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# A preliminary assessment of cognitive impairments in canine idiopathic epilepsy

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**Abstract**

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

## 1.0 Introduction

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

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

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

## 2.0 Materials and Methods

### 2.1 Animals

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

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

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

of the reward location.

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

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

The Task 1 scoring system was as follows:

1= Goes directly towards the food,

2= Finds the food within 1 minute,

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

4= Makes no attempt to search for the food.

The Task 2 scoring system was as follows:

1= Obtains all food within maximum of 2 minutes,

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

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

4= Makes no attempt to get the food.

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

**2.4 Questionnaire**

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

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

**2.5 Statistical Analysis**

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

**3.0 Results**

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

A Mann-Whitney U test found a significant difference (MU=46.0, *P*=0.016,) between groups for performance (median score of the 3 repeats) in Task 1 (IE: 2 [1-2] versus controls: 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] (Table 1). CCDR scores differed significantly between groups (MU= 50.5, *P*=0.016) (median score for IE group: 35 [34-38] versus controls: 34 [34-34], figure 3) and no dogs achieved a score of 50 or higher, the threshold for CCD diagnosis using this tool (Salvin et al 2011).

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

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

Post-hoc power analyses were conducted for both tasks. For task 1 (comparing 2 groups 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 of 0.08 was detected at a type I error rate of 5%.

## 4.0 Discussion

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

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

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

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

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

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

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

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

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**Figure legends**

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

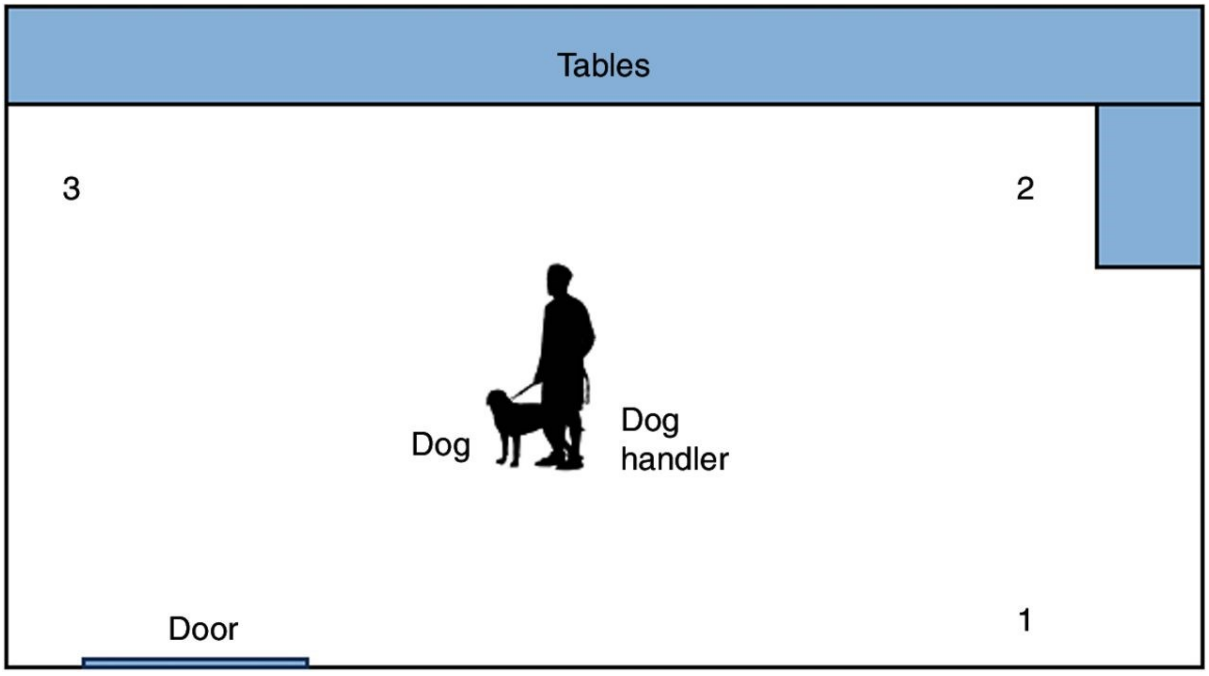

**Figure 2**: **Box and whisker diagrams of the median overall scores for each dog in each group for task 1 (*P*=0.016) and task 2 (*P*=0.683).**

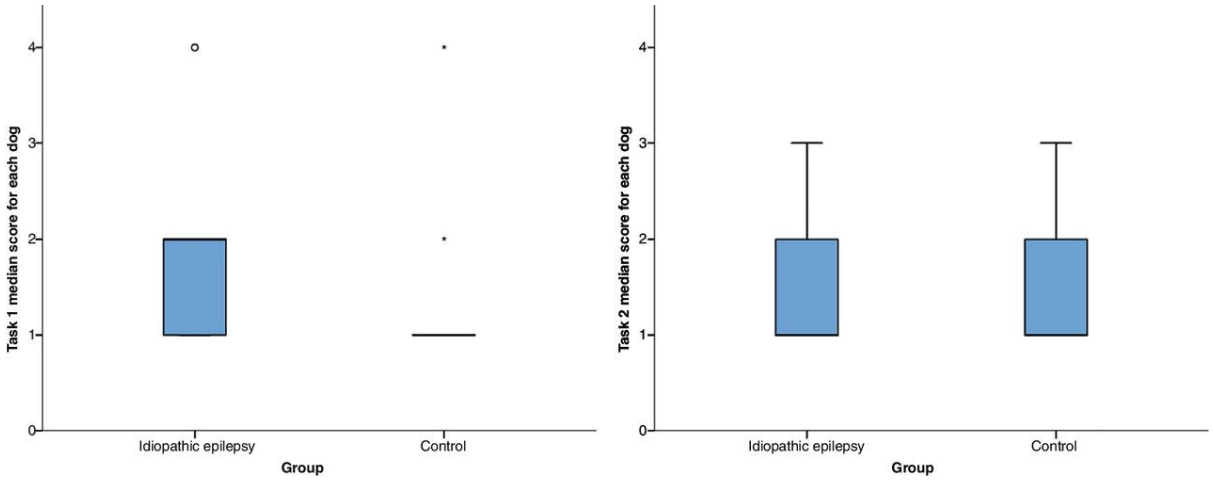

**Figure 3: A box and whisker diagram showing the distribution of CCDR scores (P=0.016) within the IE group and the control group.**

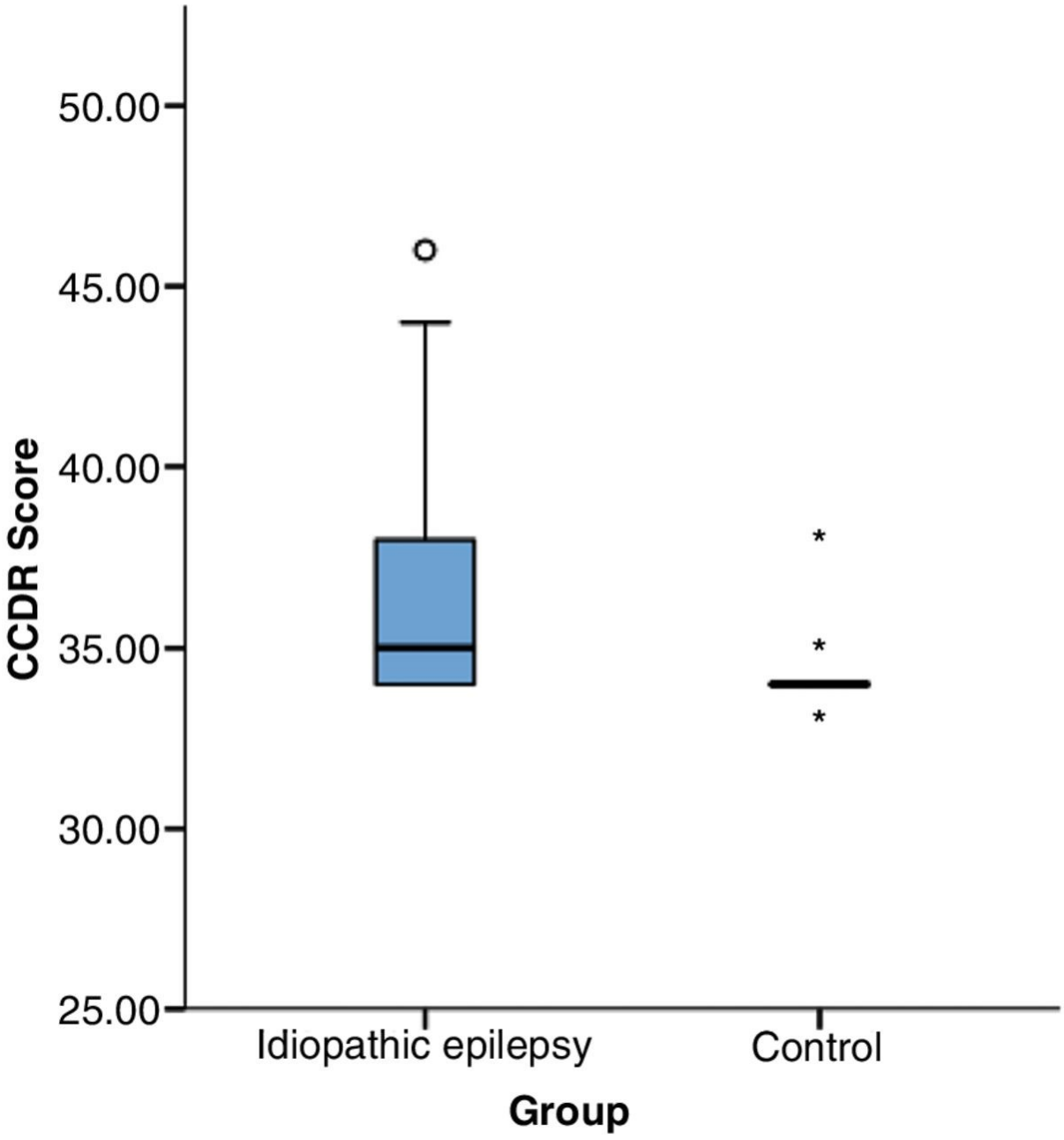

**Table legends**

**Table 1: Differences in task performance and cognitive dysfunction rating scale between the group with idiopathic epilepsy and control dogs**

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