group; v, ventriculomegaly group

We found an enlargement of the ventricular system including the lateral and 3rd ventricles as well as the mesencephalic aqueduct in the ventriculomegaly group. However, the volume of the 4th ventricle was not different between groups, a finding that contrasts with reports from other studies documenting dilation of the 4th ventricle [24, 28]. A possible reason is the low degree of ventricular enlargement in our study population, possibly a consequence of a non-pressure-related dilation. Further longitudinal studies of early-stage canine ventriculomegaly, incorporating detailed neurofunctional assessments and, where feasible, intracranial pressure measurements, are needed to clarify the role of a potential pathological progression and severity of ventricular enlargement.

Nevertheless, our study shows tissue volume alterations in animals with ventriculomegaly suggesting that this condition may represent an early stage of hydrocephalus. Specifically, changes in the cingulate gyrus and hippocampus may indicate the possible occurrence of pain and altered cognition [37], as previously observed in human patients [38]. Furthermore, alterations of the corpus callosum and thalamus point to subtly changed motor functions, which are also seen in human patients but can be difficult to assess in dogs [39].

A limitation of our study is the absence of clinical neurofunctional assessments. This is due to the fact that our study was done on previously obtained imaging data. Clinical records indicate that a large proportion of our study population suffered from idiopathic epilepsy (data not shown). Although epilepsy prevalence was similar in both groups (62% in control; 53% in ventriculomegaly group), we could not exclude a relation between ventriculomegaly and epilepsy [40]. However, all animals in this study were diagnosed as neuroradiologically normal by veterinary neuroradiologists without presenting structural alterations potentially contribute to epilepsy. Moreover, T2w TSE MR data sets were carefully reviewed for structural abnormalities which could not been identified in any subject [40]. Recently, apathy was found to be associated with impaired fronto-subcortical circuitry in humans with normal pressure hydrocephalus [41]. However, corresponding neurological data were not available in our observational assessed canine study cohort. Correlation with cognitive data would be ideal but, unfortunately, cognitive assessments are not implemented in routine veterinary diagnosis so far and the occasional studies analyzing the relationship between cognitive abilities and ventricular dilation haven't observed significant changes. Therefore, cognitive evaluation currently cannot be utilised for retrospective studies [42]. Further studies need to address also neurological examination (such as

Canine Cognitive Assessment Scale, Muscular Assessment Scale).

Conclusion

Our study shows that dogs with ventriculomegaly, correctly diagnosed as neuroradiologically normal according to current methodology, exhibit significant tissue volume alterations in subcortical GM and WM that may evoke subtle clinical symptoms. Consequently, we propose the use of a lower VBI threshold of at least 0.5 to indicate ventricle-associated tissue alterations with potential clinical manifestations. Additionally, the strict discrimination of ventriculomegaly and hydrocephalus on the sole basis of recognisable clinical symptoms may be reconsidered in favour of a gradually scaled approach to ventriculomegaly with consequent risk assessment for each degree of ventricular dilatation.

Supplementary Information

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Supplementary Material 1

Author contributions

TCC and BN created conception and design, assembled data, performed data analysis, interpreted data, wrote manuscript, finally approved the manuscript. MJS wrote manuscript, interpreted data and finally approved manuscript. EL collected and assembled data, partially wrote manuscript and critical discussion of the manuscript. JB interpreted data wrote manuscript, critical discussion of the manuscript and final approval of the manuscript. Robert Dahnke critical discussed the mansucript, supported the analysis strategy, reviewed the manuscript. Simone Fietz partially wrote and critical discussed the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Competing interests

The authors declare no competing interests.

Animal ethics and consent to participate

Not applicable.

Clinical trial number

Not applicable.

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