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1 **A preliminary assessment of cognitive impairments in canine idiopathic epilepsy**

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9

10 **Abstract**

11

12 In humans, epilepsy can induce or accelerate cognitive impairment (CI). There is emerging
13 evidence of cognitive impairment in dogs with idiopathic epilepsy (IE) from recent
14 epidemiological studies. The aim of our study was to assess CI in dogs with IE using two tests
15 of cognitive dysfunction designed for use in a clinical setting. Dogs with IE (n=17) were
16 compared against controls (n=18) in their performance in two tasks; a spatial working memory
17 task and a problem-solving task. In addition, owners completed the Canine Cognitive
18 Dysfunction rating (CCDR) scale for their dog. The groups did not differ statistically with
19 respect to age and breed. Dogs with IE performed significantly worse than controls on the
20 spatial working memory task ($P=0.016$) but not on the problem solving task ($P=0.683$). CCDR
21 scores were significantly higher in the IE group ($P=0.016$), however no dogs reach the
22 recommended threshold score for CCD diagnosis. Our preliminary data suggests that dogs with
23 IE exhibit impairments in a spatial working memory task. Further research is required to
24 explore the effect of IE on other cognitive abilities in dogs with a larger sample, characterising
25 the age of onset, nature and progression of any impairments, and the impact of anti-epileptic
26 drugs.

27

28 **1.0 Introduction**

29

30 Idiopathic epilepsy (IE) is the most common chronic neurological disorder in humans
31 and dogs, with an estimated prevalence of 0.62% in the general UK canine population
32 (Kearsley-Fleet et al., 2013). Many similarities exist between human and canine epilepsy, with
33 dogs proposed as a model of human epilepsy (Potschka et al., 2013). Epilepsy in humans is
34 recognised to be associated with an increased risk of psychiatric disorders (Austin and Caplan,
35 2007; Tellez-Zenteno, 2007) and cognitive impairment (Elger, 2004; Breuer et al., 2016). In
36 canine IE, behavioural changes such as ADHD-like behaviour (Jokinen et al., 2015; Packer et
37 al., 2016), increased fear, anxiety, abnormal perception and demented behaviour have been
38 documented (Shihab, Bowen and Volk, 2011) and there is emerging evidence of co-morbid
39 cognitive impairments (Packer, 2017; Packer, In Press).

40

41 Epilepsy is known to induce or exacerbate underlying cognitive impairments in people
42 (Motamedi, 2003), with recent studies indicating that approximately half of newly diagnosed
43 children or adults with epilepsy have demonstrable cognitive or behavioural difficulties
44 (Taylor, 2010; Witt, 2012; Witt, 2014). One key area of cognition, working memory, has been
45 found to be impaired in human epilepsy studies. Working memory deficits have been observed
46 in several epilepsy syndromes including Juvenile Myoclonic Epilepsy, Benign Childhood
47 Epilepsy with Centro-Temporal Spikes and Temporal Lobe Epilepsy (TLE) (Hommet et al.,
48 2006). Rodent models of TLE display deficits in spatial working memory with inferior
49 performance in the Morris Water Maze task (Anisman and McIntyre, 2002; Szyndler et al.,
50 2006). Tasks have been devised in canine behaviour science to test spatial working memory,
51 which is impaired in dogs with age-related cognitive dysfunction (Gonzalez-Martinez et al.,
52 2013).

53

54 The aim of our study was to investigate whether dogs with IE exhibit signs of cognitive
55 impairment in two tasks designed to assess spatial working memory and problem solving
56 ability.

57

58 **2.0 Materials and Methods**

59

60 **2.1 Animals**

61 The effects of canine IE on spatial working memory and problem-solving ability was
62 investigated in a cohort of dogs with IE and controls recruited from the Royal Veterinary
63 College (RVC) Small Animal Referral Hospital, general veterinary practices and social media.
64 Inclusion criteria for the IE group followed International Veterinary Epilepsy Task Force tier I
65 guidelines (De Risio, 2015). These are; (i) A history of two or more seizures, occurring at least
66 24 hours apart (ii) Age of seizure onset between 6 months and 6 years of age (iii) Unremarkable
67 inter-ictal physical and neurological exam [except for anti-epileptic drug (AED) induced
68 abnormalities] (iv) No clinically significant abnormalities on minimum-database blood and
69 urine tests.

70

71 The inclusion criteria for the control group were (i) No primary organ system failure,
72 severe vision or mobility deficits; (ii) No history of seizure(s); (iii) No diagnosed neurological
73 disorder. Control dogs were matched by breed and age to the IE cohort as closely as possible
74 (see supplementary table 1 for full demographic details of both groups); the two groups did not
75 differ statistically with respect to age and breed. The study was given ethical approval by the
76 RVC welfare and ethics committee (2016-U175).

77

78 **2.2 Epilepsy specific data**

79 Once each dog with IE had met the inclusion criteria, all owners of dogs with IE were
80 asked to provide information on their dogs' current AED therapy such as the date it commenced
81 and drugs used, how many seizures per month on average their dog experienced preceding the
82 most recent treatment alteration (defined as addition of an AED) and the same information
83 since after this date. From this information, we determined whether the dogs had shown a
84 complete response to medication (seizure freedom), a partial response (>50% reduction in
85 seizure frequency) or no response (<50% reduction in seizure frequency). Other information
86 gathered included duration of IE, whether or not there was a history of cluster seizures or status
87 epilepticus, and estimated total number of seizures.

88

89 **2.3 Testing procedure**

90 Several methods have been investigated for assessing spatial working memory and
91 problem solving ability in dogs (Gonzalez-Martinez et al., 2013). Two cognition tasks validated
92 by Gonzalez-Martinez et al (2013) in a study of cognitive dysfunction were chosen for their
93 speed and ease of performance in a clinical setting, with no requirement for prior training or
94 special equipment. Task one was designed to assess spatial working memory, whilst task two
95 aimed to assess problem solving ability.

96

97 **2.3.1 Task 1: Spatial working memory**

98 The food searching task aims to test the dog's spatial working memory, assessing
99 ability to search and find a food reward (ham), the location of which had previously been
100 indicated to them through vocalisation and pointing to the reward. The tasks begins with the
101 handler holding the dog in the centre of the room on a leash. The tester stood in front of the
102 dog, showed it the reward (a small piece of ham) and moved backwards, shaking the hand

103 containing reward whilst maintaining visual contact and repeatedly saying the dogs name in a
104 positive tone. The food was placed in one corner of the room which alternated for each of the
105 three repeats (Figure 1). Once there, the tester pointed at the food for 2 seconds, ensuring the
106 dog's attention through calling their name. The handler then led the dog out of the room for
107 15 seconds. After 15 seconds the dog was reintroduced into a fixed position at the centre of
108 the room, the leash removed and the dog allowed to explore the room for 1 minute. During
109 the minute, tester and dog handler stood to the side, ensuring no communication with the dog
110 (no verbal/physical cues or eye contact). Each repeat ended when the food was found or after
111 1 minute if the reward was not found.

112

113 **2.3.2 Task 2: Problem solving**

114 The problem solving task aims to test the dog's problem solving ability to access a
115 hidden food reward. To access the food, the dog must manipulate an object (a transparent
116 plastic box) that acts as a barrier to the reward. To begin the task, the tester showed the dog
117 the reward (three pieces of ham), allowing the dog to lick and sniff the hand containing the
118 reward to ensure they were aware of it. The reward was placed on the floor and covered with
119 a transparent plastic box. The dog was given two minutes to attempt to gain access to and
120 consume the reward, during which, the handler could encourage the dog to find the food and
121 point towards the box. This task was repeated three times.

122

123 **2.3.3 Modifications to tasks**

124 Slight modifications were made to the tasks from the original published protocol;

125 (i) Each task was repeated three times to improve reliability, with a median score given for
126 overall performance across all trials.

127 (ii) For Task 1, the location of the reward was altered for each repeat to reduce learning effects

128 of the reward location.

129 Alterations were also made to the scoring system published by Gonzalez-Martinez et al. (2013):

130 (i) The scoring system was altered for Task 1; dogs were not given two further attempts for
131 each repeat (thus scoring out of 12 for each repeat) if they failed to find the food reward
132 within one minute and instead had one attempt at each repeat, scored out of 4.

133

134 The Task 1 scoring system was as follows:

135 1= Goes directly towards the food,

136 2= Finds the food within 1 minute,

137 3= Searches for the food without finding it within 1 minute,

138 4= Makes no attempt to search for the food.

139 The Task 2 scoring system was as follows:

140 1= Obtains all food within maximum of 2 minutes,

141 2= Tries to get food but does not obtain all of it within maximum of 2 minutes,

142 3= Sniffs the box but does not try to get the food,

143 4= Makes no attempt to get the food.

144

145 The tasks were performed in a controlled environment with no external distractions
146 (blinds closed, in a quiet area) and without the owner present. The investigator was the same
147 for each dog (JW).

148

149 **2.4 Questionnaire**

150 All owners completed a questionnaire; the canine cognitive dysfunction rating scale
151 (CCDR). This is a psychometrically validated tool that quantifies the frequency and
152 progression of thirteen behaviours which, when abnormal, fit with veterinary diagnoses of

153 canine dementia almost 80% of the time (Salvin et al., 2011). The CCDR focuses on problems
154 related to memory, orientation, apathy, impaired olfaction and locomotion. Questions are
155 included in Supplementary table 2, with dogs receiving an overall score out of 80. The
156 diagnostic threshold for CCD is set at ≥ 50 .

157

158 **2.5 Statistical Analysis**

159

160 Live scoring data for task 1 and 2 were collated in Microsoft Excel and transferred to
161 IBM SPSS v23 for statistical analysis. Each dog received an overall median score for their
162 performance in task 1 and task 2. Dogs in the IE group were separated into those exhibiting a
163 partial AED response (>50% reduction in seizures) and no response. Partial AED response
164 was selected over complete AED response (seizure freedom) as only 2/15 dogs in the IE
165 group were seizure free. Six dogs (E16 and E17 and C15, C16, C17 and C18) were too
166 anxious to perform the tasks (e.g. scratching at the door, vocalising, uninterested in the food
167 reward) so were excluded from the analyses. Dog E15 could perform task 2 but not task 1 due
168 to severe ataxia and lethargy (AED side effects), thus was excluded from task 1 analysis.
169 Overall median score for both tasks and CCDR scores were compared between groups and
170 between partial responders/ non responders with a Mann Whitney U test. Age was compared
171 between groups with an independent samples t-test. A Friedman test was used to assess the
172 presence of a learning effect between repeats for task 1 and 2. Where medians are reported,
173 they are in the format: (Median [25th percentile- 75th percentile]).

174

175 **3.0 Results**

176

177 A total of 35 dogs were recruited into the study; 17 with IE and 18 controls (see
178 supplementary table 2) with 14 IE and 14 controls featuring in task 1 analysis, and 15 IE and
179 14 controls featuring in task 2 analysis. Within the IE group, nine dogs were considered partial
180 AED responders and five non-responders, with one dog drug naive. The mean age of the control
181 group was 63 months (standard deviation: 28) and the IE group 60 months (standard deviation:
182 25). An independent samples t-test revealed no significant age difference between groups.

183

184 A Mann-Whitney U test found a significant difference (MU=46.0, $P=0.016$,) between
185 groups for performance (median score of the 3 repeats) in Task 1 (IE: 2 [1-2] versus controls:
186 1 [1-1], figure 2), but not for Task 2 (MU=95.0, $P=0.683$) (IE: 1 [1-2] versus controls: 1 [1-2]
187 (Table 1). CCDR scores differed significantly between groups (MU= 50.5, $P=0.016$) (median
188 score for IE group: 35 [34-38] versus controls: 34 [34-34], figure 3) and no dogs achieved a
189 score of 50 or higher, the threshold for CCD diagnosis using this tool (Salvin et al 2011).

190

191 A Friedman test revealed no significant difference between repeats for the IE group in
192 task 1 ($P=0.08$, median for IE group: repeat 1; 2 [1.75-3.25], repeat 2; 2 [1-2]. Repeat 3; 2 [1-
193 2]) or 2 ($P=0.81$, median for IE group: repeat 1; 1 [1-2]. Repeat 2; 1 [1-2]. Repeat 3; 1 [1-2]).

194

195 Within the group with IE, there was no significant difference in task 1 ($P=0.524$), 2
196 ($P=0.606$) or CCDR score ($P=0.699$) between dogs that were partial drug responders (n=9) and
197 those that were not (n=5).

198

199 Post-hoc power analyses were conducted for both tasks. For task 1 (comparing 2 groups
200 in a 2-sided test) a power of 0.76 was detected at a type I error rate of 5%; for task 2 a power
201 of 0.08 was detected at a type I error rate of 5%.

202 4.0 Discussion

203

204 Our Task 1 findings, in combination with data from studies of humans with epilepsy
205 and rodent models of epilepsy, suggest that dogs with IE may also display spatial working
206 memory deficits. The majority of dogs in the IE group (13/14) made attempts to search for the
207 food reward when re-introduced to the testing area, but did not go directly towards it when let
208 off leash. This may indicate that the majority of dogs remembered the presence of a food
209 reward in the testing area, but not its precise location. This may suggest that impairment is
210 greater in spatial orientation than working memory; indeed, in a study in children with epilepsy
211 of genetic origin, children performed worse in a spatial orientation task but had no working
212 memory deficits, though this must be interpreted with caution due to the small sample size and
213 demographic studied (n=10 8-9 year old boys with genetic generalised epilepsy) (Cimadevilla
214 et al., 2014). Although the hippocampal system is well-known to be involved in memory and
215 spatial learning functions, egocentric (body-centred) spatial representations are modulated by
216 extratemporal regions such as the parietal cortices and subcortical regions (Burgess, 2001).
217 Human studies have identified that patients with temporal lobe epilepsy demonstrate strong
218 egocentric memory impairments in a virtual maze task (Weniger, 2012). In the same study,
219 smaller volumes of the left-sided postcentral gyrus were related to worse task performance,
220 which may indicate parietal cortex damage. As brain imaging was not available for the dogs in
221 this study, future work should explore the relationship between cognitive function and
222 volumetric analysis of relevant brain regions.

223

224 Four (29%) of the epilepsy group scored 1 (the best possible score) on task 1, suggesting
225 that not all dogs with IE display cognitive impairment on this task. Canine epilepsy phenotypes
226 are heterogeneous, and cognitive impairment may vary based on a number of clinical factors

227 (e.g. seizure frequency, severity, type, and age of onset) (Breuer et al., 2016). This may also
228 explain the increased variability in performance observed in the IE group compared with the
229 control group. Due to the relatively small sample size of this preliminary study, within group
230 effects cannot be fully analysed in this study population, but future larger scale studies should
231 investigate the impact of clinical and treatment based factors.

232

233 A limitation of this study is the lack of drug naïve dogs in the IE group; further studies
234 require a more balanced sample of drug naïve to AED treated dogs to examine individual AED
235 effects. In human medicine, the cognitive effects of AEDs are mixed (Breuer et al., 2016), but
236 dose-dependent negative effects of AEDs on cognitive functioning have been documented.
237 with maximal impairments seen in patients receiving polytherapy (Trimble, 1987).
238 Polyphagia is a common AED side effect in dogs with IE, associated with both first and
239 second-line AEDs including phenobarbital, imepitoïn and potassium bromide
240 (Charalambous, 2016). It is possible that polyphagia may have affected the results of these
241 tasks by increasing food motivation in some AED-treated dogs, and potentially increasing
242 their persistence in attempting to access the food rewards. As such, polyphagia is more likely
243 to enhance rather than inhibit performance in these tasks, which would not explain the poorer
244 results seen in dogs with IE compared to controls presented here. As previously noted, one
245 dog was unable to perform in the tasks due to the AED side effects ataxia and lethargy. This
246 was especially evident in Task 1 which requires a degree of agility to move in and out of the
247 room. As AED side effects are often most pronounced in the first two weeks of therapy,
248 assessing cognition in dogs with IE once they are on a stable dose is likely to yield more
249 reliable results, and for future studies, side effect screening before testing is advocated. In
250 addition, developing cognitive tasks that require limited physical abilities would allow their
251 application to a wider group of animals. Four of the control group and two of the IE group

252 were unable to perform the tasks due to high levels of anxiety, thus reducing the utility of these
253 tasks to assess cognition in anxious dogs. Dogs with IE have been shown to display increased
254 anxiety behaviours following the onset of epilepsy (Shihab, Bowen and Volk, 2011) and so
255 this may negatively affect how useful these tasks are to measure cognitive abilities in dogs with
256 IE. It should be noted that both tasks were performed without the owner present to improve
257 consistency of the handler. Separation anxiety is a common finding in the general population
258 of dogs without IE, and in a previous longitudinal study of Labrador Retrievers and Border
259 Collies, over 50% of dogs had displayed signs of separation anxiety by 18 months of age
260 (Bradshaw, 2002). In future studies, owner involvement and other anxiety-reducing methods
261 (e.g. extended habituation to the experimenter and the testing arena) may improve anxious
262 dogs' ability to perform the tasks.

263

264 The testing used in this study was easily conducted in a non-specialised testing
265 environment, and could be deployed in a clinical environment where sufficient floor space is
266 available and distractions are minimised (e.g. the presence of other animals, food sources or
267 strong scents). A key advantage of these tests of cognitive impairment over more extensive
268 testing (e.g. delayed non-matching to position tasks) are that no prior training of the dog is
269 required, and could be conducted by veterinary staff acting as the tester, and the owner as the
270 handler. Despite these advantages, modifications of these tasks may be required to improve
271 their validity and reliability, Our Task 2 findings may suggest that problem solving ability is
272 not affected by IE, however, dogs from both groups failed to access the food reward (IE: 6/15,
273 Control: 4/14). During testing, it was also noted that the transparent plastic box holding the
274 food reward could be easily flipped allowing access to the reward if the dog sniffed with enough
275 force, rather than the container being manipulated with a paw. This may indicate that the task
276 is not a valid means of assessing problem solving ability in dogs, and that amendments are

277 needed to the procedure (e.g. heavier container that cannot be accidentally flipped, or a
278 container weighted relatively to the size of the dog) and/or the scoring system (e.g. measure
279 time to food reward acquisition or means of acquiring reward) to improve this tasks' ability to
280 measure cognitive abilities. From a post-hoc power analysis for task two, this element of the
281 study was underpowered. In the control group, greater variation in performance was seen in
282 task to compared to task one, and as such a large sample size would be required to detect a
283 significant difference between these groups. This task requires further modifications to both
284 the protocol and scoring system (as suggested above), along with an increased sample size to
285 further understand this result.

286

287 The CCDR scores differed between groups, with IE dogs scoring higher than controls,
288 but no dog meeting the threshold for diagnosis of CCD ($CCDR \geq 50$). In combination with the
289 results of Task 1, this suggests that dogs with IE are cognitively impaired when compared to
290 control dogs of a similar age and breed. The fact that no dog met the threshold for diagnosis
291 suggests that the cognitive impairments seen are not as great as those observed in clinical cases
292 of age-related cognitive dysfunction, or differ in their presentation.

293

294 Further study is required to further our understanding of cognitive impairments and
295 their underlying pathology in canine IE. Our group have recently conducted extensive
296 epidemiological studies of cognitive impairment in dogs with epilepsy compared to controls
297 (n= 4051 dogs, of which n=286 meet IVETF tier 1 criteria for epilepsy diagnosis). Using two
298 metrics of canine cognition, a validated 'trainability' score (Packer, In Press) and the canine
299 cognitive dysfunction rating scale (Packer, 2017), dogs with IE exhibited poorer trainability
300 and a greater cognitive dysfunction score than controls. Within the epilepsy sup-population,
301 dogs treated with polytherapy (2 or more AEDs), potassium bromide and/or zonisamide

302 exhibited significantly lower trainability scores (Packer, In Press), and dogs with a history of
303 cluster seizures and a higher seizure frequency exhibited significantly higher CCDR scores
304 (Packer, 2017). The preliminary results of the present study combined with these findings add
305 strength to the argument that, as in people with epilepsy, dogs with naturally occurring IE are
306 also affected by impaired cognition.

307

308 In conclusion, this preliminary study suggests that dogs with IE have a significantly
309 reduced performance in a working spatial memory task compared with breed matched controls,
310 but not in a problem solving task. Although cognitive impairment may not present a direct
311 negative effect upon canine welfare, the trainability of a companion dog is considered
312 important in maintaining a positive dog-owner relationship, and avoiding relationship
313 breakdowns that may result in relinquishment {Salman, 2000 #225}. As such, identifying areas
314 of cognitive compromise associated with chronic disease is of importance in companion
315 animal. Further study utilising a larger study population and tasks exploring other areas of
316 cognition are required to confirm the presence and nature of cognitive deficits associated with
317 epilepsy and its treatment in the dog.

318

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320

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324

325

326 **References**

- 327 Anisman, H. and McIntyre, D. C. (2002) 'Conceptual, spatial, and cue learning in the Morris
328 water maze in fast or slow kindling rats: attention deficit comorbidity', *Journal of*
329 *Neuroscience*, 22(17), pp. 7809–7817.
- 330 Austin, J. K. and Caplan, R. (2007) 'Behavioral and Psychiatric Comorbidities in Pediatric
331 Epilepsy : Toward an Integrative Model', *Epilepsia*, 48(9), pp. 1639–1651.
- 332 Bradshaw, J. W., Mcpherson, J. A., Casey, R. A. & Larter, I. S. (2002) Aetiology of separation-
333 related behaviour in domestic dogs. *Vet Record* 151, 43-46.
- 334 Breuer, L. E. M., Boon, P., Bergmans, J. W. M., Mess, W. H., Besseling, R. M. H., Louw, A.
335 De, Tjihuis, A. G., Zinger, S., Bernas, A. and Klooster, D. C. W. (2016) 'Neuroscience and
336 Biobehavioral Reviews Cognitive deterioration in adult epilepsy : Does accelerated cognitive
337 ageing exist ?', *Neuroscience and Biobehavioral Reviews*. Elsevier Ltd, 64, pp. 1–11.
- 338 Burgess, N., Maguire, E. A., Spiers, H. J. & O'keefe, J. (2001) A Temporoparietal and
339 Prefrontal Network for Retrieving the Spatial Context of Lifelike Events. *NeuroImage* 14, 439-
340 453
- 341 Charalambous, M., Shivapour, S. K., Brodbelt, D. C. & Volk, H. A. (2016) Antiepileptic
342 drugs' tolerability and safety – a systematic review and meta-analysis of adverse effects in
343 dogs. *BMC Veterinary Research* 12, 79
- 344 Cimadevilla, J. M., Lizana, J. R., Roldán, M. D., Cánovas, R. and Rodríguez, E. (2014) 'Spatial
345 memory alterations in children with epilepsy of genetic origin or unknown cause', *Epileptic*
346 *Disorders*, 16(2), pp. 203–207.
- 347 De Risio, L. (2015) 'International veterinary epilepsy task force consensus proposal: diagnostic
348 approach to epilepsy in dogs', *BMC veterinary research*. *BMC Veterinary Research*, 11, p. 148.
- 349 Elger, C. E., Helmstaedter, C. & Kurthen, M. (2004) Chronic epilepsy and cognition. *The*
350 *Lancet Neurology* 3, 663-672
- 351 Gonzalez-Martinez, A., Rosado, B., Pesini, P., Garcia-Belenguer, S., Palacio, J., Villegas, A.,
352 Su??rez, M. L., Santamarina, G. and Sarasa, M. (2013) 'Effect of age and severity of cognitive
353 dysfunction on two simple tasks in pet dogs', *Veterinary Journal*, 198(1), pp. 176–181.
- 354 Hommet, C., Sauerwein, H. C., Toffol, B. De and Lassonde, M. (2006) 'Idiopathic epileptic
355 syndromes and cognition', 30, pp. 85–96.
- 356 Jokinen, T. S., Tiira, K., Metsahonkala, L., Seppala, E. H., Hielm-Bjorkman, A., Lohi, H. and
357 Laitinen-Vapaavuori, O. (2015) 'Behavioral abnormalities in Lagotto Romagnolo dogs with a
358 history of benign familial juvenile epilepsy: A long-term follow-up study', *Journal of*
359 *Veterinary Internal Medicine*, 29(4), pp. 1081–1087.
- 360 Kearsley-Fleet, L., Neill, D. G. O., Volk, H. A., Church, D. B. and Brodbelt, D. C. (2013)
361 'Paper Prevalence and risk factors for canine epilepsy of unknown origin in the UK', *The*
362 *Veterinary Record*, 172, p. 13.

- 363 Motamedi, G. & Meador, K. (2003) Epilepsy and cognition. *Epilepsy & Behavior* 4,
364 Supplement 2, 25-38
- 365 Packer, R. M. A., Law, T. H., Davies, E., Zanghi, B., Pan, Y. and Volk, H. A. (2016) 'Effects
366 of a ketogenic diet on ADHD-like behavior in dogs with idiopathic epilepsy', *Epilepsy and*
367 *Behavior*. Elsevier Inc., 55, pp. 62–68.
- 368 Packer, R.M.A., McGreevy, P., Pergande, A. & Volk, H. (In Press) Negative effects of epilepsy
369 and anti-epileptic drugs on the trainability of dogs with naturally occurring idiopathic epilepsy.
370 *Applied Animal Behaviour Science*.
- 371 Packer, R.M.A., McGreevy, P., Salvin, H., Valenzuela, M. & Volk, H. (2017) Increased
372 prevalence of canine cognitive dysfunction in dogs with epilepsy. In *The 30th ESVN-ECVN*
373 *Annual Symposium*. Helsinki, Finland.
- 374 Potschka, H., Fischer, A., Von Rüden, E. L., Hülsmeier, V. and Baumgärtner, W. (2013)
375 'Canine epilepsy as a translational model?', *Epilepsia*, 54(4), pp. 571–579.
- 376 Salman, M. D., Hutchison, J., Ruch-Gallie, R., Kogan, L., New, J. C., Kass, P. H. & Scarlett,
377 J. M. (2000) Behavioral Reasons for Relinquishment of Dogs and Cats to 12 Shelters. *Journal*
378 *of Applied Animal Welfare Science* 3, 93-106
- 379 Salvin, H. E., McGreevy, P. D., Sachdev, P. S. and Valenzuela, M. J. (2011) 'The canine
380 cognitive dysfunction rating scale (CCDR): A data-driven and ecologically relevant assessment
381 tool', *Veterinary Journal*. Elsevier Ltd, 188(3), pp. 331–336.
- 382 Shihab, N., Bowen, J. and Volk, H. A. (2011) 'Behavioral changes in dogs associated with the
383 development of idiopathic epilepsy', *Epilepsy and Behavior*, 21(2), pp. 160–167.
- 384 Szyndler, J., Piechal, A., Blecharz-Klin, K., Skórzewska, A., Maciejak, P., Walkowiak, J.,
385 Turzyńska, D., Bidziński, A., Płaźnik, A. and Widy-Tyszkiewicz, E. (2006) 'Effect of kindled
386 seizures on rat behavior in water Morris maze test and amino acid concentrations in brain
387 structures', *Pharmacological Reports*, 58(1), pp. 75–82.
- 388 Taylor, J., Kolamunnage-Dona, R., Marson, A. G., Smith, P. E. M., Aldenkamp, A. P., Baker,
389 G. A. (2010) Patients with epilepsy: Cognitively compromised before the start of antiepileptic
390 drug treatment? *Epilepsia* 51, 48-56
- 391 Tellez-Zenteno, J. F., Patten, S. B., Jetté, N., Williams, J. & Wiebe, S. (2007) Psychiatric
392 Comorbidity in Epilepsy: A Population-Based Analysis. *Epilepsia* 48, 2336-2344
- 393 Trimble, M. R. (1987) Anticonvulsant Drugs and Cognitive Function: A Review of the
394 Literature. *Epilepsia* 28, S37-S45
- 395 Weniger, G., Ruhleder, M., Lange, C. & Irle, E. (2012) Impaired egocentric memory and
396 reduced somatosensory cortex size in temporal lobe epilepsy with hippocampal sclerosis.
397 *Behavioural Brain Research* 227, 116-124
- 398 Witt, J. & Helmstaedter, C. (2012) Should cognition be screened in new-onset epilepsies? A
399 study in 247 untreated patients. *J Neurol Neurosurg Psychiatry* 259, 1727

400 Witt, J. A., Werhahn, K. J., Krämer, G., Ruckes, C., Trinka, E. & Helmstaedter, C. (2014)
401 Cognitive-behavioral screening in elderly patients with new-onset epilepsy before treatment.
402 *Acta Neurologica Scandinavica* 130, 172-177

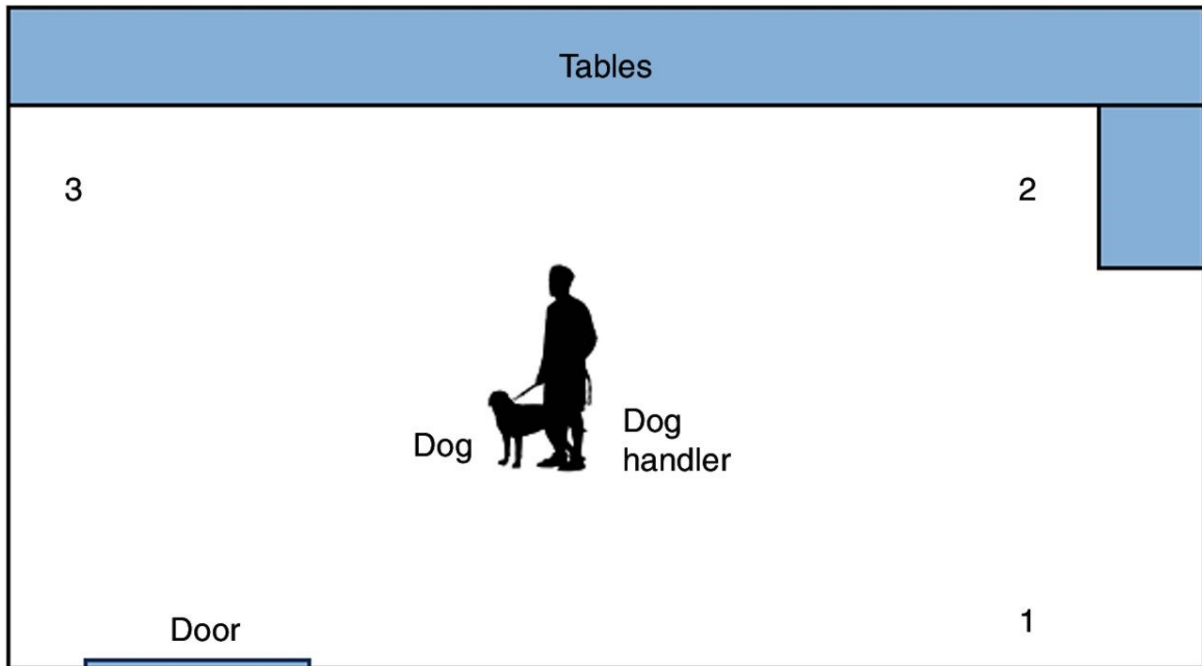
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405 **Figure legends**

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407 **Figure 1: Diagram of the study room and locations of dog, owner and rewards during**
408 **the tasks.** Room dimensions: 6.5m x 5.5m. 1,2,3 denote food reward placement for task 1 on
409 the 1st, 2nd and 3rd repeats respectively.

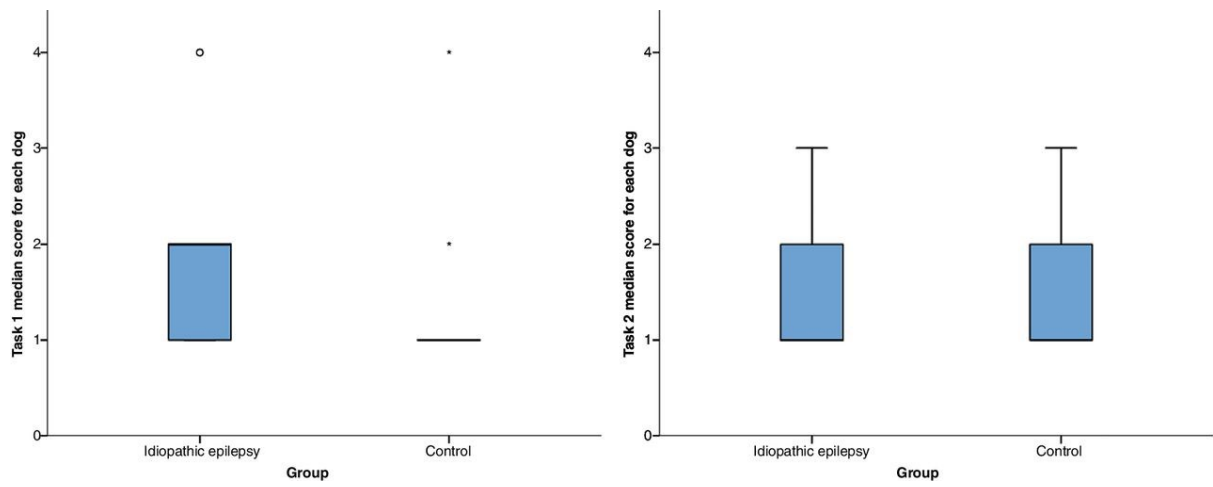


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413 **Figure 2: Box and whisker diagrams of the median overall scores for each dog in each**
414 **group for task 1 ($P=0.016$) and task 2 ($P=0.683$).**

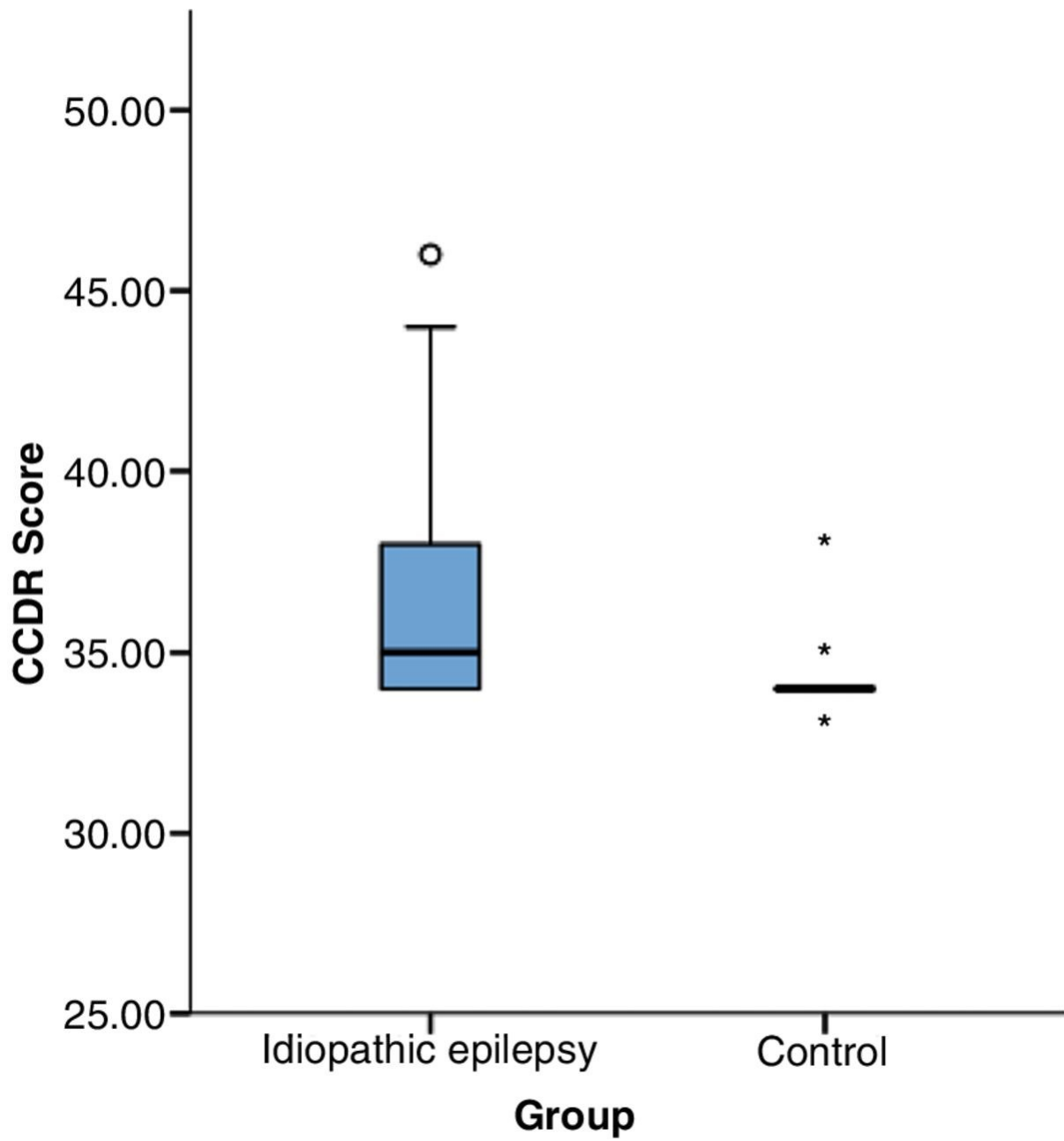


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418 **Figure 3: A box and whisker diagram showing the distribution of CCDR scores**
419 **(P=0.016) within the IE group and the control group.**



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423 **Table legends**

424 **Table 1: Differences in task performance and cognitive dysfunction rating scale between**

425 **the group with idiopathic epilepsy and control dogs**

426

	Idiopathic epilepsy group		Control group (n=14)	<i>P</i> value
	Median score [25 th & 75 th percentiles]	Number of dogs	Median score [25 th & 75 th percentiles]	
Task 1	2 [1-2]	14	1 [1-1]	<i>P</i> = 0.009
Task 2	1 [1-2]	15	1 [1-2]	<i>P</i> = 0.683
CCDR	35 [34-38]	15	34 [34-34]	<i>P</i> = 0.016

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