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Diagnostic techniques to detect the epileptogenic zone: Pathophysiological and presurgical analysis of epilepsy in dogs and cats

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Highlights

- To establish 'epilepsy surgery' in veterinary medicine, the concepts of the 'epileptogenic zone (EZ)' are essential.
- EZ consists of 5 different zones: symptomatogenic, irritative, seizure-onset, structurally abnormal, and functional deficit.
- These 5 zone is detected by semiology, EEG, video-EEG, structural MRI, and functional imaging, respectively.
- In veterinary medicine, these techniques have to be standardised and studied sufficiently.

Abstract

The use and availability of magnetic resonance imaging (MRI) and other neurosurgical devices is rapidly increasing in the field of veterinarian medicine. Coincident with these technological advances, there is an increased expectation to treat drug resistant epilepsy in dogs and cats by epilepsy surgery. However, the presurgical evaluation of epileptic animals, by using methodologies to detect the epileptogenic zone for example, have yet to become established in common practice.

The epileptogenic zone, defined as the minimum amount of cortex to produce seizure freedom, consists of five conceptual cortical abnormal 'zones': symptomatogenic, irritative, seizure-onset, structurally abnormal (epileptogenic lesion) and functional deficit. These zones can now be detected by suitable modalities including ictal video monitoring, interictal non-invasive or invasive electroencephalography (EEG), ictal video-EEG, magnetoencephalography, structural and functional MRIs, or nuclear imaging. These diagnostic techniques are essential for selecting both appropriate patients and surgical techniques, and are also important in understanding the pathophysiology of epilepsy. This review describes the diagnostic techniques available for detecting each abnormal zone while considering the current veterinary status to realise future surgery for canine and feline epilepsy.

Keywords: Electroencephalography; Epilepsy; Epilepsy surgery; Epileptogenic zone;

45 Magnetic resonance imaging

46

Introduction

Epilepsy is a chronic and functional pathophysiology of the cerebrum that is likely to occur in all mammalian species and is encountered most frequently in dogs, cats, and humans (Löscher, 1984, 1997; Hasegawa et al., 2002; Sanders, 2015). Recently, international consensus reports of canine and feline epilepsy have been published by the International Veterinary Epilepsy Task Force (IVETF) and proposed to standardise a range of factors relating to epilepsy in animals. The IVETF particularly focussed upon classification and terminology (Berendt et al., 2015), diagnostic approaches (De Risio et al., 2015) including routine magnetic resonance imaging (MRI) (Rusbridge et al., 2015), medications (Bhatti et al., 2015), outcomes (Potschka et al., 2015), methods for obtaining brain samples (Matiasek et al., 2015), and provided an overview of the predisposition of canine epilepsy with relation to genetics and breed (Hülsmeyer et al., 2015). These consensus proposals are generally acceptable for both generalists and specialists dealing with small animal epilepsy. However, important issues such as electroencephalography (EEG), drug resistant (refractory) epilepsy, guidelines for status epilepticus and/or cluster seizures, feline epilepsy and alternative therapeutic methods, have yet to be debated fully since these are more complicated.

It has been reported that approximately 30% of canine epileptic patients show resistance to anti-epileptic drugs (AEDs), so-called refractory epilepsy, intractable epilepsy, or drug resistant epilepsy (Muñana, 2013; Martlé et al., 2014). Drug resistant epilepsy in humans is defined by the International League Against Epilepsy (ILAE) as '*drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom*' (Kwan et al., 2010). Although the IVETF agreed with the ILAE's definition and that complete seizure control, i.e. 'seizure freedom', is also an ideal (primary)

goal in veterinary medicine, the IVETF recommended 'partial therapeutic success' as a secondary treatment goal, taking into account the results of past studies in veterinary patients and also differences of the implication between human and veterinary patients (Potschka et al., 2015).

In humans, surgical treatment for drug resistant epilepsy ('epilepsy surgery') is performed positively, and comparatively good prognosis has been achieved. With the development and increased availability of MRI and other neurosurgical devices such as the surgical microscope, ultrasonic aspirator and neuronavigator in the veterinary field, it has been possible to identify a variety of veterinary epilepsy pathologies. Consequently, epilepsy surgery has begun to attract increasing attention as a challenging area of veterinary neurology and neurosurgery. Martlé et al. (2014) summarised epilepsy surgery in humans and remarked upon the relative lack of progress with this condition in the veterinary field. In order to realise epilepsy surgery in the veterinary field in the near future, it is the intention of the current paper to provide a synopsis of the relevant presurgical diagnostic tests, along with each conceptual area of the epileptogenic zone. Needless to say, knowledge of the epileptogenic zone, and the diagnostic tests with which to target these zones, are essential in analysing and understanding the pathophysiology of epilepsy across different species.

Concepts of the epileptogenic zone

Epileptic seizures, particularly focal epileptic seizures, are thought to originate from a certain region or network of the cortex, historically referred to as the 'epileptic (epileptogenic) focus'. However, as advancements were made with epilepsy surgery in human medicine, this terminology has since changed to 'epileptogenic zone'. The concepts of the epileptogenic zone were first described by Hans O. Lüders (Rosenow and Lüders, 2001;

Lüders et al., 2006), with the epileptogenic zone defined as *'the minimum amount of cortex that must be resected (or completely disconnected) surgically to produce seizure freedom'*. In other words, the epileptogenic zone cannot be defined pre-operatively, and therefore epileptologists, and neurosurgeons perform epilepsy surgery, must carry out various examinations with which to detect the 'presumed' epileptogenic zone. Conceptually, the (presumed) epileptogenic zone consists of five different abnormal cortical zones: symptomatogenic, irritative, seizure-onset, structurally abnormal (or epileptogenic lesion), and functional deficit zones. An IVETF proposal reports discussed the concept of the epileptogenic zone briefly from the viewpoint of pathology (Matiasek et al., 2015); however, it may be not understandable for veterinary clinicians. The precise definitions for these cortical zones, along with the respective diagnostic technique, are summarised in Table 1 and described below with reference to potential application in veterinary medicine.

It is very easy to determine the epileptogenic zone when those five zones indicated the same location. For instance, let us consider a human patient with focal limbic seizures (orofacial automatisms). The epileptogenic zone of such a patient can be determined in the unilateral hippocampus and selective amygdalohippocampectomy will be performed if the following indications are evident: (1) EEG reveals unilateral temporal spikes (irritateive zone); (2) video-EEG captured ipsilateral temporal onset epileptiform activities with clinical seizures (symptomatogenic and seizure-onset zone); (3) MRI showing ipsilateral hippocampal sclerosis (structural abnormal zone); and (4) interictal positron emission tomography (PET) using ^{18}F-fludeoxyglucose (FDG-PET) suggests ipsilateral hippocampal hypometabolism (functional deficit zone). However, an important aspect to consider is that these five zones are not always present in the same location, and the spatial relationship between these areas may differ between individuals. For example, in another epileptic patient, although EEG study

suggested interictal spikes in the frontal lobe (irritative zone), an MRI revealed hippocampal malformation (structural abnormal zone). A similar situation has been reported in a veterinary patient recently (Shihab et al., 2014) (see 'Clinical relevance and conclusion'). Therefore, detecting each abnormal zones and deciding upon a 'true' epileptogenic zone (i.e. operation site) are still very challenging issues for epileptologists and neurosurgeons, even in human medicine.

Symptomatogenic zone

The symptomatogenic zone is defined as *'the area of cortex which, when activated by an epileptiform discharge, produces the ictal symptoms'*. In other words, this zone is implicated when clinical signs are apparent during seizure. The symptomatogenic zone can be detected by careful analysis of seizure symptoms using ictal video recording with or without EEG (video-EEG is described later – see 'seizure-onset zone'). The initial symptoms of a seizure are very important since they may be related to the laterality and/or seizure-onset zone, and a sequential change of symptoms relates to the propagation of seizure activities. Ictal (and post-ictal) symptoms in human focal seizure have been well documented corresponding with ictal EEG and/or postsurgical outcome (Jan and Girvin, 2008; Rossetti and Kaplan, 2010; Tufenkjian and Lüders, 2012). Some seizure semiological signs observed in humans may also be observed in dogs and cats, and a list of examples is given in Appendix: Supplementary material S1.

Digital devices, such as smartphones, have now become very advanced and are commonplace amongst the community. Consequently, it is now very easy for owners to record videos of their dogs and cats undergoing seizure. Such videos are helpful in describing or detecting seizure semiology and seizure type. In a study analysing the inter-observer

agreement of canine and feline semiologic videos, it was found that the agreement of differentiation between seizure types was moderate while the highest agreement was with primary generalised seizures (Packer et al., 2015). Videos recorded from a seizure onset (i.e. including the initial sign) are especially useful in distinguishing between a primary generalised epileptic seizure and a secondarily generalised seizure (focal epileptic seizure evolving to become generalised). However, videos that are already generalised (acquired during the middle of a tonic-clonic convulsion) convey little information and cannot distinguish between primary or secondary generalised, and/or some reactive seizures. This problem was also pointed out by Packer et al. (2015). Therefore, in order to determine the symptomatogenic zone, and/or seizure type, in animal patients, veterinarians are required to interview the owners in detail with regard to the clinical signs of true seizure onset, as well as other conditions (De Risio et al., 2015). Indeed, the author of this review has often experienced orofacial automatism, forced head turning, gazing, ictal aggression, unilateral tonic/clonic or dystonic posture, hypermotor seizure such as running fits and postictal paresis, although all these signs were not confirmed by ictal or interictal EEGs. Some of these signs have also been demonstrated in feline and canine seizure models (Tanaka et al., 1992; Hasegawa et al., 2002, 2014; Shouse et al., 2004). On the other hand, for instance, paroxysmal behavioural changes such as fly-biting, tail chasing, and rage syndrome, have not been definitively associated with epilepsy as yet, and such clinical signs are not defined as epileptic seizures, although some of these cases do respond to AEDs (Wrzosek et al., 2015). Therefore, both general veterinarians and veterinary neurologists need to make special efforts to accumulate seizure semiologic symptoms correlated with the findings of various diagnostic modalities. Currently, a user-friendly seizure (generalised convulsion) alert system using an accelerometer synchronised with a video recorder has been developed (M Saito, personal

communication: patent pending in Japan[1]; application number 2013-100046, publication number 2014-217649). This system is able to record a movie tracing back several minutes prior to an alerted generalised epileptic seizure, and is not too expensive. This type of system may therefore be very useful to practitioners and owners for evaluating seizure semiology and managing epileptic animal patients.

Irritative zone

The irritative zone is defined as *'the area of cortical tissue that generates inter-ictal spikes'*. Consequently, the irritative zone in human patients can be detected by non-invasive (scalp) and/or invasive EEG, magnetoencephalography (MEG), and EEG-triggered functional MRI (fMRI). The following section describes scalp EEG, MEG and EEG-triggered fMRI, while invasive EEG is described in a subsequent section relating to seizure-onset zone.

Scalp EEG

In human medicine, the EEG is a gold standard diagnostic method and plays an important role in the classification of epilepsies or seizure types. In veterinary medicine, however, the EEG is not commonly used, except in specific neurological referral hospitals such as university teaching hospitals. It has been reported previously that the detection rate of EEG abnormalities ranges from 65 to 86% in dogs with epilepsy (Berendt et al., 1999; Jaggy and Bernardini, 1998). However, more recent studies using propofol and rocuronim bromide with photic activation and hyperventilation have claimed detection rates of 25% and 29% for canine idiopathic epilepsy and structural (symptomatic) epilepsy, respectively (Brauer et al., 2012b). In another EEG analysis of dogs with epilepsy using propofol, only 5/40 dogs (12.5%) showed epileptiform discharges, all of these dogs having structural epilepsy

[1] See and input application and /or publication numbers into: https://www4.j-platpat.inpit.go.jp/eng/tokujitsu/tkbs_en/TKBS_EN_GM101_Top.action (accessed 20 October 2015).

(Pakozdy et al., 2012). Detection rates for cats with epilepsy were 46% (propofol only) and 85% (propofol with photic activation) (Brauer et al., 2012a).

Although human scalp EEGs are recorded globally by a standardised electrode arrangement (the 'international 10-20 system'), there is no standardised recording method for animals in veterinary medicine, and thus no specific consideration of electrode arrangement, montage, or immobilisation. Although some veterinary researchers have suggested some recommended conditions (Redding, 1978; Holliday and Williams, 1999; Bergamasco et al., 2003; Pellegrino and Sica, 2004; Wrzosek et al., 2009; Lewis et al., 2011; James, 2014), there is no consensus as yet, even in recent IVETF reports. However, the IVETF (Berendt et al., 2015; De Risio et al., 2015) and Martlé et al. (2014) have also recognised and described the importance of EEG, and note that the development of a standardised EEG protocol is an urgent priority for veterinary neurology in order to promote epilepsy surgery in the future. Fortunately, because digital EEGs have become common place, it is possible to change the derivation montages ('re-montage'), and some recording conditions, after the recording in an ad libitum manner. The present review, therefore, suggests a proposal for scalp EEG recording conditions in dogs and cats which integrates the findings and suggestions of earlier studies (Fig. 1, Table 2 and Appendix: Supplementary material S2). Although this electrode arrangement tentatively places the reference electrode on the tip of the nose, the author prefers to use the average reference (AV) derivation. This particular derivation does not use a specific referential electrode and instead, uses an average potential from all electrodes as a reference (Dien, 1998). Therefore, although the amplitudes of each derivation are reduced, the differences or paroxysmal discharges, and their sources, are recognised clearly without the disadvantage of conventional referential derivation such as contamination by muscle activity, or problems associated with volume conduction or the activating reference electrode. AV

derivation has already been used for electrocorticograms in dogs (Davis et al., 2011; Howbert et al., 2014). The other advantages of digital EEG, such as quantitative analysis and topography, have been described in other reports (Holliday and Williams, 2001, 2003; Bergamasco et al., 2003; Wrzosek et al., 2009; Lewis et al., 2011). The present review merely proposes a set of conditions for recording, to enable us, as a veterinary community, to reach a consensus of opinion upon the evaluation of EEGs in veterinary practice.

MEG

The generation of electrical activity simultaneously creates a magnetic field. While the EEG is a caption and tracing of electrical activities from the cerebral neurons, MEG measures the magnetic fields generated from the cerebral neurons (Stufflebeam, 2011; Kharkar and Knowlton, 2014). The appearance of the MEG is very similar to the EEG, however, it is not influenced by muscle activity or the skull. Since the neurons of the cerebral cortex are arranged perpendicularly to the surface of the brain and the electrical current spreads in a vertical direction, the magnetic fields occur horizontally to the neuronal arrangement. Therefore, in human medicine, MEG is a superior method for detecting activity from the neurons that form gyri within the sulci. Furthermore, MEG is also more accurate than EEG at estimating the source of electrical currents, i.e. equivalent current dipole, and is therefore frequently used for detecting the epileptogenic zone in human epilepsy. Since the magnetic field from the brain is very faint (on the order of 10^{-5} tesla), an extremely sensitive field detector called 'superconducting quantum interference device (SQUID)' and a strictly magnetic shield room, such as an MRI room, is needed. Unfortunately, these field detectors are highly expensive and there is a lack of such a device specifically for animal, which prevents the use MEG in veterinary patients. However, because the signal-to-noise ratio of MEG is attenuated by distance from the source (cerebral cortex), this strategy may become a

problem in dogs with thick temporal muscle covering the cranium. To date, there is only one experimental report in the literature investigating MEG in a dog (Jäntti et al., 1995).

EEG-triggered fMRI

Blood oxygen level dependent fMRI (BOLD-fMRI or simply 'fMRI') is the representative functional imaging in current human neuroscience. fMRI monitors the rate of blood flow and oxygen consumption in neurons by evaluating the rate of increased diamagnetic oxyhaemoglobin and reduced paramagnetic deoxyhaemoglobin, with active neurons requiring oxygen to be delivered at a higher rate. fMRI results are obtained by subtracting images obtained during rest phases from images obtained while a certain task (e.g. finger tapping, speech) is being performed. EEG-triggered fMRI uses interictal spikes, that are recorded from simultaneously recording EEG, as the task and have been studied as a non-invasive method for the detection of the epileptogenic (irritative) zone in human epileptic patients (Warach et al., 1996; Krakow et al., 1999; Flanagan et al., 2014; Kay and Szaflarski, 2014). In general, fMRI is carried out while patients are awake. There have been recent reports of using fMRI on awake dogs to localise the cognitive function area (Berns et al., 2012; Cook et al., 2014; Jia et al., 2014; Dilks et al., 2015). However, it is necessary for subject dogs to be trained for a few months to remain immobile within the noisy scanner, which is not practical. EEG-triggered fMRI, on the other hand, does not require patients to be awake since the EEG recordings and spikes used as the task are obtained under sedation. Therefore it is expected that EEG-triggered fMRI could more feasibly be used clinically for detecting epileptogenic zones in canine and feline epileptic patients.

Seizure-onset zone

The seizure-onset zone is defined as *'the area of the cortex that initiates clinical seizures'*. It is determined primarily by non-invasive or invasive EEG with or without video monitoring, but also by MEG and ictal single photon emission tomography (SPECT; described in the section of functional deficit zone).

Invasive EEG and video-EEG

In human medicine, long-term video-EEG monitoring and invasive EEG are essential presurgical evaluations for epilepsy surgery (Rosenow and Lüders, 2001; Cascino, 2002; Asano et al., 2013). Video-EEG monitoring is a simultaneous recording of patient's physical behaviour during an EEG. It is useful for collating clinical seizure symptoms with EEG findings, for the evaluation of symptomatogenic and seizure onset zones or for the exclusion of non-epileptic seizures.

Invasive EEGs, such as electrocorticography (ECoG) and depth EEG, with/without video monitoring, or those of intraoperative recording, are used to detect epileptogenic zones that were not sufficiently detected using non-invasive methods. ECoGs are recorded from the surface of the cortex via subdural strip and grid electrodes, and is useful for detecting not only the epileptogenic zone but also the eloquent area (combined with evoked potential tests) of the cortex. Depth EEGs are recorded from selective deep structures of the brain such as the hippocampus, amygdala and thalamus, using stereotactically-inserted needle-like depth electrodes.

With the spread of digital EEGs which can record wideband EEG, the ability of high-frequency oscillations (HFO) recorded from ECoG or EEG to detect the epileptogenic zone more accurately, has become the hottest topic in human epileptology. Using >1000 Hz of

sampling frequency, HFOs are recorded as small high-frequency (>60 Hz) burst discharges that are thought to be generated from the true epileptogenic zone, and are classified as a ripple (80-250 Hz) or fast ripple (>250 Hz). It has been reported that surgical resection of the area that generated ripples on ictal-onset ECoG resulted in good prognoses (Ochi et al., 2007; Fujiwara et al., 2012). Fast ripples recorded on interictal ECoG are thought to be a useful biomarker for epileptogenicity (Jacobs et al., 2008, 2010; Akiyama et al., 2011).

Currently, the use of video-EEG monitoring and invasive EEG in small animals has been mostly limited to experimental application. A craniotomy is needed to place the subdural electrodes for ECoG, and stereotaxic devices and procedures are required for the placement of depth electrodes. Historically, placement of depth electrodes had been carried out using a stereotactic frame (e.g. Kopf stereotactic frame) (Hasegawa et al., 2002, 2014). However, the favoured technique at present is to use a frameless stereotactic technique using a neuronavigator (e.g. Brainsight) (Long et al., 2014). The biggest problem in applying these techniques to dogs and cats which are awake and freely moving is the requirement of connectors and cables between the animal and the EEG device which can get easily tangled. Historically, a rotary connector, referred to as a 'slip-ring' was used for long term EEG monitoring in freely-moving animals, which allowed continuous electrical signal recording without cable coiling, even if the animal is circling (Hasegawa et al., 2014). It may be difficult to obtain approval from owners to fix their pets with invasive electrodes and connect them to many devices. Consequently, the best techniques to deploy are telemetry EEG (ECoG) recording (Davis et al., 2011; Bassett et al., 2014), the seizure alert system (Coles et al., 2013) and the forecasting seizures system (Howbert et al., 2014), which are all synchronised with video recording. Studies have shown that using a telemetry device (NeuroVista Seizure Advisory System) to analyse epileptic dogs showed sensitivity and

specificity of the seizure alert system to be 100% and 91%, respectively (Coles et al., 2013), and the rate of seizure prediction was 73% to 89% (Howbert et al., 2014). While the long-term fixation of scalp electrodes to pet animals for video-scalp EEG is comparatively difficult (James et al., 2011), several studies analysing epileptic dogs using telemetric EEG with video monitoring have been reported recently (Poma et al., 2010; James et al., 2015; Wielaender et al., 2015).

Structural abnormal zone (epileptogenic lesion)

The structural abnormal zone, also known as the epileptogenic lesion, is defined as *'the macroscopic lesion which is causative of the epileptic seizures because the lesion itself is epileptogenic or by secondary hyperexcitability of adjacent cortex'*. At present, the most reliable diagnostic equipment for detecting structural abnormalities is the MRI. In human epileptology, 'non-lesional' epilepsy refers to 'MRI invisible' epilepsy. Therefore, MRI is indispensable in that it can distinguish between idiopathic epilepsy and structural epilepsy in both humans and animals. Consequently, the IVETF have incorporated MRI into their criteria for the diagnosis of idiopathic epilepsy (as the tier II confidence level, as well as the analysis of post-prandial bile acids and cerebrospinal fluid) (De Risio et al., 2015).

Introduction of the MRI into the field of veterinary medicine led to a significant breakthrough in the diagnosis of intracranial diseases. MRI was able to diagnose causes of structural epilepsy such as degenerative encephalopathies, malformations, brain tumours, encephalitis and cerebrovascular accidents. In particular, malformations of the cerebral cortex, or 'cerebral cortical dysplasia', are specifically related to epilepsy (i.e. epileptogenic lesions) in dogs and cats, as they are in humans (Table 3 and Fig. 2). Malformation of the human brain is classified by developmental stage (Barkovich et al., 2001; Bano et al., 2012). Cortical

dysplasia related to epilepsy is predominantly included in the neural proliferation, migration, and organisation stage. As the relative contribution of genetic factors becomes increasingly evident, a new classification has recently been published (Barkovich et al., 2012). Although these classifications, and/or associated gene mutations, have not yet been established in veterinary medicine, it is likely that a combination of specific cases and future research may reveal more about the role of cortical dysplasia in canine and feline epilepsy.

On the other hand, the study of idiopathic (genetic, unknown or 'non-lesional' cases) epilepsy by MRI represents a particularly challenging area, even in human medicine. Idiopathic epilepsy generally presents with normal appearance of the brain; however, there have been some reports of visible, or invisible, yet statistically identifiable findings, in canine and feline idiopathic epilepsy:

Firstly, visible MRI changes referred to as epileptic brain damage, secondary brain injury, peri-ictal encephalopathy or epileptic seizure-associated (post-ictal) MRI changes have been identified in both idiopathic and structural epilepsies. This can be predominantly identified as hyperintensity on T2-weighted or FLAIR images in certain regions, particularly limbic structures, and is induced by severe recurrent seizures such as cluster seizures and status epilepticus (Mellema et al., 1999; Hasegawa et al., 2003, 2005; Viitmaa et al., 2006; De Risio et al., 2015; Rusbridge et al., 2015). These signal changes originate from focal cytotoxic and/or vasogenic oedema due to excessive neuronal excitation (excitotoxic theory) in the epileptic focus or the areas closely connected with the focus, and are can be either transient or permanent.

368 Secondly, hippocampal atrophy and/or necrosis with or without signal changes have
369 also been reported as one of the pathologies in canine and feline epileptic patients that may be
370 closely related to 'hippocampal sclerosis (HS)' (or mesial temporal sclerosis) which is
371 observed in human patients with temporal lobe epilepsy (Wieser, 2004; Blümcke et al., 2013).
372 HS is a hippocampal pathology featuring neuronal loss of the pyramidal layer with gliosis,
373 and is observed as hippocampal atrophy with hyperintensity on T2-weighted/FLAIR images.
374 HS is thought to be either a cause or a result of epilepsy. In one study that investigated
375 asymmetry of the hippocampus in epileptic dogs, 12% of cases revealed a visually atrophic
376 hippocampus while 48% of cases were statistically identified as atrophy (Kuwabara et al.,
377 2010a). In epileptic cats, hippocampal pathologies, such as swelling (inflammation), necrosis
378 and HS, have been reported comparatively far more frequently than in dogs (Brini et al.,
379 2004; Schmied et al., 2008; Pakozdy et al., 2011; Mizoguchi et al., 2014; Wagner et al., 2014;
380 Fors et al., 2015).
381
382 While some studies using 3D volumetry in animal brains are evaluated by manual
383 tracing (Milne et al., 2013; Mizoguchi et al., 2014), the protocol for MRI is somewhat
384 different. Structural MRIs, especially those showing volumetric changes, are evaluated in a
385 manner that is routinely subject to observer subjectivity. In human medicine, such structural
386 changes, and/or functional imaging, are evaluated statistically by comparing a patient with a
387 standard (reference) brain, voxel by voxel, a technique referred to as voxel-based
388 morphometry (VBM) (Ashburner and Friston, 2000; Keller and Roberts, 2008). If VBM is to
389 be deployed clinically in dogs and cats, it will be imperative to create a standard brain model
390 for every breed of dog and cat. However, more objective evaluation may also allow the
391 detection of other brain disorders in addition to epilepsy (Tapp et al., 2006; Ogata et al.,
392 2013).

Recently, the IVETF suggested a 'veterinary epilepsy-specific MRI protocol' in order to standardise imaging sequences and directions of the slice plane that are known to vary so much across different institutions or researchers (Rusbridge et al., 2015). One feature of this new protocol is that the angles of the transverse and dorsal planes are respectively modified to being parallel and perpendicular to the long axis of the hippocampus obtained in the sagittal plane. These cross-sectional planes are also adopted in the evaluation of the human hippocampus. In addition, this protocol is suggested for both low-field and high-field machines and is likely to be acceptable in all institutions. In the near future, it is expected that MRI studies of canine and feline epilepsy will be easy to compare and will be far more objective.

Functional deficit zone

The functional deficit zone is defined as *'the area of cortex that is functionally abnormal in the interictal period'*. In humans, this area is determined by not only diagnostic functional imaging but also from neurological and psychological examinations. In general, abnormal neurological findings in the interictal phase are indicative of structural epilepsies in dogs and cats, and may be revealed by structural MRI as described in the preceding section of this review (Bush et al., 2002; Pákozdy et al., 2008, 2010; Vite and Cross, 2011). However, the functional deficit zone relates to not only macroscopic (MR visible) lesions but also microstructural and true areas of functional abnormality, especially in idiopathic (non-lesional) epilepsies. In contrast to structural (conventional) MRI, some advanced MRI sequences, including BOLD-fMRI and nuclear imaging, have been developed to evaluate brain function. Since epilepsy is a functional disorder of the brain, it is logical to presume that

such methods might also be useful methods with which to diagnose epilepsy, in addition to EEGs.

PET and SPECT

In human epilepsy, PET and SPECT have become established techniques with which to perform useful presurgical evaluations (la Fougère et al., 2009; Kumar and Chugani, 2013a, 2013b). For example, interictal FDG-PET – an indicator of cerebral glucose metabolism, is able to successfully identify the epileptogenic focus as the focal hypometabolic area. Meanwhile, cerebral perfusion SPECT using ^{99m}Tc is suitable for ictal studies. Ictal and postictal perfusion SPECT is capable of revealing hyperperfusion in the epileptogenic zone and propagation area. Interictal SPECT is also able to reveal hypoperfusion, but the detection rate of this technique is lower compared with ictal SPECT or interictal FGD-PET. Therefore, subtraction images (i.e. ictal images minus interictal images) fused with structural MRI, referred to as subtraction ictal SPECT co-registered to MRI (SISCOM), represent very useful evaluations for the clinically use. Furthermore, PET and SPECT allow us to image the distribution of neurotransmitters and/or receptors. In human epilepsy, GABA/central benzodiazepine receptor imaging is commonly carried out using ^{11}C- or ^{18}F-flumazenil for PET, and ^{123}I-iomazenil for SPECT. The epileptogenic zone is indicated as an area of reduced binding area in the images acquired.

In epileptic veterinary patients, there is a distinct lack of reports using either PET or SPECT technology, although a Finnish group reported two epileptological studies; Jokinen et al. (2014) showed cortical hypometabolism corresponding with EEG changes in epileptic juvenile Lagotto Romagnolo dogs, and Viitmaa et al. (2014) also demonstrated hypometabolism in multiple regions of the brain in Finnish Spitz dogs exhibiting idiopathic

focal epilepsy. In these reports, the sensitivity of FDG-PET was found to be superior to EEG for localising or lateralising the epileptogenic focus and the authors concluded that FDG-PET was a useful diagnostic test for epileptic animals as well as human patients. In addition, Martlé et al. (2009) investigated interictal SPECT in 12 epileptic dogs with generalised seizures and showed significant hypoperfusion in the subcortical area (thalamus) compared with controls.

Diffusion and perfusion MRI

Diffusion-based MRI such as diffusion-weighted imaging (DWI) and diffusion tensor imaging (DTI) evaluates the diffusibility of water molecules thereby indicating abnormalities of microscopic structures. Seizures induce cytotoxic oedema by excitotoxicity at early stage in the epileptogenic focus. DWI detects these areas as hyperintensity from analysing the images and evaluating the associated reduction in apparent diffusion coefficient (ADC) values (Fig. 3). DTI is able to evaluate anisotropy of diffusibility, which is the direction of white matter and layer structures such as the arrangement of cortical or hippocampal neurons. DWI and DTI have been used to detect the epileptogenic zone, potential epileptic brain damage and abnormalities in the network or neuronal fibers in both human epileptic patients and animal models of epilepsy (Hasegawa et al., 2003, 2015; Yogarajah and Duncan, 2008).

Perfusion-weighted image (PWI) assesses the haemodynamics of the brain such as cerebral blood volume, cerebral blood flow, and mean transient time, as well as CT perfusion and SPECT. PWI can be obtained using a constant injection of a contrast agent (dynamic susceptibility contrast method) or without the use of a contrast agent (arterial spin labeling method). Interictal, ictal and postictal PWI have become to be used for diagnosing the

epileptogenic zone instead of PET or SPECT in human patients and animal models (Heiniger et al., 2002; O'Brien et al., 2007; Pizzini et al., 2013; Hasegawa et al., 2015; Oner et al., 2015).

Diffusion-based and perfusion MRI methods in canine and feline epileptic patients have not yet been reported. However, since the use of PET and SPECT is very limited in veterinary medicine (due to factors such as costs, facilities, and licencing regulations), diffusion and perfusion MRI should be developed as a feasible alternative for detecting the epileptogenic focus in canine and feline epilepsy.

MR spectroscopy

MR spectroscopy (MRS) measures the concentration of metabolites within a sample volume by analysing the chemical shift of protons, usually ^{1}H protons, referred to as ^{1}H-MRS, and displaying the shifts as a spectrogram (Fig. 4). Examples of metabolites that can be measured are N-acetyl aspartate (NAA), creatine (Cr) and phosphocreatine, choline-containing compounds, lactate (Lac), myoinositol, and glutamate-glutamine complex (Glx). Decreased levels of NAA, increased levels of Glx, and the appearance of Lac peaks have been reported in the epileptic brain, especially in the epileptogenic side or focus, in both human and animal models (Neppl et al., 2001; Hiremath and Najm, 2007; Caruso et al., 2013; Pittau et al., 2014). In the veterinary field, several studies using MRS have been reported (Warrington et al., 2013; Carrera et al., 2014, 2015; Ono et al., 2014; Stadler et al., 2014). However, there is only one preliminary study investigating canine epilepsy, which reported an inter-hemispheric difference in the ratio of NAA/Cr in 6/10 epileptic dogs (Olszewska et al., 2015). A consensus has not yet been established regarding which acquisitions conditions, such

as single or maltivoxel, 35 ms or 144 ms of TE, should be employed for MRS to obtain the best results.

Clinical relevance and Conclusions

In this review, the author has introduced the concept of the epileptogenic zone and explored methodologies which can be used to detect abnormal cortex areas for presurgical evaluation to aid future epilepsy surgery in veterinary medicine. Modalities such as scalp EEG and structural MRI are already performed in veterinary practice, and other advanced techniques such as invasive EEG, video-EEG, functional MRIs and nuclear imaging are currently being investigated worldwide to assist in epilepsy surgery treatments. These modalities to detect the epileptogenic zone are not only essential for presurgical evaluations for selecting appropriate patients and/or surgical techniques, but are also very important in helping to understand the pathophysiology of canine and feline epilepsy. Although this is just a personal opinion, presurgical evaluations that we should/can perform when epilepsy surgery is considered for canine or feline drug resistant epilepsy in current veterinary medicine are suggested in Table 4. A good example of this concept was published recently which related to a canine case report in which temporal lobe surgery was performed (Shihab et al., 2014). In this report, the dog had several orofacial automatisms with and without evolving into generalised seizures. This suggested the symptomatogenic zone was in the limbic system, and MRI subsequently revealed a haemorrhagic lesion (finally cavernous haemagioma) within the right mesial temporal lobe as a structural abnormal zone (epileptogenic lesion). Additionally, neurological examination also suggested dysfunction in the right forebrain (laterality of the functional deficit zone). In this case, the three abnormal zones indicated the same location and the authors performed lesionectomy. However, focal seizures were still persisted following surgery. This result suggested that the epileptogenic zone of this case existed outside of the

resected lesion (i.e. in the remaining cortex). This case report highlights caution in terms of the relative importance of determining other zones, namely the irritative zone (EEG), seizure-onset zone (video- and intracranial-EEG) and/or functional imaging. As another example, a summary of a series of experiments in familial epileptic cats which applied the concept of the epileptogenic zone is shown in Appendix: Supplementary material S3. It is hoped that such studies will be considered as models for the presurgical evaluations of candidates for future epilepsy surgery in veterinary medicine. Lastly, it is hoped that the relevant authorities such as IVETF, European College of Veterinary Neurology (ECVN), American College of Veterinary Internal Medicine (ACVIM) or surgery (ACVS) soon establish a scientific and ethical consensus on the use of these presurgical evaluations and epilepsy surgery including criteria of case or technic selection, before unscientific or inadequately evaluated surgical reports are published.

Conflict of interest statement

The author has no financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Appendix: Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi: …setters please insert doi number

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Figure legends

Fig. 1. Suggested electrode arrangement for scalp electroencephalography. (A) dorsal and (B) lateral view for dolichocephalic and mesaticephalic breed dogs. (C) dorsal view for brachycephalic breed dogs. (D) and (E) for cats. Yellow electrodes, i.e. pair of frontal (F3/F4), central (C3/C4), temporal (T3/T4), occipital (O1/O2) and three longitudinal midline electrodes (Fz, Cz, Pz), are essential and pink electrodes, i.e. a pair of frontal pole (Fp1/Fp2), are optional. Details of each electrode position, with the exception of T3, T4 and Fz are based upon the results of Pellegrino and Sica (2004). Additionally, on large dolichocephalic dogs, a pair of parietal (P3/P4) electrodes (not shown) can be positioned between C3/C4 and O1/O2. The referential electrode (R) is positioned on the dorsal aspect of nose tip (subcutaneous just caudal to the apex nasi), and the grand electrode (E) is positioned at the level of the spinous process of axis. The utility of Fp3/Fp4 had been reported (Pellegrino and Sica, 2004); however, this is impractical in small breed dogs and cats, and these electrodes may lead activity of the eyeballs and eyelids. Midline electrodes (Fz, Cz, Pz) will be responsive to the activities from the longitudinal fissure of the cerebrum, i.e. medial aspect of hemispheres, and are useful in evaluating asymmetries of bilateral hemispheres using transverse bipolar montages. Examples of derivation montages using this electrode arrangement are shown in Appendix: Supplementary material S2.

Fig. 2. T2-weighted transverse MR image of suspected polymicrogyria (white arrow) and subependymal heterotopia (black arrowhead) in a 12 year-old, neutered male miniature Dachshund with late-onset epilepsy.

Fig. 3. A conventional T2-weighted image (A), isotropic diffusion-weighted imaging (DWI) (B) and apparent diffusion coefficient (ADC) colour map (C) obtained immediately after a focal epileptic seizure evolving into a generalised seizure in a 6 year-old male mix-breed dog with idiopathic epilepsy. (A) showing slight high intensity in the left temporal lobe, but no obvious abnormal findings. (B) showing hyperintensities in the left mesial and lateral temporal lobe. (C) showing low ADC values (purple to black) corresponding with hyperintensity area on DWI (B).

Fig. 4. An example of MR spectroscopy (MRS) in a familial spontaneous epileptic cat (Kuwabara et al., 2010b; Hasegawa et al., 2014; Mizoguchi et al., 2014). This MRS data was obtained by single-voxel PRESS (TR/TE = 2000/35 ms) sequence with 3.0 Tesla MRI system (GE Health care) and analysed using the LC Model[2]. The 10 x 10 x 10 mm volume of interest was located in the thalamus in each side (A). Spectrograms of the left and right thalamus are shown as (B) and (C) respectively. Results are shown in the table (C). The ratios of NAA+NAAG/Cr+PCr on both sides of this epileptic cat were significantly lower than controls (Conts, the mean ± SD of six healthy cats). NAA, N-acetyl-aspartate; NAAG, N-acetyl-aspartyl-glutamate; Glx, glutamate-glutamine complex; Cr, creatine; PCr, phosphocreatine; GPC, glycerophosphorylcholine; PCh, Phosphocholine; mIns, myo-Inositol.

[2] See: http://s-provencher.com/pages/lcmodel.shtml (accessed 20 October 2015).

Table 1

Definitions of the epileptogenic zone and associated diagnostic techniques [a].

Cortical zone	Definition	Diagnostic techniques
Epileptogenic zone	The minimum amount of cortex that must be resected surgically to produce seizure freedom	Postoperative seizure outcome
Symptomatogenic zone	Area of cortex which, when activated, produces the initial ictal symptoms or signs	Seizure semiology (video; video-EEG)
Irritative zone	Area of cortex which generates interictal spikes	EEG; ECoG; MEG; EEG-triggered fMRI
Seizure-onset zone	Area of cortex that initiates clinical seizures	EEG; video-EEG; ECoG; (ictal SPECT; MEG)
Structural abnormal zone (epileptogenic lesion)	Structural lesion that is causally related to the epilepsy	Structural MRIs
Functional deficit zone	Area of cortex that is not functioning normally in the interictal period	Neurological exams; functional imaging (ictal SPECT; interictal PET; functional MRIs)

ECoG, electrocorticography; EEG, electroencephalography; fMRI, functional MRI; MEG, magnetoencephalography; PET, positron emission tomography; SPECT, single photon emission computed tomography.

[a] Modified from Lüders et al. (2006).

Table 2

Suggested standardised scalp EEG recording conditions for use on dogs and cats.

Sedation		Medetomidine 20–40 µg/kg, IM (recommend)
Patient position		Sternal recumbent
Electrode type		Surface disk; subcutaneous needle; sub-dermal wire
Electrode arrangement [a, c]		(Fp1, Fp2) [d], F3, Fz, F4, C3, Cz, C4, (P3, P4) [d], T3, T4, O1, Pz, O2
Montages [b, c]	Referential	Use a reference electrode (nose tip) or AV
	Bipolar	Longitudinal, Transverse
Sampling frequency		>200 Hz [e]
Low-cut filter (TC) [c]		0.5–1.5 Hz (TC = 0.3-0.1)
High-cut filter [c]		60–120 Hz
AC filter [c]		Appropriate
Sensitivity [c]		5–10 µV/mm
Tracing (paper) speed [c]		3 cm/sec (analogue); 10–15 sec/view (digital)

AC, alternating current; AV, average reference; EEG, electroencephalography; TC, time constant.

[a] Electrode arrangement is shown in Fig. 1.

[b] An example of montages is shown in Appendix: Supplementary material S2.

[c] These conditions are changeable on digital EEG.

[d] Fp1, Fp2, P3 and P4 electrodes are optional.

[e] If possible, >1000 Hz is recommended for detecting high-frequency oscillations.

Table 3

Epileptic seizures and malformations of the brain reported in dogs and cats.

Category (developmental stage)	Type of malformation	Epileptic seizures	References
Dorsal induction (formation of the neural tube)	Anencephaly[a]	N/A	Huisinga et al. (2010)
	Cephalocele	+	Dewey et al. (2011); Jeffery, (2005); Martlé et al. (2009)
	Chiari (-like) malformation[b]	+/–	Driver et al. (2013); Rusbridge and Knowler, (2004)
Ventral induction (formation of the brain segment)	Holoprosencephaly	+/–	Gonçalves et al. (2014)
	Dandy-Walker (-like) malformation[c]	+/–	Bernardino et al. (2015); Gerber et al. (2015)
	Cerebellar hypoplasia[c]		
Neural proliferation	Microencephaly	+/–	Herrmann et al. (2011)
	(Hemi) megalencephaly	(+)	N/A in dogs and cats
Migration	Lissencephaly	+	Herrmann et al. (2011); Lee et al. (2011); Saito et al. (2002)
	Heterotopia	+	Author experienced (unpublished, Fig. 2)
	Heterotopic cell cluster (in hippocampus)	+	Buckmaster et al. (2002)
Organisation and myelination	Polymicrogyria	+	Cantile et al. (2001); Jurney et al. (2009); Nye et al. (2015), author experienced (unpublished, Fig 2)
	Schizencephaly	(+)	N/A in dogs and cats
	Focal cortical dysplasia	+	Cantile et al. (2001); Casey et al. (2014); Klang et al. (2014, 2015); Nye et al. (2015)
Acquired (not congenital malformation)	Porencephaly	+/–	Davies et al. (2012); Hori et al. (2015); Machado et al. (2012); Schmidt et al. (2012)

+, evident; (+), evident in humans; +/–, occasional or unclear; –, no evident; N/A, not available.

[a] There is no evidence that the anencephalic dog showed epileptic seizures. The anencephalic dog in the paper (Huisinga et al., 2010) was delivered dead by caesarean.

[b] Chiari-like malformation and epilepsy in Cavalier King Charles Spaniels are suspected to be unrelated.

[c] Relationship between epilepsy and Dandy-Walker-like malformation and/or cerebellar hypoplasia is unclear.

Table 4

Suggested presurgical evaluations with which to detect the 'presumed' epileptogenic zone when considering epilepsy surgery for canine and feline drug-resistant epilepsy.

Epileptogenic zone	Modalities	Recommendation [a]	Notes
Symptomatogenic zone	Ictal video analysis (seizure semiology)	Minimum	Requires movie from initial signs of seizure onset to postictal signs
Irritative zone	Scalp EEG (under sedation)	Minimum	Repetitive recordings are recommended
	MEG	N/A	
	EEG-triggered fMRI	N/A	
Seizure onset zone	Video-EEG (awake) +/- telemetry	Recommended	Ictal video-EEG from seizure onset
	Video-invasive EEG (+/- telemetry) or Intraoperative ECoG/depth EEG	Advanced	Requires surgical intervention to place intracranial electrodes and others
Structural abnormal zone	Structural MRI	Minimum	According to the IVETF epilepsy-specific protocol
	3D volumetry	Recommended	Requires >1.5 T MRI system
Functional deficit zone	Neurological examination in interictal state	Minimum	
	Advanced MRI (DWI, PWI, MRS, etc)	Recommended	Requires >1.5 T MRI system
	Interictal FDG-PET	Recommended	If available

	SPECT (SISCOM)	Advanced (N/A)	If available
	Receptor binding PET/SPECT	Advanced (N/A)	Fulmazenil-PET or Iomazenil-SPECT

DWI, diffusion-weighted imaging; ECoG, electrocorticography; EEG, electroencephalography; FDG, fluorodeoxyglucose; fMRI, functional MRI; IVETF, the international veterinary epilepsy task force; MEG, magnetoencephalography; MRS, magnet resonance spectroscopy; PET, positron emission tomography; PWI, perfusion-weighted imaging; SISCOM, substraction ictal SPECT co-registered to MRI; SPECT, single photon emission tomography; T, tesla.

[a] The author recommends that at least 'minimum' modalities should be addressed, and can be readily carried out in current veterinary practice. 'Recommended' modalities should be performed in cases where epilepsy surgery is being considered. When generalised epilepsy surgery, such as corpus callosotomy or vagus nerve stimulation, is planned, these modalities need to be evaluated in order to detect seizure type or to estimate prognosis. 'Advanced' modalities provide more detailed information for focal epilepsy surgery such as resection, lobectomy, amygdalohippocampectomy, or multiple subpital transections. However, the reliability of these modalities has yet to be established in veterinary medicine. 'N/A' means not available in current veterinary medicine and no information available for dogs and cats.