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RESEARCH ARTICLE

Hippocampal size did not differ between epileptic and non-epileptic dogs using volumetric and subjective methods

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ABSTRACT

Hippocampal changes in epilepsy may manifest as hippocampal atrophy/sclerosis. A recent human study suggests that the demonstration of hippocampal volume loss is more reliable using quantitative evaluation methods. The aim of the present study was to obtain volumetric data in both epileptic and healthy dogs, to compare hippocampal volumes in both groups, and to compare subjective and volumetric assessment. Volumetric measurements of the hippocampi, lateral ventricles and hemispheria were performed in 31 epileptic and 15 control dogs. There was a positive association between the body weight and the hemispheric volume, as well as between the hemispheric volume and the ipsilateral hippocampal volume. There was no significant correlation between age and the volume of any measured brain structures. There was no statistically significant difference between the hippocampal volumes of the control group and the epileptic group. A statistically significant difference between the two groups for hippocampus/hemispherium ratio or hippocampal asymmetric ratio was not identified. An extrapolated hippocampal volume based on body weight was not possible in this study population.

KEYWORDS

canine, epilepsy, hippocampus, MRI, volumetry

INTRODUCTION

Epilepsy is one of the most common neurologic disorders in dogs, affecting about 0.6–7.5% of the canine population (Chandler, 2006). Analogous to the human International League Against Epilepsy (ILAE), the International Veterinary Epilepsy Task Force (IVETF) has been established to standardise the definition, terminology and diagnostics of epilepsy in veterinary medicine (Berendt et al., 2015; De Risio et al., 2015). Magnetic resonance imaging (MRI) plays an important role in the diagnosis of epilepsy. The IVETF recommends a specific epilepsy MRI protocol containing 6–7 sequences (Rusbridge et al., 2015).

The IVETF created a three-tier system for the diagnosis of primary/idiopathic epilepsy. Tier I confidence level is based on a history of two or more unprovoked epileptic seizures

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occurring at least 24 h apart; the dog's age at the epileptic seizure onset being between 6 month and 6 years; unremarkable inter-ictal physical and neurological examinations; and no significant abnormalities in the basic blood and urine tests. Tier II confidence level is based on the factors listed in tier I, in addition to unremarkable fasting and post-prandial bile acids; MRI of the brain (based on an epilepsy-specific brain MRI sequence protocol); and cerebrospinal fluid analysis. Tier III confidence level is based on all factors listed in tier I and tier II, in addition to the identification of characteristic electroencephalographic (EEG) abnormalities for seizure disorders (De Risio et al., 2015). However, at this time, EEG is not a routine diagnostic modality in veterinary medicine and its results are currently not very reliable (Sanders, 2015).

The hippocampus plays an important role in human epilepsy. It is located in the medial temporal lobe of the forebrain and belongs to the limbic system. In humans, hippocampal sclerosis is the most common pathology underlying pharmacologically intractable cases of the so-called (mesial) temporal lobe epilepsy (Bernasconi et al., 2000; Scott et al., 2003). In these cases, the hippocampus represents the seizure focus – i.e. the epileptogenic lesion – in the brain (Rosenow and Lüders, 2001). Conversely, there are further forms of human epilepsy with a dual pathology, where hippocampal abnormalities are associated with extrahippocampal lesions that generate the seizure focus (Okujava et al., 2002). In those cases, hippocampal changes are likely to be secondary to chronic seizuring (Wieser, 2004). Whether temporal lobe epilepsy and the associated hippocampal sclerosis represents a discrete form of canine epilepsy is debatable. According to a histological study, temporal lobe epilepsy – if present – is not a common cause of medically intractable epilepsy in dogs (Buckmaster et al., 2002). However, hippocampal changes, especially hippocampal necrosis is a separate and quite common cause of feline epilepsy, resulting in seizures with orofacial involvement (Fatzer et al., 2000; Brini et al., 2004; Schmied et al., 2008; Pákozdy et al., 2010; Pakozdy et al., 2011).

Hippocampal changes in epilepsy manifest as hippocampal atrophy or sclerosis. Although these terms are used as synonyms, hippocampal atrophy is more a morphological/radiological term (volume loss and T2-hyperintensity), whereas sclerosis represents more a histopathological description. Histologically, there is evidence of neuronal loss, gliosis and secondary shrinking of the hippocampus (Grünewald et al., 1994; Bernasconi et al., 2000). Hippocampal sclerosis can be detected subjectively on MRI (Cendes et al., 1993). The MRI criteria for hippocampal atrophy/sclerosis are: volume loss, elevated hippocampal signal intensities on T2-weighted images (indicating increased amounts of tissue-free water), and loss of internal structure (Okujava et al., 2002). Other pathologies resulting in high signal intensities on the water-sensitive MRI sequences, including oedema, hyperaemia and inflammation, are also detectable as postictal features in the hippocampus. In contrast with hippocampal sclerosis, these changes are reversible, without apparent volume loss (Mellema et al., 1999). A recent human study reported that quantitative measures were superior in detecting bilateral and mild abnormalities (Singh et al., 2013).

The aims of the present prospective study are to (1) acquire normative data of hippocampal volumes to establish a reference value; (2) given the variable size/weight of dogs, investigate whether a reliable ratio can be determined by comparison with body weight and/or cerebral volume; (3) to ascertain if hippocampal volume differed between seizuring and non-seizuring dogs; (4) to evaluate and compare the qualitative and quantitative assessment of hippocampi in dogs with and without epilepsy.

MATERIALS AND METHODS

Subjects

Two groups of client-owned dogs were included in this prospective study. The owners were informed about the study and gave consent prior to imaging.

The epileptic group comprised 31 dogs. Twelve dogs did not have biochemical and urine tests but otherwise met the criteria for tier I confidence level. The other 19 dogs met the requirements of the tier I confidence level for the presumptive diagnosis of primary epilepsy (De Risio et al., 2015).

The control group comprised 15 dogs that had not shown any seizure activity or brain-associated neurological signs in their entire life, and were presented for MR imaging for other reasons. These included otitis evaluation (n = 7), tetraplegia (n = 3) and suspected wobbler syndrome (n = 5).

Image acquisition

The MRI studies were performed in the Institute of Diagnostic Imaging and Radiation Oncology of Kaposvár University, Hungary (today: Medicopus Nonprofit Ltd.)

All dogs underwent general anaesthesia using propofol intravenously (Narcofol®, CP-Pharma GmbH, as a 4–7 mg/kg body weight bolus injection). Following intubation, the narcosis was maintained using isoflurane–oxygen inhalation (Forene®, AbbVie Deutschland GmbH & Co, 1–5 Vol%, oxygen flow 2–3 l/min).

The MRI examinations were performed using a 1.5T MRI scanner (Siemens Magnetom Avanto, Siemens, Erlangen, Germany) in ventral recumbency. Identical MRI protocols were used consistently in each case, covering the entire brain. The MRI protocol and parameters are summarised in Table 1.

The first and second author (B.A.L. and A.A.) were blinded for the history and the grouping (epileptic or control group) and reviewed all MR studies independently for subjective assessment of the hippocampus using criteria listed in the Introduction: volume loss, elevated hippocampal signal intensities on T2-weighted images and loss of internal structure, and to evaluate for other pathologies that could result in seizure activity.

Table 1. Magnetic resonance parameters

Sequence	Plane	TE/TR (ms)	Slice thickness (mm)	FoV (mm)
T2w	transverse	105/ 2,900	3	224 × 320
T2w	sagittal	105/ 2,900	3	224 × 320
T2w	dorsal *	105/ 4,520	3	224 × 320
FLAIR	transverse	113/ 8,500	3	224 × 320
ToF	transverse	7.15/25	1	224 × 320
T1w MP-RAGE	sagittal *	4.24/913	0.9	224 × 320

* The dorsal planes (T2W and T1W MP-RAGE) were oriented perpendicular to the long axis of the hippocampus with planning and placing the tilted dorsal slice on the sagittal plane.
Abbreviations: fluid-attenuated inversion recovery (FLAIR), time of flight (ToF), magnetisation-prepared rapid gradient-echo (MP-RAGE), time of echo (TE), time of repetition (TR), field of view (FoV).

Volumetric measurements were performed by the first author (B.A.L.) in the T1-weighted MP-RAGE images using Amira 6 (FEI Visualization Sciences Group, Mérignac, France). Transverse and dorsal plane reconstructions were made based on the sagittal series. The following structures were assessed: the cerebral hemispheres, the ventricular system, and the hippocampi. The windowing and labelling of the ventricular system (lateral ventricles, 3rd and 4th ventricles, mesencephalic aqueduct) were performed separately and semi-automatically. Subsequently, manual segmentation of the hippocampi and hemispheria was performed. The investigated anatomical structures were labelled in all slices. After their demarcation in one of the planes, their boundaries were validated and refined in the other two planes (Fig. 1).

Statistical analysis

Median, mean and SD values were calculated for each group and for each anatomical area as a total volume and as a separated left and right hemisphere (lateral ventricles, hippocampi and hemispheria). The hemispheric volumes were calculated both with and without the lateral ventricular volume.

The lower and upper reference limits for the hippocampi were based on data of the control group (mean ± 2 SD). Individual analysis was also performed – values outside of the range were considered suspect for hippocampal alterations.

The Kolmogorov–Smirnov test was applied to test the assumption of normal distribution. The hippocampal and

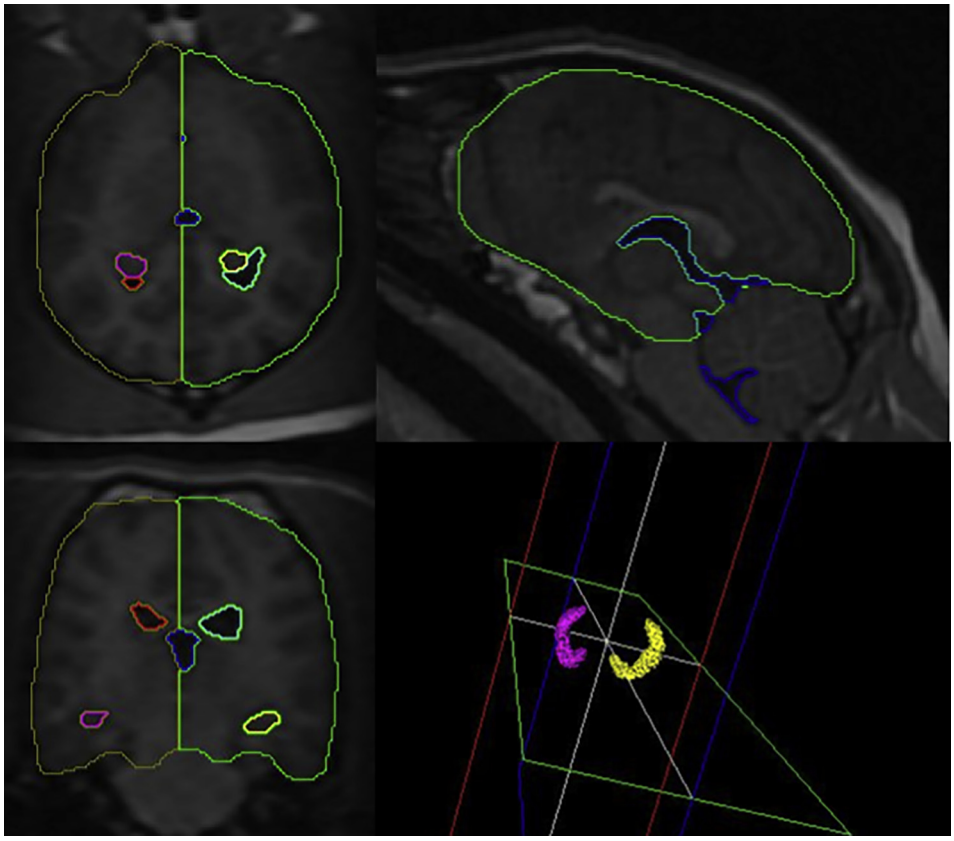

Fig. 1. Manually traced anatomical areas on the dorsal, sagittal and transversal MR-RAGE images and 3D visualisation of the hippocampi (left/right hippocampus – yellow/pink, left/right lateral ventricle – turquoise blue/red, median ventricle system – blue, left/right hemispherium – green/brown)

cerebral hemispheric (both with and without ventricles) volumes exhibited a normal distribution. The lateral ventricles did not show a normal distribution, thus non-parametric tests were used for assessment of the lateral ventricles and parametric tests for assessment of the rest of the anatomical structures.

Pearson's correlation coefficient was used to check for correlations between hippocampal volumes/hemispheric volumes and body weight, and between hippocampal volumes/hemispheric volumes and age in each group. The correlations involving the lateral ventricles were assessed using the Spearman's correlation coefficient.

A regression model was also performed to investigate if a reference for hippocampal volume for dog size (i.e. body weight) could be established. Other factors (age, sex) were also tested whether to assess for influence on hippocampal volume.

A hippocampal asymmetric ratio was also calculated. A *t*-test was performed to compare the hippocampal asymmetric ratios between the groups. Asymmetric values with a size difference over 6% were considered abnormal and their proportions were evaluated separately in the groups (Kuwabara et al., 2010).

RESULTS

The epileptic group consisted of 31 dogs: 11 females and 20 males, aged 4.34 ± 2.7 (0.3–10.5) years, weighing 23.25 ± 16.4 (1.8–72) kg. The following breeds were represented: Mongrel (n = 6); Labrador Retriever (n = 4); French Bulldog, Hungarian Vizsla, German Shepherd (n = 3); Golden Retriever, Bolognese (n = 2); American Bulldog, Beagle, English Cocker Spaniel, Dachshund, Miniature Schnauzer, Moscow Watchdog, Husky, Jack Russell Terrier, Pit Bull Terrier, Rhodesian Ridgeback, Australian Shepherd and Sarplaninac (n = 1).

The control group consisted of 15 dogs – 4 females and 11 males, aged 4.4 ± 1.7 (2–8) years, weighing 15.7 ± 9.6 (4–32) kg. The following breeds were represented: Mongrel (n = 8), Dachshund (n = 2), Boxer (n = 2), as well as one Miniature Pinscher, Spitz and Welsh Corgi, respectively.

All of the studies of both groups were assessed as normal by both observers in the subjective (qualitative) visual assessment.

The objective results of the volumetric measurements are reported in Table 2. A visual representation of hippocampal volume in one dog is shown in Fig. 2.

The minimum and maximum hippocampal volumetric cut-off values were set based on the control group data (mean ± 2 SD): 182.9 and 502.5 mm^3 respectively for the left and 145.8 and 487.8 mm^3 respectively for the right hippocampus. In the epileptic group, the measurements of only seven dogs were outside the normal range, two dogs with lower values (one unilaterally and one bilaterally), and five dogs with higher values (three unilaterally and two bilaterally). All of these dogs were classified as normal in the subjective visual assessment.

There was also a significant positive correlation between hippocampal volumes and body weight ($P < 0.05$) for both groups and between hippocampal volumes and the ventricular volumes ($P < 0.01$) within the epileptic group. Furthermore, there was a positive correlation between the body weight and the hemispheric volume (both with and without the ventricles, $P < 0.05$) for both groups, as well as between the hemispheric volume (both with and without the ventricles) and the ipsilateral hippocampal volumes ($P < 0.01$) for both groups. There was no significant correlation between the animal's age and the volumes of any measured brain structures.

In the regression model, we found an association between the hippocampal volume and the body weight. However, the results show an approximate predictive value of merely 15%, for dogs of both the epileptic and the control

Table 2. Numerical volumetric results

Brain area	Volume (mm^3) mean/median ± SD minimum/maximum	
	Control group	Epileptic group
Left hippocampus	**342.73**/329.87 ± 79.90 193.81/495.50	**336.74**/331.87 ± 113.79 115.94/573.37
Right hippocampus	**316.78**/327.07 ± 85.49 170.61/455.34	**349.89**/327.70 ± 142.04 124.10/810.79
Left lateral ventricle	**938.02**/335.86 ± 1,766.96 95.09/6,915.04	**858.97**/450.99 ± 1,137.59 35.26/5,424.03
Right lateral ventricle	**721.23**/224.36 ± 1,427.56 17.95/5615.83	**745.57**/292.44 ± 1,289.95 25.29/5,330.93
Left hemispherium (without ventricle)	**38,521.10**/35,424.28 ± 11,266.91 26,087.16/66,801.16	**40,493.89**/41413,98 ± 8,901.93 21,876.44/62,527.86
Right hemispherium (without ventricle)	**36,683.00**/33,703.26 ± 9,961.84 23,724.25/62,259.62	**40,444.08**/42,979.71 ± 9,779.09 20,612.58/65,828.29
Left hemispherium (with ventricle)	**39,459.12**/35,678.56 ± 12,102.60 26,647.47/66,896.25	**41,352.86**/42,117.44 ± 9,419.64 22,087.11/63,939.48
Right hemispherium (with ventricle)	**37,404.24**/33,872.15 ± 10,557.44 24,193.73/62,277.57	**41,222.98**/43,922.62 ± 10,308.35 20,712.39/67,182.35

The bold values indicate significant difference of $P < 0.05$

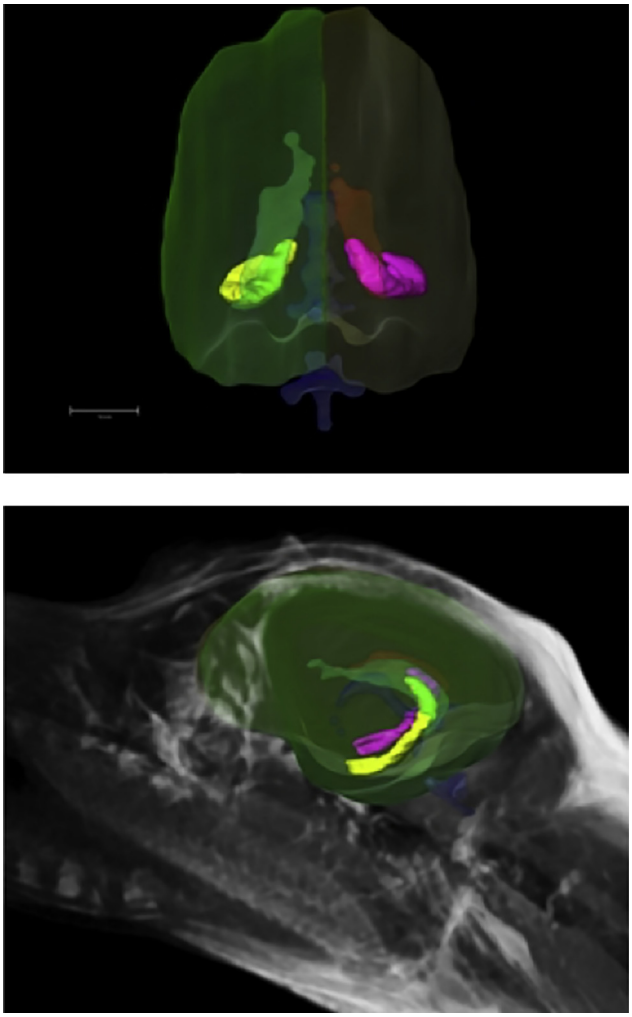

Fig. 2. 3D visualisation of the brain structures (left/right hippocampus – yellow/pink, left/right lateral ventricle – turquoise blue/red, median ventricles – blue, left/right hemispherium – green/brown)

groups ($R^2 = 0.152$). Taking into account additional factors, such as age and sex, this predictive value increased slightly (approx. 20%, $R^2 = 0.204$), but did not change significantly (Fig. 3).

No statistically significant differences could be found in hippocampal volumes between the control and the epileptic group. There were no statistically significant differences in the hippocampus/hemispherium ratio between the two groups. The cut-off value of hippocampal asymmetric ratio was set at 6%, as described earlier (Kuwabara et al., 2010). There was no significant difference between the two groups with regard to the number of cases for asymmetry: 60% of the control group had a hippocampal asymmetric ratio higher than 6% compared with 77.4% of the epileptic group.

DISCUSSION

We recorded the mean left/right hippocampal values as 342.73 ± 79.9/316.78 ± 85.49 mm^3 in the control group, and 336.74 ± 113.79/349.89 ± 142.04 mm^3 in the epileptic group. This generated cut-offs of 182.9 and 502.5 mm^3 respectively for the left hippocampus and 145.8 and 487.8 mm^3 respectively for the right hippocampus. These volumes were lower for both groups than those identified in previous studies both by MRI (Kuwabara et al., 2010; Milne et al., 2013) and histology (Vullo et al., 1996). Vullo et al. (1996) reported bigger hippocampal volumes (476 ± 79.5 mm^3 *in vivo*), but they worked with a smaller sample size and the dogs' size was not reported. Kuwabara et al. (2010) described even higher values (486 ± 104 mm^3 in the control group, 411 ± 92 mm^3 in the epileptic group). Milne et al. (2013) have reported the largest volume to date, setting a lower reference limit of 560 mm^3 on the right and 550 mm^3 on the left, based on a population of healthy dogs. Were we to apply the cut-offs suggested by the work of Milne et al. (2013), the control dogs from this study would be considered pathological. We speculate that the reason for the variance of the reported measurements is that the method is very dependent on the observer's experience and the technical specifications (such as MR-sequence and slice thickness).

There are several differences in the imaging and labelling technique of the earlier reported data. In the study of Vullo et al. (1996) the images were acquired with a 2T MR, while Kuwabara et al. (2010) and Milne et al. (2013) used data obtained by a 1.5T magnet, similar to that used in our study. Vullo et al. (1996) found the transverse plane of the proton density sequence best for the measurements and used 1 mm slice thickness. No other studies relied on the proton density imaging sequence. Nine mongrel dogs were examined in the study; there is no information about their body weight. Kuwabara et al. (2010) had a heterogeneous imaging protocol due to the retrospective design of the study with a slice thickness varying between 2.2 and 4 mm. The delineation was performed in the T2w transverse plane images and the boundaries were not corrected based on the other two imaging planes. Milne et al. (2013) used uniformly thin sliced (1 mm) 3D T1w sequence in dorsal plane for delineation, similar to that used in our study. The labelling was performed in the dorsal plane with the help of the T2w transverse and reformatted T1w or T2w sagittal planes. In our study, the other two planes were reconstructed from the imaging dorsal plane and the labelling was performed in all three planes simultaneously. The correction of the boundaries relied on the plane which provided the best visibility. In the study of Milne et al. (2013), the anatomical boundaries were determined based on the study of Jung et al. (2010), who imaged three healthy beagles in a 7T MR unit using thin-sliced (0.5 mm) 3D T1w sequence in the dorsal plane (MP RAGE similar to our study). Due to the very high magnetic field, the resolution of the images was far better than in all of the above-discussed studies, evidenced by delineation of the hippocampal subregions. However, even Jung et al. (2010) mentioned some difficulties in the exact delineation of the structure. Unfortunately, they did not report the hippocampal volumes as a result, possibly due to the small sample size.

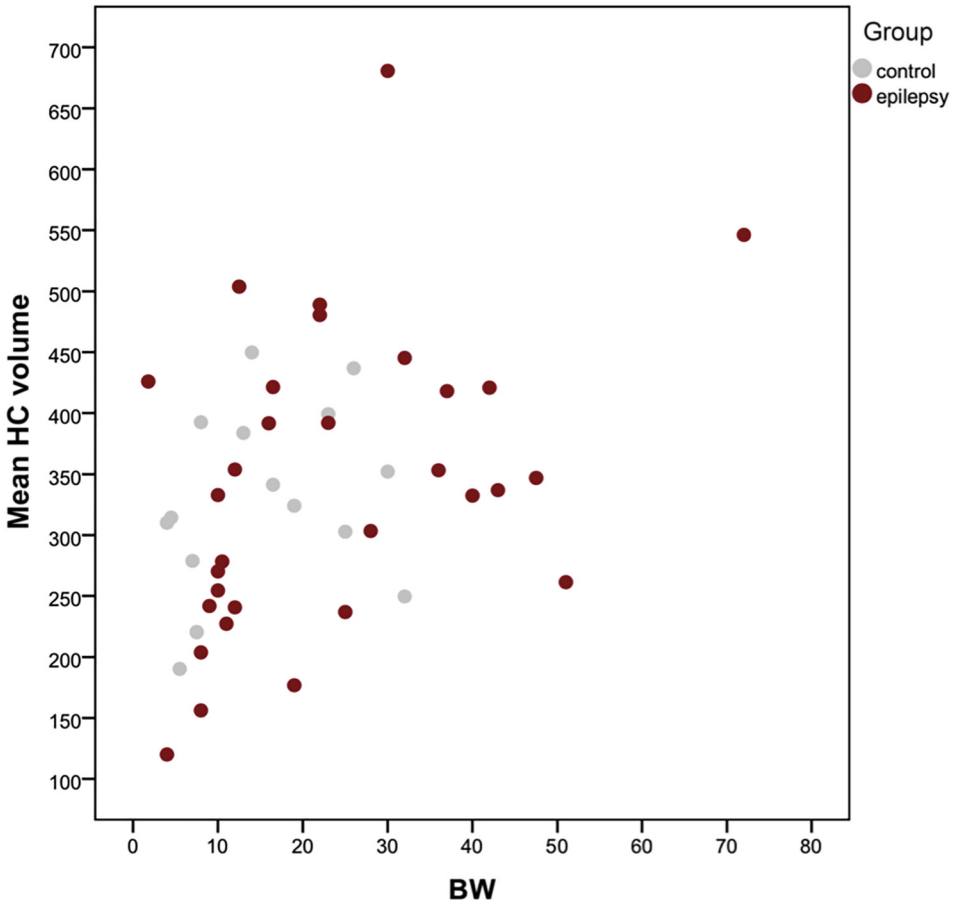

Fig. 3. Visualisation of the regression model – correlations between the hippocampal (HC) volumes and the body weight (BW) in the epileptic and non-epileptic group

The labelling method of the present study was very similar to that used in the work of Jung et al. (2010).

Hippocampal volumetry is a routinely used method in neuroradiology of human epileptic patients (Jack, 1996). Given its long history in human medicine, the method is considered reliable. In humans, the radiologist uses automatised methods relying on pixel signal intensity with manual corrections subsequent to automatised labelling. In contrast, in veterinary imaging there are significant differences in imaging technique (field strength, sequence, slice thickness, labelling plane); the labelling is not automatised in most of the cases, and there is no clear consensus about the hippocampal/labelling boundaries (for example that the fimbria should be labelled or not). Consensus on these factors would need to be reached before a reliable method in veterinary imaging can be established.

The present study is believed to be reliable due to the use of thin-sliced 3D images labelled semi-automatically with subsequent manual correction in all three imaging planes. However, because of the pathologic results, we could not prove the exact and correct histological boundaries.

This study, consistent with the previous studies, supports a positive association between hippocampal volume and body weight (Kuwabara et al., 2010; Milne et al., 2013). Furthermore, hippocampal MR volumetry is a very observer-dependent method with a low inter-observer agreement (Milne et al., 2013). Thus, the usefulness and reliability of canine hippocampal volumetry are questionable. Assessment of the hippocampus and hemispheria with respect to body weight was suggested in both recent studies (Kuwabara et al., 2010; Milne et al., 2013). According to our results, there was no significant difference in the relative values in either of the groups. A significant difference of the asymmetric hippocampal ratio between groups was also not identified.

Based on the regression model of our data, it is not possible to set expected hippocampal volumes to certain body weights. We speculate that other, currently undefined factors also influence the hippocampal volume. In addition, the increase of hippocampal volume was disproportionately low with respect to the relative increase in body weight. In order to identify a normal range, it would be essential to establish an agreed standardised methodology (volumetry, imaging plane, weighing, slice thickness and anatomical borders), that unfortunately is lacking today.

In the present study, no significant differences were found in the hippocampal volumes of epileptic and non-epileptic dogs. Analysis of the volumetric data in the epileptic dog group was performed using the mean values of the normal group as a reference. Mild variance in

hippocampal volume was identified in 7 dogs in the epileptic group; however, these were not statistically significant.

Several studies have proven the occurrence and importance of hippocampal changes in human (Cendes et al., 1993; Grünewald et al., 1994; Rosenow and Lüders, 2001; Wieser, 2004; Singh et al., 2013) and feline epilepsy (Fatzer et al., 2000; Brini et al., 2004; Schmied et al., 2008; Pákozdy et al., 2010; Pakozdy et al., 2011). Whether canine temporal lobe epilepsy and hippocampal atrophy are a genuine entity is questionable (Buckmaster et al., 2002). Further studies are needed to determine reliable and repeatable hippocampal reference values that could aid the confirmation or rule out the presence of hippocampal sclerosis and canine temporal lobe epilepsy.

According to some human studies (Grünewald et al., 1994; Bernasconi et al., 2000; Okujava et al., 2002; Scott et al., 2003), hippocampal changes (sclerosis or atrophy) with special regard for bilateral abnormalities are better detectable with more sensitive MR methods, such as T2 relaxometry. The current study population was assessed by T2 relaxometry in a previous study (Lőrincz et al., 2017). In the individual analysis, 6 dogs in the epileptic group showed prolonged T2 relaxation values. These particular cases may represent genuine hippocampal changes and related suspected temporal lobe epilepsy. The hippocampi of these dogs measured within normal limits. This serves to further question the diagnostic value of hippocampal volume assessment.

In the present study, the MP-RAGE sequence (a T1w thin-sliced 3D sequence) was used for the volumetric evaluation, as recommended in a canine hippocampal volumetric study (Kuwabara et al., 2010). Previous studies demonstrated the suitability of this sequence for precise delineation of the anatomical boundaries of the canine hippocampus (Jung et al., 2010).

The main limitation of this study was the heterogeneous subject group and the lack of postmortem evaluation. There were several referring veterinarians with different pre-imaging examination protocols and this may have led to the misclassification of reactive epileptic cases as primary epilepsy. Another limitation was the incomplete seizure classification in some dogs of the epileptic group. No histopathological examinations were performed, thus it was not possible to generate sensitivity and specificity for the use of hippocampal volume assessment on MRI as a diagnostic tool. This would have been of particular benefit for the dogs that measured below the lower cut-off value. Thus we cannot say if these dogs were truly pathological or if they were within the 2.5% of the normal population outwith the bell curve.

In conclusion, setting lower reference limits of canine hippocampal volume is of debatable value and is not recommended by the authors based on the data available at this time. The subjective and objective assessments of hippocampal changes did not differ and, as volumetric evaluations are quite time consuming (0.5–1 hour per subject), they are unlikely to be of practical benefit at this time. A reliable ratio either to another intracranial structure or to body weight was not identified in this population. That is not to say that a ratio could not be identified with a larger population, but the differences in our groups were not statistically significant.

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