

Title: Behavioural Changes in Dogs with Idiopathic Epilepsy

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1 Abstract

2 Breed-specific and broader cohort studies have shown behavioural changes in dogs
3 following the onset of idiopathic epilepsy (IE). A cross-sectional, case-control questionnaire
4 study was carried out to strengthen this body of evidence. Owners of eight breeds of dog
5 completed an online questionnaire about their dogs' behaviour; once for control dogs and
6 twice for dogs with IE, for both pre- and post-IE onset behaviour. Ninety-six (24.74%) dogs
7 with IE and 292 (75.26%) age and breed matched control dogs met the inclusion criteria.
8 Control dogs had significantly higher "Trainability" scores than dogs with IE ($p=0.04$). Post-IE,
9 dogs had significantly higher "Dog-Directed Fear or Aggression" ($p=0.02$), "Non-Social Fear"
10 ($p=0.01$), "Attachment/Attention-Seeking Behaviour" ($p=0.04$), "Attention-Deficit" ($p=0.02$)
11 and significantly lower "Trainability" ($p=0.02$) than prior to the onset of IE. Medication status
12 did not significantly affect any behavioural factor, but drug-resistant dogs had significantly
13 less "Trainability" than drug-responsive ($p=0.04$) and partially drug-responsive dogs ($p=0.03$).
14 Behavioural differences related to cognitive function are seen between dogs with IE and
15 controls. Behavioural changes related to anxiety, attention and cognition are seen in dogs
16 following the onset of IE. The ability to clinically define and diagnose behavioural
17 comorbidities in dogs is much needed from both a clinical and research perspective.
18

19 **Introduction**

20 Psychological and neurodevelopmental comorbidities are reported to effect up to 50%
21 of people with epilepsy¹⁻⁵, alongside neuropsychiatric and cognition impairments⁶. These
22 comorbidities can have a drastic negative effect on health-related quality of life (QoL),
23 sometimes more so than seizure frequency⁷⁻¹². Carer-perceived QoL of a dog with idiopathic
24 epilepsy (IE) is associated with the carers own QoL¹³, and seizure activity can increase carer
25 stress¹⁴. Breed-specific studies have reported behavioural changes in dogs with IE¹⁵⁻¹⁷. Larger
26 studies have shown differences in behaviour of dogs pre- and post-onset of IE and between
27 dogs with IE and controls¹⁸⁻²⁰. Similar studies have used the Canine Behavioural Assessment
28 and Research Questionnaire (CBARQ) but did not use the standard method for analysis¹⁹.
29 Using the established tool and analysis method would allow more comparability between
30 studies. A cross-sectional case-control questionnaire study was carried out with the aim to
31 increase and strengthen the existing evidence base.

32

33 **Method**

34 Research was approved by the RVC animal and welfare ethical review board (URN
35 M2015 0053). Owners of eight breeds of dog previously identified to be at increased risk of
36 IE compared to cross breeds (Golden Retriever, Labrador, Cocker Spaniel, Border Terrier,
37 German Shepherd Dog, Parson Jack Russell Terrier, Boxer, and Border Collie)²¹ were
38 recruited. Dogs aged between 6 months and 10 years old without neurological disease,
39 aside IE were eligible for inclusion. Owners were recruited via social media to complete an
40 online questionnaire containing two previously validated behavioural questionnaires
41 (Appendix 1); the C-BARQ²² and Dog-ADHD²³ rating scale in regards of their dogs' behaviour;
42 current behaviour only for the controls, and behaviour both current and prior to onset of IE
43 for the dogs with IE. Medication information, such as medications taken and change in
44 seizure frequency on them, was collected to allow for allocation of drug-responsive,
45 partially drug-responsive and drug-resistant categories²⁴.

46 Statistical analysis was carried out on IBM Statistical Package for the Social Sciences
47 (SPSS) Version 23. Dogs were matched for age and breed. A mean score was calculated for
48 each behavioural factor. Normality was assessed statistically, and the appropriate statistical
49 test was utilised accordingly to compare groups such as control behaviour vs. current IE
50 group behaviour, or behaviour of sub-categories of dogs with IE, e.g. medication status. All

51 p-values were False Discovery Rate (FDR) corrected^a. General Linear Mixed Models (GLMM)
52 for binary outcomes using backwards selection were applied following univariate analyses
53 to identify variables liberally associated ($p < 0.1$) with the study group.

54

55 **Results**

56 Of 834 responses, 388 dogs were included; 96 (24.74%) with IE and 292 (75.26%)
57 controls. Responses were excluded if they did not meet inclusion criteria, were incomplete,
58 or to allow for matching. Average time since onset of IE was 32 months (range: 0-111
59 months). Controls had a significantly higher "Trainability" score, compared to the current IE
60 group scores ($p = 0.04$). Dogs with IE received significantly higher post-onset CBARQ scores
61 for "Dog-Directed Fear or Aggression" ($p = 0.02$), "Non-Social Fear" ($p = 0.01$),
62 "Attachment/Attention-Seeking Behaviour" ($p = 0.04$), "Attention-Deficit" ($p = 0.02$) and
63 significantly lower "Trainability" ($p = 0.02$) than prior to the onset of IE (Figure 1, Table 1). In
64 a GLMM, these behavioural factors were not affected by other variables tested (e.g. age,
65 seizure frequency, cluster seizures).

66 Twelve dogs (12.50%) were drug-naïve, 44 (45.83%) were receiving monotherapy
67 and 40 (41.67%) were receiving polytherapy. Owner-reported medication status did not
68 significantly affect any behavioural factor. Excluding drug-naïve dogs and dogs whose
69 owners could not recall specific medication information; 21 (32.8%) were drug-responsive,
70 20 (31.3%) were partially drug-responsive and 23 (35.9%) were drug-resistant. Drug-
71 resistant dogs had significantly less "Trainability" than drug-responsive ($p = 0.04$) and
72 partially drug-responsive dogs ($p = 0.03$).

73

74 **Discussion**

75 Dogs with IE obtained significantly lower scores for "Trainability" than controls,
76 similar to findings elsewhere^{15,25}. Additionally, "Trainability" decreased following the onset
77 of IE. This may reflect an impairment in learning and/or memory, which could be due to
78 progressive damage from seizure activity, due to effect of the AED, due to ADHD-like
79 behaviour or due to broader cognitive deficits without specific comorbidities like ADHD⁴.
80 Cognition is a concern in people with epilepsy²⁶, and in dogs with IE^{27,28}. Both Winter, et al. ,

^a <http://www.sdmproject.com/utilities/?show=FDR>

81 (2018)²⁷ and Packer, et al., (2018)²⁸ showed increased canine cognitive dysfunction in dogs
82 with IE compared to controls, but factors such as aetiology, progression and age of onset
83 were different from classic canine cognitive dysfunction, suggesting a different aetiology in
84 dogs with IE²⁸. A decrease in "Trainability" may mirror reduced memory or learning abilities
85 or early onset of canine cognitive dysfunction in the dogs in this study. Interestingly no
86 effect from AEDs was found in this study or in Packer, et al., (2018)²⁸. Though not the
87 validated form of analysis, it may be pertinent to the reader to learn that changes in the
88 pre- to post-onset "Trainability" C-BARQ scores were mostly impacted by reduced obeying
89 of the sit command, reduced response to correction or punishment and increased
90 distraction by sights, sounds and smells.

91 Behavioural changes were seen in the dogs with IE compared to the same dogs pre-
92 IE onset, which can be categorised under anxious and attention-related behaviours,
93 corroborating findings from other veterinary studies¹⁷⁻¹⁹, despite using a different patient
94 cohort, a different sampling method and different questionnaire tool, thereby strengthening
95 the conclusions made by all studies.

96 In people, neurodevelopmental and psychiatric comorbidities have been found to
97 have a bidirectional relationship with epilepsy^{26,29-32}, likely due to shared pathophysiological
98 pathways via the hippocampus, amygdala and neuronal pathways³³⁻³⁵. Anxiety disorders are
99 common amongst the general human population, but prevalence is higher in people with
100 epilepsy³³. Similarly, increased incidence of ADHD is seen in people with epilepsy compared
101 to the healthy population²⁹. In people, both anxiety and ADHD have been shown to have a
102 bidirectional relationship with epilepsy^{30,31,36}.

103 No behavioural differences were found between drug-naïve dogs and those treated
104 with monotherapy or polytherapy, contrary to findings elsewhere^{17,25}, potentially resulting
105 from low numbers of drug-naïve dogs. Recent veterinary literature has discussed side
106 effects of anti-epileptic drugs³⁷, their effect on anxiety in dogs with epilepsy^{38,39} and use as
107 anxiolytics⁴⁰. Deciphering which behavioural changes are the result of a true comorbidity
108 with epilepsy, and which are a consequence of medication is challenging^{10,11,41}. Further
109 prospective, longitudinal studies are required to untangle these effects in dogs with IE.

110 Drug-resistant and partially drug-resistant dogs received significantly lower scores
111 for the C-BARQ subscale "Trainability" than partially drug-responsive dogs. Shihab, et al.
112 (2011)¹⁸ classified dogs as drug-responders or drug non-responders and reported significant

113 changes in “controlling aggression”, “demented behaviour” and “abnormal perception”, the
114 latter two potentially contributing to decreased “Trainability” seen here. The relationship
115 between drug-resistance and behaviour is a contentious issue in human epilepsy research,
116 which poses the question of whether it is a result of the initial epilepsy phenotype or due to
117 progressive degeneration of the brain with ongoing seizures, with supportive evidence for
118 both sides^{8,41–44}. It remains unknown whether treating a comorbidity might improve a dog’s
119 response to AEDs³⁹, but it is important to consider that a drug-resistant dog may be more
120 likely to exhibit clinical side-effects of medication thereby affecting a perceived behavioural
121 difference¹⁷. A holistic approach, providing a considered and well-balanced treatment of the
122 comorbidity alongside seizure frequency or intensity, should be adopted in such cases.
123 Limitations of this study include owner-reported IE and normalcy, and potential for recall
124 and population bias.

125

126 **Conclusion**

127 Behavioural differences related to cognitive function are seen between dogs with IE
128 and controls, and behavioural changes related to anxiety, attention and cognition are seen
129 in dogs following the onset of IE, which could impact QoL. This suggests shared semiology
130 and pathologic mechanisms of disease with epilepsy in people and support the dog as a
131 naturally occurring model of IE. The ability to clinically define and diagnose behavioural
132 comorbidities in dogs is much needed from both a clinical and research perspective. Further
133 work should investigate the effects of specific AED protocols on behaviour.

134

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136 questionnaire and to the reviewers for their time and input.

137

138 **Conflict of Interest:**

139 **Holger Volk:** Served as paid consultant for Boehringer Ingelheim and CEVA animal health.
140 Served as contract researcher for: Nestle 2012–2014 and 2017–2019, dietary modification
141 of epilepsy in dogs; Desitin Pharma, 2012, the role of levetiracetam in a referral hospital;
142 industrial Funding, 2014–2015, investigating the effects of imepitoin behavioural,
143 physiologic and owner reported indicators of anxiety in dogs treated for idiopathic epilepsy.
144 Received competitive research grants for: RCVS pump primer grant, 2010–2013,

145 pharmacometabonomic profiling of epileptic dogs; Waltham Foundation, 2011–2014,
146 determination of plasma omega-3 fatty acid status in dogs with primary epilepsy and
147 relationship to antiepileptic drug metabolism; CASE BBSRC PhD studentship, 2012–2016
148 metabolic profiling of epilepsy in dogs; American Kennel Club, American Health Foundation,
149 2016– 2018, Investigating the Effect of a Ketogenic Medium Chain Triglycerides Supplement
150 on the treatment of Canine Idiopathic Epilepsy and its behavioural comorbidities; BBSRC,
151 2017-2020, Investigating the relationship between epilepsy, drug-resistance and affective
152 disorders in the domestic dog.

153

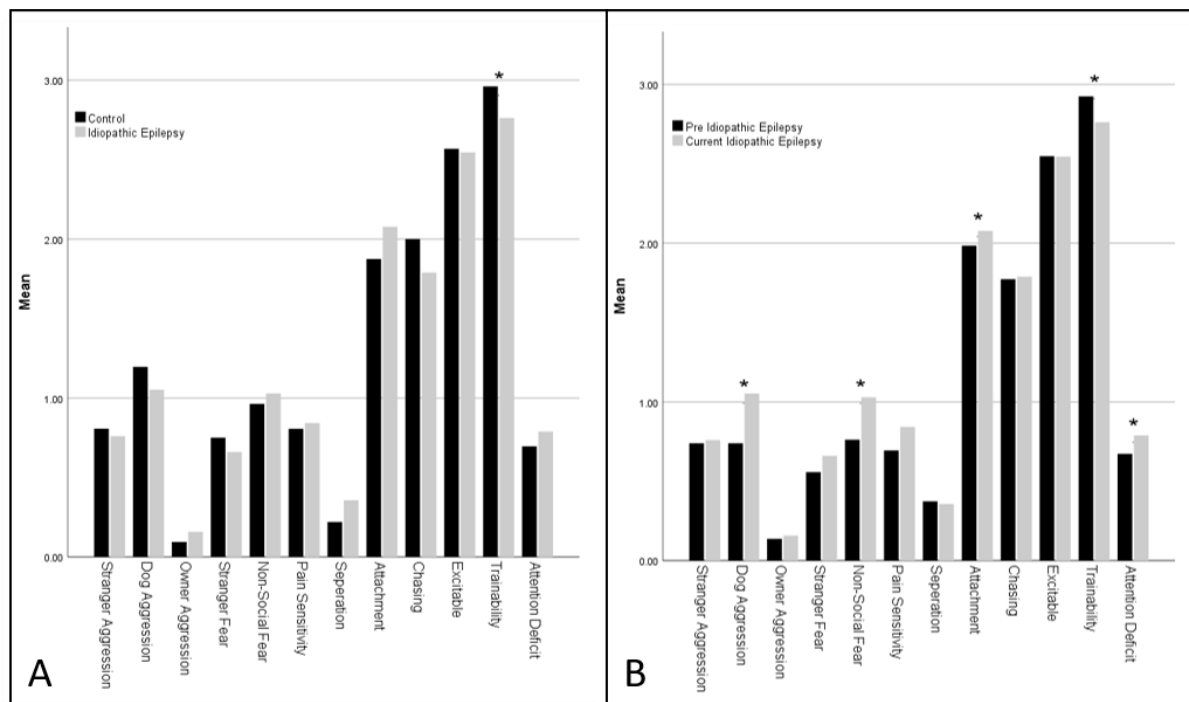
154 **Clare Rusbridge:** Employed by the University of Surrey and Fitzpatrick Referrals Ltd, Surrey,
155 GU7 2QQ. She has served as a paid consultant for Boehringer Ingelheim. The University of
156 Surrey and Fitzpatrick Referrals did not play a role in the study design, data collection and
157 analysis, decision to publish, or preparation of the manuscript and only provided financial
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159

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161 (2014–15; Investigating the effects of imepitoin on behavioural, physiologic and owner-
162 reported indicators of anxiety in dogs treated for idiopathic epilepsy) and Nestle (2017–19;
163 Dietary modification of epilepsy in dogs). Received competitive research grants from the
164 American Kennel Club (2016–18; Investigating the effect of a ketogenic medium chain
165 triglycerides supplement on the treatment of canine idiopathic epilepsy and its behavioural
166 comorbidities); BBSRC (2017–20; Investigating the relationship between epilepsy, drug-
167 resistance and affective disorders in the domestic dog; BB/P001874/1) and (2017–2020;
168 Comorbidity and characteristics of canine neurodevelopmental disorders and their impact
169 on animal welfare; BB/P 010881/1).

170

171 **Figure 1:** Mean score for each behavioural factor for dogs with IE and controls (A) and mean
172 score for each behavioural factor for dogs pre- and post-onset of IE (B). * = $p < 0.05$



173

174

175 **Table 1:** Mean scores for each behavioural factor across each group, value and FDR-

176 corrected p-value.

Behavior Factor	Control Mean (SD)	Current IE Mean (SD)	Z	p (FDR corrected)	Pre IE Mean (SD)	Current IE Mean (SD)	Z	p (FDR corrected)
Stranger Aggression	0.807 (0.871)	0.759 (0.898)	-1.175	0.240 (0.360)	0.654 (0.819)	0.783 (0.950)	-0.364	0.716 (0.859)
Dog Aggression	1.196 (1.143)	1.053 (1.220)	-1.568	0.117 (0.248)	0.700 (1.050)	1.112 (1.277)	-2.284	0.005 (0.020)*
Owner Aggression	0.095 (0.257)	0.158 (0.359)	-1.977	0.048 (0.180)	0.143 (0.351)	0.1308 (0.299)	-0.169	0.866 (0.945)
Stranger Fear	0.751 (0.956)	0.660 (0.945)	-0.840	0.401 (0.535)	0.479 (0.765)	0.664 (0.948)	-1.387	0.166 (0.285)
Non-Social Fear	0.963 (0.798)	1.029 (0.940)	-0.284	0.776 (0.847)	0.740 (0.792)	1.038 (0.887)	-3.380	0.001 (0.012)*
Pain Sensitivity	0.806 (0.886)	0.842 (0.949)	-0.423	0.672 (0.806)	0.652 (0.930)	0.805 (0.896)	-2.110	0.035 (0.070)
Separation	0.220 (0.453)	0.357 (0.660)	-1.539	0.124 (0.248)	0.351 (0.747)	0.357 (0.689)	-0.031	0.975 (0.975)
Attachment	1.875 (0.855)	2.078 (0.754)	-2.431	0.015 (0.090)	1.960 (0.852)	2.077 (0.788)	2.402	0.017 (0.048)*
Chasing	2.000 (1.012)	1.789 (1.106)	-1.881	0.060 (0.180)	0.784 (1.095)	1.856 (1.114)	0.749	0.455 (0.683)
Excitable	2.568 (1.001)	2.545 (1.011)	-0.174	0.862 (0.862)	2.588 (1.053)	2.595 (0.962)	0.379	0.705 (0.859)
Trainability	2.961 (0.537)	2.762 (0.636)	-2.932	0.003 (0.036)*	2.914 (0.731)	2.741 (0.657)	-2.821	0.005 (0.020)*
Attention	0.696 (0.414)	0.789 (0.513)	-1.350	0.177 (0.303)	0.675 (0.521)	0.806 (0.534)	-2.685	0.007 (0.021)*

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179

180

Current IE = behavioural score for dogs with idiopathic epilepsy at present

Pre IE = behavioural score for dogs with idiopathic epilepsy prior to the onset of seizure activity

* denotes a statistically significant result following false discovery rate (FDR) processing

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