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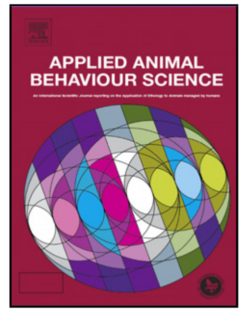

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Negative effects of epilepsy and antiepileptic drugs on the trainability of dogs with naturally occurring idiopathic epilepsy

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Highlights

- Epilepsy and antiepileptic drugs (AEDs) induce cognitive deficits in humans
- We studied the impact of epilepsy on trainability in adult dogs
- Dogs with epilepsy exhibited significantly lower trainability than controls
- Trainability of dogs treated with polytherapy and specific AEDs showed the most impairment
- History of training and use of reward-based methods increased trainability

Abstract

Epilepsy and anti-epileptic drug (AED) treatment have been found to induce or exacerbate underlying cognitive impairments in people, affecting learning ability, attention and memory. Idiopathic epilepsy (IE) is the most common chronic neurological condition in dogs. Whether IE impairs cognition, which may be reflected in affected dogs' trainability, has not been explored. The aim of this study was to

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investigate whether IE and/or AED treatment compromise the trainability of dogs with IE compared to controls. An online cross-sectional study was conducted, resulting in a sample of 4051 dogs, of which 286 had been diagnosed with IE. Owners reported their dog's trainability using a previously validated research questionnaire, along with their dogs' training history (type of activities and training methods used) and clinical history. Four factors were significantly associated with trainability in a generalised linear mixed model: (i) epilepsy diagnosis: dogs with IE had significantly lower trainability than controls; (ii) age: dogs aged >12 years had significantly lower trainability than all other age groups; (iii) adult training history score: dogs with greater exposure to training activities were more trainable; and (iv) training method: dogs whose owners used a mix of both reward and punishment-based methods had lower trainability than those using solely reward-based methods. Within the sub-population of dogs with IE, those treated with (i) polytherapy (2-3 AEDs), (ii) zonisamide and/or (iii) potassium bromide exhibited lower trainability. This study provides initial evidence of cognitive impairment associated with IE and treatments for it, as measured by a metric of trainability. Further study is required to characterise these deficits. However, if these effects are confirmed, the merits of using the dog as a model of spontaneously occurring epilepsy will be strengthened, further consideration of the effects of AEDs will be required, and strategies to enhance cognition in affected dogs should be explored.

Keywords: canine, dog, epilepsy, seizure, cognition, trainability

1. Introduction

The trainability of a dog, including its obedience to commands, is considered important in maintaining healthy relations between companion dogs and their owners, and avoiding relationship breakdowns that may result in relinquishment (Salman et al., 2000). Trainability is described as "the ability and motivation to attend and respond in a positive way to human cues or signals"(Serpell and Hsu, 2005). A common assessment of trainability, using the C-BARQ questionnaire tool (Hsu and Serpell, 2003) includes owner assessments of their dogs' attentiveness, distractibility and speed of learning(Hsu and

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Serpell, 2003). Identifying factors associated with reduced trainability has implications both for the owner-animal bond, the utility value of dogs in both working and companion roles, and for their welfare (Serpell and Hsu, 2005). Multiple factors are known to influence trainability in the dog, including breed and breeding purpose (with trainability being better in working lines than in show lines), pointing towards genetic influences upon trainability (Serpell and Hsu, 2005). Environmental effects on trainability have also been identified, including attendance of professional training courses, with dogs who had attended at least three types of professional training courses (e.g. puppy class, obedience, agility) exhibiting a significant boost in mean trainability (Kubinyi et al., 2009). In addition, depending on the reinforcements used, trainability may be related to aspects of personality, arousal and affective (Starling et al., 2013), and has been positively correlated with playfulness (Svartberg, 2005).

Both natural and pathological processes may influence cognitive processes, and thus the trainability of a dog. Ageing has negative effects on trainability, with younger dogs being reported as more trainable than older dogs, and deficiencies in attentional control (that may compromise trainability) being reported in older dogs (Wallis et al., 2014). The effects of neurological disease on cognition and general trainability have yet to be studied in the dog, but merit consideration when examining effects of neurological conditions upon cognitive processes in humans. Epilepsy is the most common chronic neurological disorder in humans and dogs, affecting around 0.6% of the general canine population (Kearsley-Fleet et al., 2013). It is characterised by an enduring predisposition to epileptic seizures (Fisher et al., 2014; Berendt et al., 2015), and is known to induce or exacerbate underlying cognitive impairments in people (Motamedi and Meador, 2003). Recent studies have indicated that approximately half of newly diagnosed children or adults with epilepsy have demonstrable cognitive or behavioural difficulties (Taylor et al., 2010; Witt and Helmstaedter, 2012; Witt et al., 2014). Prospective longitudinal studies in humans have demonstrated a mild, but definitive, relation between recurrent seizures, particularly generalized tonic–clonic seizures, and cognitive decline (Dodrill, 2002). These effects are reflected in neuroanatomical changes, with imaging studies indicating that seizures

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can cause slow progressive atrophy of the hippocampus and cerebral cortex (Pitkänen and Sutula, 2002; Liu et al., 2003).

The degree of cognitive compromise in epilepsy is diverse, with a variety of factors contributing to these deficits, including epilepsy syndrome, seizure type and age of onset (Motamedi and Meador, 2003). Most canine epilepsy cases are diagnosed as 'idiopathic' (IE) in that there are no gross neuroanatomical or neuropathological abnormalities nor other relevant underlying diseases causing seizure activity, and a predominantly genetic or purely genetic origin is presumed (Shorvon, 2014; Berendt et al., 2015). Idiopathic generalised epilepsies are also the most common type of epilepsy in humans, constituting ~15–20% of all epilepsies (Jallon and Latour, 2005). Although people with IE exhibit milder deterioration in cognitive function than those with symptomatic epilepsy (where neuroanatomical or neuropathological abnormalities underlie seizure activity) (Elger et al., 2004), their cognitive abilities are often lower than that of the general population (Mirsky et al., 2001). In a recent meta-analysis of the effects of IE on cognition, many areas of cognitive functioning appeared to be affected, with medium-large disease effects that affect everyday function to a moderate degree in many patients and, to a larger degree, in a smaller subset of patients (Loughman et al., 2014). For example, an estimated 25% of patients with IE are considered to have intellectual disability or 'borderline' cognitive abilities compared to just 9% in the general population (Loughman et al., 2014). In addition to cognitive compromise induced by epilepsy itself, further cognitive deficits can be induced by antiepileptic drug (AED) treatment (Vermeulen and Aldenkamp, 1995).

Whether either of these effects are seen in dogs with IE is currently unknown. The aim of this study was to test the hypothesis that IE will negatively influence the trainability of affected adult dogs when compared to healthy adult controls, and within the population with idiopathic epilepsy, that dogs treated with AEDs will show less trainability than drug-naïve individuals. IE is considered a valuable epilepsy syndrome to study to gain insight into the exclusive effects of the underlying 'seizure condition' on cognitive function, rather than those caused by any brain lesion. As such, in addition to

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its direct benefit to the management and diagnosis of affected dogs, studying cognition in dogs with IE is potentially of translational value.

2. Materials and methods

2.1 Study design

An online cross-sectional study was conducted using an online survey platform (©SurveyMonkey; www.surveymonkey.co.uk) between June and September 2016, to explore the impact of IE upon trainability. To avoid response bias associated with revealing the main study question, the survey was entitled the 'Mature Dog Study', with the aim being described as a study to explore the impact of canine dogs' health and training upon their behaviour. Consent was gained via a statement in the opening page detailing the storage and use of their data in accordance with the Data Protection Act 1998. The survey was primarily promoted via social media, breed clubs and veterinary practices. The study was approved by the local ethics committee (approval number RVC Animal Welfare and Ethics Committee 2016/U301), and the methods were carried out in accordance with the approved guidelines.

2.2 Subjects

The study was designed to recruit both dogs affected by IE, and controls with no history of recurrent seizure activity. Dogs were screened for IE by consecutive diagnostic questions. Firstly, owners were asked to report whether their dog was known to have ever had a seizure (yes/no). Those owners answering in the negative were categorised into the control group. For those answering in the affirmative, three further screening questions were posed: (i) whether their dog had 2 or more seizures that were at least 24 hours apart; (ii) whether their dog's first seizure occurred between the ages of 6 months and 6 years; and (iii) whether their veterinarian had carried out blood and urine tests on the dog and found no identifiable cause for the dog's seizures. If the owner answered affirmatively for all three questions, the dog was considered to meet the Tier I diagnostic criteria for the International Veterinary

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Epilepsy Task Force (Berendt et al., 2015) and thus classed as affected. Dogs who had experienced seizure activity, but whose owners responded 'yes' to only one or two of the above screening questions, were excluded from the study.

A lower age limit of three years was an inclusion criterion of the study to include only adult dogs and promote behavioural stability at age of sampling. Behavioural maturity of the domestic dog varies between individuals and breeds, with sexual maturity being reached at 6–9 months of age (later in some giant breeds) and social maturity at 1–3 years of age (Landsberg and Denenberg, 2016). Previous studies have demonstrated that trainability increases up to around 4 years and then stabilises (Eken Asp et al., 2015).

2.3 Behavioural data

Trainability was assessed with the trainability items of the Canine Behaviour and Research Questionnaire (C-BARQ)(Hsu and Serpell, 2003), a questionnaire tool previously validated for use in various study populations (Duffy et al., 2008; Duffy and Serpell, 2012). The trainability subscale consists of eight items (Table 1), the scores of which are averaged to derive an overall trainability score. Previous studies have demonstrated that there is little cross-loading between trainability and any other C-BARQ factor, and that trainability has a Cronbach's alpha coefficient of 0.8 (Hsu and Serpell, 2003; Serpell and Hsu, 2005).

To account for the effect of environmental factors upon trainability, a history of priot training was taken using questions from a recent study (Blackwell et al., 2008a). For an indication of relevant early life experience, owners were asked to report the number of puppy classes attended using the following categories: 0 (never attended), 1-10, 11-20, >20. For adult training, owners were asked to report attendance of six activities: obedience classes, agility, gundog training, ringcraft, conformational showing and flyball. For each category, owners responded with their dog's current or previous attendance and were allocated a score from 0-2 (0 = No: Never attended, 1= Yes: Attended but has now

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stopped, 2 = Yes: Still attends), and an overall adult training score out of 12 was calculated. Finally, owners were asked to report what training aids and methods they used to train their dog. Thirteen aids/methods listed were punishment-based: bark-activated citronella collar, prong collar, Pet Corrector^{TM}, bark collar, water pistol, verbal punishment (e.g. shouting or telling off), electric collar, choke chain, electronic boundary fence, smacking when the dog does something wrong, Husher muzzle, shutting away when the dog behaves badly, pulling back on the lead when the dog pulls. Five aids/methods listed were reward-based: food reward, stroking or patting, verbal praise, playing and clicker training. Whether the owner reported using solely punishment-based methods, solely reward-based methods, or a mix of both methods was recorded.

2.4 Clinical data

Owners reported their dog's breed, sex, neuter status, age and weight (kg). For the sub-population of dogs with IE, additional clinical data were collected on: age at first seizure, time since first seizure, experience of cluster seizures (more than one seizure in a 24-hour period) and status epilepticus (a seizure lasting >5 minutes or two seizures with incomplete inter-ictal recovery of consciousness) (Berendt et al., 2015). Owners documented their dog's current AED treatment, response to the current AED regime and side-effect profile.

2.5 Statistical analysis

Statistics were performed in SPSS Statistics v 23 (SPSS, Inc., Chicago). Current trainability score was used as the outcome variable (a mean score on a scale of 0-4), along with scores for each of the eight sub-questions (on a scale of 0-4). The effects of the following predictors on trainability score were investigated: age (months), sex, neuter status, bodyweight (kg), purebred status, previous training (puppy class attendance and adult training score), and IE diagnosis. Linear regression modelling was used to evaluate these variables separately to measure their effect upon trainability score. Results of the univariate analyses were used to determine whether to include the factors in

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the subsequent models, with those liberally associated (p<0.2) carried forward. A generalised linear mixed model was performed to model the effect of IE on trainability score, with breed included as a random effect to take into account this source of non-independence.

Within the idiopathic epilepsy group, the following predictors of interest were considered for their effect on trainability: age at first seizure, time since first seizure (epilepsy duration), experience of cluster seizures and/or status epilepticus, current AED treatment and number of AEDs used. To characterise specific differences in trainability between control and IE cases, differences in the scores of the eight sub-questions were compared at the univariate level using Mann-Whitney U test. All tests were two-sided and $P < 0.05$ was considered to be significant. Data are presented as mean ± standard deviation (SD), or median (25^{th}-75^{th} quartile), where appropriate.

3. Results

3.1 Study population

Responses were received from the owners of 4710 dogs, of which 4051 were eligible. The remainder were excluded due to a history of seizures without meeting diagnostic criteria of a Tier I level diagnosis, or due to being incomplete. Almost three quarters of the sample were purebred (71.4%), over half of which were registered with a kennel club in their country (66.7%, n=1923). There were 173 different breeds represented, the top three being the Border Collie (9.2%, n=371), Cavalier King Charles Spaniel (6.5%, n=265) and Labrador Retriever (6.1%, n=248). Most dogs in the sample were neutered, with 42.1% (n=1707) of females being neutered and 38.3% (n=1553) of males being neutered, 12.2% (n=494) of males being entire, and 7.3% (n=297) of female being entire. The median weight (kg) was 20.0kg (11.0-28.0) and the median age (months) 98.0 (67.0-129.0). Nearly one third of dogs were aged 3-6 years (29.4%), 30.0% 6-9 years, 24.8% 9-12 years, and 15.8% over 12 years. A total of 286 dogs met the minimum three criteria required for IVETF Tier I diagnostic certainty for IE, with 17% achieving Tier II certainty (Berendt et al., 2015).

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3.1.1 Differences between case and control dogs

Dogs with IE (n=286) were significantly younger than controls, with 48.6% IE dogs aged 3-6 years *vs*. 27.9% of controls (p<0.001), and were heavier than control dogs (IE: 23.0kg (14.0–34.0); control: 20.0kg (11.0-28.0); U=422111.0, p<0.001) (n=3765). Dogs with IE were more likely to be male (IE: 65.38%; control: 49.40; X^2=27.16, p<0.001) and neutered (IE: 86.71%; control: 80.0%; X^2=27.16, p<0.001). Dogs with IE had a significantly lower adult training score (epilepsy: 0 (0-1); control: 1 (0-2); U=464709.0, p<0.001), but there was no difference in the level of puppy class attendance (% no classes; IE: 49.2%; control: 47.765; X^2=1.78, p=0.62) or the training method used (% reward only: IE: 31.4%, control: 29.3%; X^2=0.57, p=0.450).

3.2 Factors associated with trainability

Six factors were associated with trainability score at the univariate level: epilepsy diagnosis, age category, bodyweight, adult training score, puppy class attendance and training method. (Table 2). No significant effects of sex, neuter status or purebred status were found (p>0.05).

When taken forwards into a generalised linear mixed model, with breed included as a random effect, four factors remained significant:

(1) Epilepsy diagnosis: Dogs diagnosed with IE had significantly lower trainability than controls (p<0.001)
(2) Age: Dogs in the over 12 age category had significantly lower trainability than all other age groups (p<0.001)
(3) Adult training score: Dogs with higher adult training scores (who had attended more training activities and continued to participate in training activities) had higher trainability (p<0.001)
(4) Training method: Dogs whose owners used a mix of both reward- and punishment-based methods had lower trainability than those owners using only reward-based methods (p<0.001)

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3.3 Differences in individual trainability components

When trainability score was broken down into its eight sub-components, five of the eight measures were significantly lower in dogs with IE than in controls (Table 4): dogs with IE were less likely to return immediately when called while off leash or obey a stay command immediately, and were more likely than controls to be slow to respond to correction or punishment, learn new tricks or tasks and become easily distracted by interesting sights, sounds or smells ($p<0.05$) (Figure 1).

3.4 Epilepsy sub-population

Of the 286 dogs meeting the criteria for IE diagnosis, the majority (70.3%) were purebred, with the most common breeds being the Border Collie (n=34, 11.9%) and Labrador Retriever (n=16, 5.6%). The median age (months) was 72.0 (54.5-90.5) and weight (kg) was 22.0 (14.0-34.0). Nearly two-thirds of dogs were male (n=187, 65.4%) and the majority were neutered (n=248, 86.7%). The median age at first seizure (months) was 32.0 (18.0-48.50), with the median time since first seizure 33.0 months (19.0-56.0). The majority (75.5%, n=216) of dogs had been observed to have cluster seizures (mean trainability: cluster: 2.55 ± 0.75, no clusters: 2.72 ± 0.73), and 40.9% (n=117) were reported by owners to have entered status epilepticus (mean status: 2.50 ± 0.75, no status: 2.64 ± 0.74). The median number of seizures/month (calculated over the past three months) was 1.0 (0.0-1.67). There was no effect of any of these variables upon trainability ($p>0.05$).

3.4.1 Anti-epileptic drugs

Nearly all dogs were receiving anti-epileptic medication (88.8%, n=254), with 131 being treated with AED monotherapy, 82 being treated with two AEDs, 41 being treated with three AEDs and 1 being treated with four AEDs. The most common AEDs used were phenobarbital (63.3%, n=181), followed by potassium bromide (KBr: 30.4%, n=87), levetiracetam (LEV: 25.9%, n=74), imepitoin (IMP: 15.7%,

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n=45) and zonisamide (ZNS: 10.8%, n=31). Dogs being treated with KBr or ZNS had a significantly reduced trainability score than those not treated with these AEDs (Table 6). Being treated with a higher number of AEDs was associated with a reduced trainability scores, with significant reductions seen when being treated with 2 (p=0.039) or 3 (p=0.011) AEDs compared to drug-naïve patients. However, there was no difference between dogs treated with monotherapy compared to drug-naïve patients (Table 6). One fifth of dogs had not been observed to have a seizure since the commencement of their most recent AED regime (19.8%, n=53), with a further third having a ≥50% reported reduction in seizure frequency following the implementation of their most recent medication regime (37.7%, n=101), and 4.1% (n=10) having <50% reported reduction. Nearly one quarter of dogs had no reported change in seizure frequency (23.6%, n=57), while 8.7% (n=21) had a reported increase in seizure frequency. No effect upon trainability was associated with drug response Table 5).

4. Discussion

This study is the first to investigate the impact of epilepsy and AED treatment on the trainability of dogs. Significant impairment in trainability was observed in dogs with IE compared to control dogs in a large, multi-breed population (n=4051), with greater impairment seen in those dogs treated with multiple AEDs within the IE sub-population (n=286). The C-BARQ trainability measure incorporates behaviours relevant to several areas of cognition in dogs including attention and learning speed, both of which are impaired in epilepsy in humans. From these results, it appears that IE may also compromise canine cognition, such that dogs with IE were slower to learn new tricks or tasks, and slower to respond to correction or punishment than controls. Slowed learning speed is seen in people with epilepsy, and is also observed in rodent models of epilepsy, when assessed with approaches such as the radial-arm maze, conditioned taste aversion task and Morris water maze (Majak and Pitkänen, 2004). Impaired cognition in epilepsy in people is so prevalent that there are calls for cognitive screening of all children affected by epilepsy, with the International League Against Epilepsy considering neuropsychological assessment a pivotal investigation in the routine care of people with epilepsy (Wilson et al., 2015). From

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these results, it appears that further investigation of cognition in canine epilepsy is warranted to more fully diagnose this disorder beyond simply the presence of recurrent seizures.

There are several potential mechanisms leading to epilepsy-related cognitive impairments, and it has been postulated that epilepsy interferes with the trajectory of developmental brain networks underlying cognition (Ibrahim et al., 2014). Recurrent seizures may modify, slow down, or accelerate those processes that take place during development and are essential for the correct formation and function of brain circuitry (Holmes, 2001). In addition, impairments may worsen over time, with experimental and clinical evidence suggesting that seizures could produce progressive neuronal damage, resulting in cumulative neuropsychological disabilities (Tasch et al., 1999). To better understand these effects, further study should characterise the nature, onset and progression of cognitive impairments in dogs with epilepsy. Objective behavioural testing is required to confirm these findings because trainability, as estimated by the CBARQ, does not assess abilities to perform complex tasks, such as problem-solving, or tasks that require dogs to perform independently from their owners (Svartberg, 2005).

In addition to protracted learning speed, dogs with epilepsy exhibited increased levels of behaviours that may be indicative of impaired attention. Attention is the ability to selectively process one aspect of the environment over others, and can be considered as compromising at least five separate components: focused, sustained, selective, alternating, and divided attention (Sohlberg and Mateer, 2001). Dogs with IE were more easily distracted by sights, sounds or smells, and were less likely to return immediately when called while off leash, which may indicate impairments in selective attention (the ability to focus on task-relevant goals to the exclusion of salient distracters). The main evidence of cognitive compromise for people with IE is reported to be attention-related (Hommet et al., 2006), with attentional deficits being reported across all seizure types in children with IE (Bhise et al., 2010) and being observed irrespective of the intellectual level of the patient (Williams, 2003). Further studies utilising testing, such as those recently demonstrated to measure sustained and selective attention in dogs (Chapagain et al., 2017), may reveal which components of attention are retained or impaired in canine IE. Finally, there may be evidence of increased impulsivity associated with IE, in that dogs with IE are

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less likely to obey a stay command, while their compliance with a sit command did not differ from that of controls. In a previous study, difficulty maintaining a stay on command emerged as a measure of hyperactivity-impulsivity (Lit et al., 2010). Further training tasks assessing inhibitory control, with specific measures of motor and cognitive impulsivity, may further characterise these apparent deficits.

In addition to seizure activity, an extensive and complex network of comorbidities associated with epilepsy is emerging in both humans and dogs with epilepsy. These comorbidities are conditions that occur in association with epilepsy at frequencies that are significantly greater than in the appropriate control group, and may be (i) causes of epilepsy, (ii) consequences of epilepsy, or (iii) a separate, associated condition that occurs due to a common cause for epilepsy and the comorbidity (Brooks-Kayal et al., 2013). Some co-morbid neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD), have the potential to induce cognitive deficits. ADHD is diagnosed in up to one third of epilepsy patients (Thome-Souza et al., 2004), and is characterised by chronic inattention, hyperactivity and impulsivity. ADHD-like behaviour has been seen in a strain of epilepsy-prone laboratory rats (Anisman and McIntyre, 2002), with high levels of impulsivity and distractibility resulting in learning deficits in tasks of spatial working and reference memory (e.g. the delayed alternation test and the Morris water maze) (Anisman and McIntyre, 2002). ADHD-like behaviour has recently been identified in dogs with IE and may contribute to the reduced observed trainability reported in this study. In a single-breed study of Lagotto Romagnolo dogs with or without a history of Benign Familial Juvenile Epilepsy (BFJE; where dogs often undergo spontaneous seizure remission before 13 weeks of age), dogs with BFJE showed significantly higher scores on the behavioural factors 'Inattention' and 'Excitability/Impulsivity' than those in the control group (Jokinen et al., 2015). In a second study, dogs with epilepsy that had been enrolled in a randomised, placebo-controlled, double-blinded crossover dietary trial were noted to show high levels of excitability, contrasted with low levels of trainability (as measured by the CBARQ) (Packer et al., 2016). Further characterisation of ADHD-like behaviour in dogs with epilepsy, alongside measures of cognitive ability may further disambiguate the effects on cognition of recurrent seizure activity *and* behavioural co-morbidities. In addition to ADHD-like behaviour, anxiety has been reported as a behavioural co-

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morbidity of dogs with epilepsy (Shihab et al., 2011). Anxiety is known to have a detrimental effect upon learning and memory (Eysenck, 1979), and it is possible that co-morbid anxiety in the IE population may have reduced trainability scores. Further investigation screening for multiple co-morbidities to dissect their individual effects upon cognition would be of value.

The use of multiple AEDs (polytherapy) and two specific AEDs (ZNS and KBr) were associated with reduced trainability. These findings align with evidence of the cognitive side-effects of chronic AED treatment on humans (Vermeulen and Aldenkamp, 1995). Dogs treated with two or three AEDs showed less trainability than drug-naïve dogs or dogs on monotherapies. In humans, AEDs have a dose-dependent effect on cognitive functioning, with maximal impairments seen in patients receiving polytherapy (Trimble, 1987). Adverse cognitive side-effects of AEDs are mostly reversible and may resolve after complete withdrawal or even after dose reduction (Witt and Helmstaedter, 2012), and a reduction in the number of AEDs or change to monotherapy usually generates cognitive improvement (Brodie et al., 1987). The conflict of seizure control *vs*. side-effect management is the common challenge to clinicians seeking to address the adverse effects of AED and optimise patient welfare (Packer and Volk, 2015).

ZNS is an established AED for humans but has only been recently used for epilepsy treatment in dogs, with initial studies indicating efficacy in seizure control (Dewey et al., 2004; von Klopmann et al., 2007; Chung et al., 2012). In line with the results of the current study, ZNS-induced cognitive deficits are seen in humans. For example, in a longitudinal study of patients being treated with ZNS, after 1 year of treatment, nearly half of patients (47%) complained of cognitive deficits, most commonly memory deficit (35%) and attention/concentration deficit (26%) (Park et al., 2008). In addition, again after 1 year of treatment, reduced performance was seen in 7/14 cognitive tasks compared to baseline, with patients on higher doses being more likely than those on lower doses to experience cognitive problems (Park et al., 2008). The mechanism of ZNS-induced cognitive impairment is not yet known. As ZNS increases GABA release from the hippocampus (Ueda et al., 2003), it has been postulated that ZNS (along with other GABAergic AEDs) may cause cognitive

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dysfunction by increasing GABAergic activity in the cerebral cortex. GABAergic activity in the prefrontal cortex could lead to mental slowing and language dysfunction (Aldenkamp and Bodde, 2005). Of the 31 dogs in this study treated with ZNS, only one third received it as a monotherapy (32.3%); further study of the cognitive effects in isolation, rather than as an add-on medication, are required to fully reveal its impact.

KBr was the first effective AED in humans, first used in the 1850s (Pearce, 2002). Prior to its use as an AED, KBr was noted to produce general sedation and mental slowing (Huette, 1850), and because more recently developed AEDs produce fewer such side-effects, it is now rarely used in humans. In contrast, KBr is a valued and commonly used AED in dogs, showing efficacy as an anticonvulsant (Podell and Fenner, 1993; Trepanier et al., 1998; Boothe et al., 2012). However, following ataxia, sedation is the second most common adverse effect of KBr (Charalambous et al., 2016), but its effects on mental abilities have not previously been quantified. Although seizure control may be prioritised above cognitive side-effects of AEDs in treatment decision-making, further investigation of cognitive side-effects alongside traditionally recognised physical side-effects (e.g. polyphagia, ataxia) may be valuable for owner education, to increase awareness and monitoring of potential changes in their dog following AED initiation. In the current cohort, the use of KBr as an add-on medication was even more common than that of ZNS, with only 2 out of 87 cases being treated with KBr as a monotherapy

In addition to the effects of epilepsy and anti-epileptic drug treatment on trainability, several other effects were identified. Dogs aged over 12 years old were significantly less trainable than all other age groups, with no differences in trainability detected among dogs in the four other age groups (3-6, 6-9 and 9-12 years old). This was anticipated, with previous studies demonstrating that trainability increases up to around 4 years and then stabilises (Eken Asp et al., 2015).The decline in trainability in dogs >12 years old may reflect the increased prevalence of canine cognitive dysfunction (CCD) in this age group, with CCD prevalence estimates of 23.3% in dogs aged 12–14 years and 41% in

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dogs aged >14, compared with just 3.4% aged 8–10 years and 5% aged 10–12 years (Salvin et al., 2011).

Across both case and control dogs, the use of exclusively reward-based training methods was associated with more trainability compared to a mixture of reward- and punishment-based methods. In this study, 29.4% of owners reported using positive training methods exclusively; more than described in previous studies (16-20%) (Hiby et al., 2004; Blackwell et al., 2008b). This may reflect the increased promotion of positive methods over time. Previous studies have had similar findings, for example, significantly higher obedience scores are seen in dogs trained exclusively using reward-based methods (Hiby et al., 2004). In addition, the greatest numbers of problematic behaviours have been reported by owners who used punishment only, or a combination of punishment and reward to train their dog (Hiby et al., 2004). As the current study was cross-sectional, it is possible that the use of exclusively reward-based training methods may lead to increased trainability, but it is also possible that when dogs show an initial high level of trainability, their owners are more inclined to use reward-based methods or that, following a decline in trainability, owners include punishment-based methods in their training. Regardless of the direction of this relationship, there is mounting evidence that using aversive training methods can jeopardize both the physical and mental health of dogs and, although positive punishment *can* be effective, there is no evidence that it is more effective than reward-based training (Ziv, 2017).

In addition to training method, dogs with a history of greater engagement in training activities (e.g. obedience, agility) had higher trainability. This is in line with previous findings. For example, in one study, dogs who had attended at least three types of professional training courses (e.g. puppy class, obedience, agility) exhibited the highest mean trainability (Kubinyi et al., 2009), and in a second study, dogs that had obedience training were more likely to obey commands than those that had not (Kobelt et al., 2013). In addition, several studies have confirmed that attendance at obedience training classes has been associated with a reduced prevalence of undesirable behaviors in companion dogs (Clark and Boyer, 1993; Jagoe and Serpell, 1996; Bennett and Rohlf, 2007). Finally, in a problem-solving task, more dogs trained in various disciplines (agility, search and rescue, Schutzhund, freestyle

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and gun-dog working) completed the task successfully compared to untrained dogs (Marshall-Pescini et al., 2008). With strong evidence of the beneficial effects of training, it is perhaps surprising that only a minority of owners (8.1%) in the current cohort continued to attend obedience classes with their dogs, with 33.2% having previously attended but stopped. This low attendance rate aligns with the 24% reported in a previous study (Coren, 1999). Dogs with epilepsy had lower overall adult training scores than controls, and whether increased levels of formal training such as obedience classes could compensate for deficits in trainability induced by epilepsy *per se* and anti-epileptic drug treatment requires further investigation.

Conclusion

Overall, this study provides initial evidence of cognitive impairment associated with canine epilepsy and its treatment, as estimated by a metric of trainability. Further study is required to characterise these deficits but if they are confirmed, the dog will be further strengthened as a model of spontaneously occurring epilepsy. Further study is required to characterise the nature, onset and progression of cognitive impairments in dogs to better understand these deleterious effects. Objective behavioural testing would confirm and expand upon the current findings. This study replicated the findings of previous studies on the beneficial effects of adult training and using exclusively reward-based training methods, strengthening claims these tools should be advocated to promote good canine behaviour and welfare. Whether these trainability enhancers can be used to compensate for cognitive deficits in dogs with epilepsy should be explored.

Contributions

RMAP, PDM and HAV conceived and designed the study. RMAP and AP compiled the data. RMAP analysed the data and prepared the figures. RMAP wrote the first draft of the manuscript. PDM and HAV edited the manuscript and all authors reviewed and agreed the contents.

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Competing interests

The authors declare no competing financial interests.

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Figure 1. Significantly lower scores in five sub-components of the trainability in dogs with epilepsy compared to controls (N.B. * p<0.05, ** p=0.01, *** p<0.001)

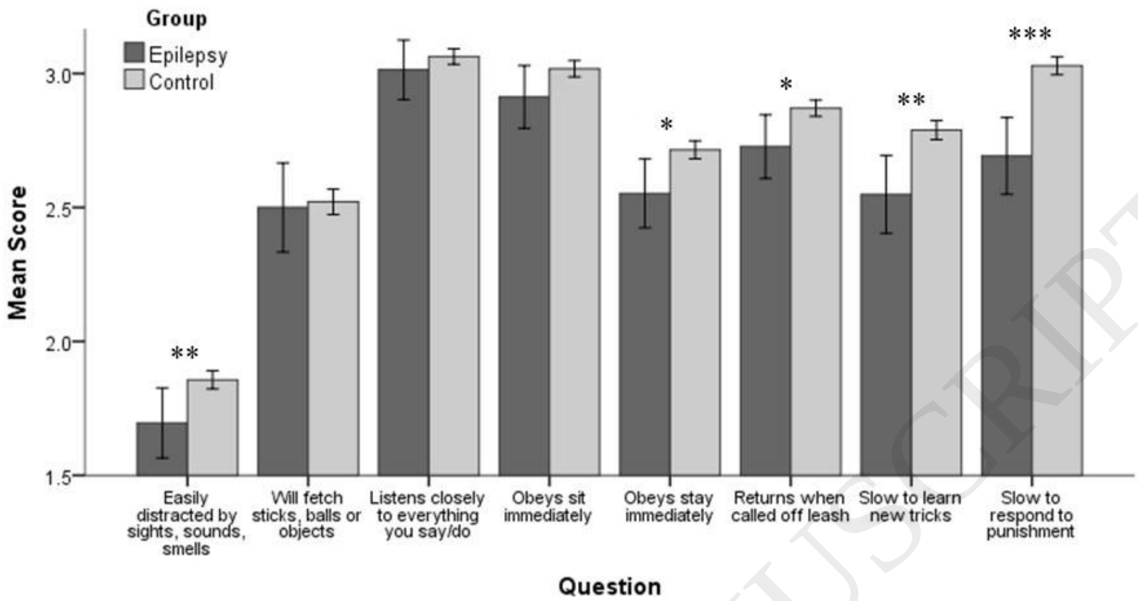

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Table 1. Eight questions and frequency scoring that appear in the trainability subscale of the C-BARQ.

[a] Scores for questions 6-8 are reversed as these are considered negative traits with regard to trainability

Question	Observed frequency of behaviour				
	Never	**Seldom**	**Sometimes**	**Usually**	**Always**
1. Returns immediately when called while off leash	0	1	2	3	4
2. Obeys a sit command immediately	0	1	2	3	4
3. Obeys a stay command immediately	0	1	2	3	4
4. Will fetch or attempt to fetch sticks, balls and other objects	0	1	2	3	4
5. Seems to attend to or listen closely to everything the owner says or does	0	1	2	3	4
6. Is slow to respond to correction or punishment[a]	*4*	*3*	*2*	*1*	*0*
7. Is slow to learn new tricks or tasks[a]	*4*	*3*	*2*	*1*	*0*
8. Is easily distracted by interesting sights, sounds or smells[a]	*4*	*3*	*2*	*1*	*0*

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Table 2. Univariate associations between signalment, training and health variables with trainability in 4051 dogs. N.B. Significant results are highlighted in bold.

Variable	Category	N	Mean trainability score ± SD	B	95% CI	p
Age category	3-6 years	1184	2.80 ± 0.62	0.354	0.290-0.418	**<0.001**
	6-9 years	1207	2.75 ± 0.64	0.299	0.236 – 0.362	**<0.001**
	9-12 years	998	2.75 ± 0.64	0.308	0.243 – 0.374	**<0.001**
	Over 12 years	626	2.45 ± 0.78	Reference		
Bodyweight (kg)	-	3938	-	0.004	0.002 – 0.005	**<0.001**
Adult training score	-	3556	-	0.102	0.090 – 0.114	**<0.001**
Sex	Female	1985	2.72 ± 0.68	-0.003	-0.044 – 0.038	0.882
	Male	2030	2.74 ± 0.02	Reference		
Neuter status	Entire	783	2.77 ± 0.67	0.066	0.014 – 0.118	0.013
	Neutered	3232	2.71 ± 0.6	Reference		
Purebred status	Crossbred	1146	2.73 ± 0.63	0.018	-0.028 – 0.063	0.445
	Purebred	2869	2.71 ± 0.68	Reference		
Idiopathic epilepsy	Case	286	2.58 ± 0.74	-0.152	-0.232 - -0.072	**<0.001**
	Control	3765	2.73 ± 0.66	Reference		
Puppy class attendance	None	1568	2.67 ± 0.70	Reference		
	1-10	1151	2.80 ± 0.61	0.124	0.075 – 0.173	**<0.001**
	11-20	204	2.82 ± 0.54	0.147	0.053 – 0..241	0.241
	>20	353	2.96 ± 0.60	0.293	0.219 – 0.368	**<0.001**
Training method	Reward only	1149	2.87 ± 0.67	-0.203	-0.249 - -0.158	**<0.001**
	Mixed	2757	2.66 ± 0.65	Reference		

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Table 3. Generalised linear mixed model of the effects of signalment, training and health factors upon trainability score. Breed was included as a random effect to account for non-independence. N.B. Significant results are highlighted in bold.

Variable	Category	N	B	95% CI	P
Intercept	-	-	2.338	2.249 – 2.427	**<0.001**
Age category	3 – 6 years		0.377	0.315 – 0.438	**<0.001**
	6 – 9 years		0.352	0.291 – 0.413	**<0.001**
	9 -12 years		0.323	0.260 – 0.386	**<0.001**
	Over 12 years		Reference		
Idiopathic epilepsy	Case	286	-0.139	-0.218 - -0.059	**<0.001**
	Control	3729	Reference		
Adult training score	-	-	0.006	0.062 – 0.086	**<0.001**
Training method	Mixed	2757	-0.210	-0.252 - -0.167	**<0.001**
	Reward only	1149	Reference		

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Table 4. Differences in the eight sub-components of the trainability score between dogs with IE and controls

Question	Control (Mean ± SD)	Epilepsy (Mean ± SD)	Mann-Whitney U	p
Is easily distracted by interesting sights, sounds or smells	1.86 ± 1.05	1.70 ± 1.13	485793	**0.008**
Will fetch or attempt to fetch sticks, balls and other objects	2.52 ± 1.45	2.50 ± 1.43	521964	0.536
Seems to attend to or listen closely to everything the owner says or does	3.06 ± 0.89	3.01 ± 0.96	521798	0.515
Obeys a sit command immediately	3.02 ± 0.95	2.91 ± 1.01	501437	0.065
Obeys a stay command immediately	2.72 ± 1.04	2.55 1.11	489828	**0.014**
Returns immediately when called while off leash	2.87 ± 0.94	2.73 ± 1.02	495554	**0.028**
Is slow to learn new tricks or tasks	2.79 ± 1.11	2.55 ± 1.25	479270	**0.003**
Is slow to respond to correction or punishment	3.03 ± 1.03	2.69 ± 1.23	455410	**<0.001**

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Table 5. Effects of anti-epileptic drug treatment on trainability score in dogs with epilepsy (n=286)

N.B. Significant results are highlighted in bold.

Variable	Category	N	Trainability	B	95% CI	p
Number of AEDs	0	31	2.79 ± 0.70	Reference		
	1	131	2.68 ± 0.74	-0.114	-0.400 – 0.172	0.433
	2	82	2.48 ± 0.74	-0.319	-0.621 – -0.017	**0.039**
	3	41	2.35 ± 0.69	-0.441	-0.781 – -0.100	**0.011**
Phenobarbital	Yes	181	2.54 ± 0.77	-0.087	-0.267 – 0.092	0.339
	No	105	2.64 ± 0.07	Reference		
Imepitoin	Yes	45	2.66 ± 0.54	0.092	-0.145 – 0.330	0.445
	No	241	2.57 ± 0.78	Reference		
Potassium Bromide	Yes	87	2.38 ± 0.76	-0.285	-0.470 – 0.099	**0.003**
	No	199	2.67 ± 0.72	Reference		
Levetiracetam	Yes	74	2.45 ± 0.75	-0.181	-0.378 – 0.015	0.071
	No	212	2.63 ± 0.74	Reference		
Zonisamide	Yes	31	2.32 ± 0.84	-0.289	-0.566 - -0.012	**0.041**
	No	255	2.61 ± 0.04	Reference		
AED response	Increase	21	2.57 ± 0.80	-0.142	-0.518 – 0.234	0.458
	No change	57	2.63 ± 0.65	-0.074	-0.352 – 0.205	0.602
	< 50% reduction	10	2.46 ± 0.89	-0.245	-0.748 – 0.258	0.338
	≥ 50% reduction	101	2.49 ± 0.79	-0.222	-0.470 – 0.025	0.078
	Seizure free	53	2.71 ± 0.67	Reference		