

# **The link between neurology and behavior in veterinary medicine: a review.**

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## **Abstract**

In veterinary behavioral medicine and in veterinary neurology, there is an effort to collaborate with different consultants, as seen both in human psychiatry and in human neurology. This cooperation can lead to a complete assessment of any case, to a more holistic collection of information regarding the development of the case, and to a synergetic vision regarding the therapy. In other words, it is essential to understand how behavioral medicine and neurology are linked together to improve diagnosis and therapy process. This review emphasizes the bond between neurology and behavior starting with the neuroanatomic basis of anomalies in veterinary behavioral medicine such as: limbic system, temporal and frontal lobe, pituitary gland, spinal cord, meninges and peripheral nerves. After that, the review deals with some disorders which overlap between neurology and behavior and it will conclude by analyzing the differential diagnoses of the neurological diseases and their relationship with behavioral signs.

Keywords: neurological diseases; behavior problems; dogs; cats

## **Introduction**

The link between neurology and behavior is well recognized in human medicine (Carls et al., 2020; Haut et al., 2019; Thorpy and Krieger, 2014). Similarly, for more than 20 years this joint approach has been recommended by veterinarian specialists, and at the moment the need for this collaboration is well recognized also in veterinary medicine (Landsberg, 2013, Overall, 2013, Horwitz, 2015). This awareness usually leads to a better management of single clinical cases, whilst it has not led yet to a data collection that is standardized and connected to databases, as it occurs for human psychiatrists and neurologists; any effort by veterinarian boarded specialists to collect standardized and accessible data should be encouraged and supported for the potential benefits.. Fatjó and Bowen, (2020) proposed a multi-axis assessment of behavioral problems, aligned with the current research approach in human

35 psychiatry that avoids some of the limitations of classification systems. This model supports the  
36 clinician in making a complete and exhaustive assessment of a case by collecting and organizing  
37 information about all the factors that contribute to behavioral and mental health problems in companion  
38 animals. This cooperation is desirable, as it could improve diagnosis and therapy of different diseases  
39 such as epilepsy, narcolepsy, chronic pain/neuropathic pain (Berendt et al., 2004; Berk et al., 2019;  
40 Erath et al., 2020; Gulyani et al., 2002; Lascelles et al., 2019; Levitin et al., 2019; Mills et al., 2020;  
41 Packer et al., 2017; Packer and Volk, 2015; Shihab et al., 2011).

42

43 For epilepsy, numerous studies in humans have led to the hypothesis that common pathogenic  
44 mechanistic pathways might exist between epilepsy and mood dysfunction. In the pathophysiology of  
45 both epilepsy and emotional disorders the role of altered neurosteroids levels, GABAergic and  
46 glutaminergic neurotransmitter disturbance or abnormalities in serotonergic, noradrenergic, and  
47 dopamine transmission has been proposed (Biagini et al., 2010; Frye, 2009; Kanner et al., 2012;  
48 Richerson and Buchanan, 2011). **Reactive astrocytes are also involved in these disorders.**  
49 **Astrocytes play a crucial role for the neuronal homeostasis, neurotransmitter uptake and immune**  
50 **response (Dong and Benveniste, 2001; Ranson, 2003; Chung et al., 2015). Changing in astrocytes,**  
51 **as a consequence to a variety of insults to brain tissue, consist not only of morphological**  
52 **alterations but also of functional changes (Pekny and Pekna, 2014; Hubbard et al., 2016;**  
53 **McConnell, 2019). In particular reactive astrogliosis and alteration of astrocyte markers such as**  
54 **glial fibrillary acidic protein (GFAP), the water channel aquaporin-4 (AQP4) and glutamatergic**  
55 **markers including the excitatory amino acid transporters 1 and 2 (EAAT1, EAAT2), have been**  
56 **found in both mental disorders such as major depression and focal epilepsy in particular mesial**  
57 **temporal lobe. These findings not only suggested a physiologic correlation between the two**  
58 **disorders but targeting the different types of reactive astrocytes has important**  
59 **implications for the development of new therapeutic strategy as well (McCullumsmith, R. E., &**  
60 **Meador-Woodruff, J. H. (2002). Rajkowska, G., & Stockmeier, C. (2013; Kandratavicius et al.,**  
61 **2015; Kobylarek et al., Liddel and Barres, 2017; 2019; Lu et al., 2019)**

62

63 Evidence in humans suggests that, between neurological and psychiatric conditions, a bidirectional  
64 relationship exists. **Kanner (2016) estimated that one third of patients with epilepsy have lived**  
65 **through experienced a psychiatric disorder during the course of their life, whereas as reported by**  
66 **Salpekar and Moula (2019) 50% or more of persons with epilepsy show psychiatric comorbidity.**  
67 **Moreover according to Josephson and Jetté (2017) patients with epilepsy experienced psychiatric**  
68 **disorder rates 2-3-fold or higher than the general population without epilepsy. In particular**

69 depression is the most psychiatric comorbidity exhibited with a prevalence in epileptic patients  
70 (EP) of 10–24,9 % compared to 10,2–11,2 % in the general population without epilepsy (GP) as  
71 described by Tellez-Zenteno (2007), and a prevalence of 20–55 % in EP compared to 1.5–19 %  
72 GE according to Gilliam et al., (2004) and Hamed (2011) . Anxiety is the second most frequent  
73 comorbidity with a prevalence of 14.8-30,9% in EP versus 10.8-11.7 GP and a coexistence of  
74 anxiety and with depression in 73% of EP (Tellez-Zenteno et al., 2007; Habibi et al., 2016).  
75 Moreover, mood disorder have been presented in 25.0-43.5% of in EP and in 19.0-20,2% of GP,  
76 whereas panic disorder are presented in 2,9-10,3% of EP versus 3,3-3,9 % of GP. Suicide  
77 ideation rate is prevalent in 17,4-32,54 % of EP versus 12.8-13.82 % in the GP according to  
78 Tellez-Zenteno et al. (2007) and in 25% of EP versus 13,225% of GPas reported by Habibi,  
79 whereas Christensen et al., (2007) reported a three higher rate of suicides in EP compared to GP.  
80 Cognitive disorders are also a common comorbidity both in children and adults with epilepsy and  
81 they may precede the onset of seizures (Cornaggia et al., 2006; Kanner, 2020). Berg (2011)  
82 described that children with epilepsy were two to three times as likely as controls to have met  
83 criteria for Attention deficit disorder and deficit hyperactivity disorder (ADHD), whereas Nickels  
84 a (2016) found that ADHD is seen in 28–70% of people with epilepsy.. Concurrently, a history of  
85 major depression or anxiety increases the risk of unprovoked seizures and epilepsy (Habibi et al., 2016;  
86 Josephson and Jetté, 2017; Kanner, 2016; LaFrance et al., 2008; Thome-Souza et al., 2004).

87  
88 As concerning dogs, Shibab et al. (2011) described that at least one behavior had changed since  
89 the onset of idiopathic epilepsy (IE) in 71% of all dogs of their study. In particular dogs with IE  
90 and under no antiepileptic drugs (AEDs) showed a significant difference ( $p \leq 0,05$ ) between pre-  
91 epilepsy and post-onset for some behaviors such as fear/anxiety, defensive aggression and  
92 abnormal perception, whereas the epileptic dogs under AEDs displayed significant difference  $p \leq$   
93 0,05 for fear/anxiety, abnormal perception, abnormal reactivity, attachment disorder, demented  
94 behavior, and apathetic behavior. Levitin et al. (2019) investigated also the correlation with this  
95 behavioral changes and antiepileptic treatment with a monotherapy vs polytherapy, and in  
96 addition examined the behavioral changes displayed in different phases of a seizure  
97 (prodrome, post ictal and interictal phase). De Risio (2015) also reported that 55% of epileptic  
98 dogs under no AEDs seemed to develop behavioral abnormalities a epilepsy and that these were  
99 most commonly associated with abnormal perception and anxiety. Jokinen et al. (2015) found a  
100 significantly higher scores on the factors of inattention ( $P = .003$ ) and excitability/impulsivity ( $P$   
101  $= .021$ ) in dogs with benign familial juvenile epilepsy compared to the control samples, and also  
102 Packer et al. (2016) reported ADHD-related behavioural (excitability, chasing and trainability) in

103 **dogs with IE. According with Winter et al. (2018) dogs with IE performed significantly worse**  
104 **than controls on the 20 spatial working memory task (P=0.016) but not on the problem solving**  
105 **task (P=0.683).**

106 Identifying and treating cognitive impairment and psychiatric comorbidities in epileptic patients, is as  
107 important as seizure treatment. Because psychiatric disorders and comorbid epilepsy can worsen each  
108 other, , their treatment should be incorporated into the overall management of patients with epilepsy  
109 (Haut et al., 2019; Kanner, 2016; Leeman-Markowski and Schachter, 2017; Lopez et al., 2019;  
110 Michaelis et al., 2017; Mittan, 2009; Rudzinski and Meador, 2013; Salpekar and Mula, 2019). **Indeed,**  
111 **neurological diseases represent a particularly fascinating example of the complex connection**  
112 **between behavioral medicine and somatic conditions, whose interactions are clearly established**  
113 **also for other conditions such as urinary, dermatological and gastrointestinal ones ( (Overall et**  
114 **al., 2003; Seibert et al., 2008; Frank et al., 2014; Stelow et al., 2020) .**

115 Behavioral interventions could be an adjunctive treatment for epilepsy in dogs. Behavioral medicine  
116 techniques such as management of crisis triggers, stress reduction therapies and specific relaxation-  
117 based activities could reduce stress and improve the mental health of the epileptic dog. Behavioral  
118 medicine specialists could have an important role in the management of epilepsy patients alongside  
119 with neurologists and general practitioners (Forsgård et al., 2019; Packer et al., 2019; Packer and Volk,  
120 2015; Watson et al., 2018).

121 Specialists in both neurology and behavior are poised to be mindful of the possible interactions  
122 between antiepileptic drugs (AEDs) and psychoactive medications, treating epileptic patients with the  
123 comorbidity of behavioral disorders. Consequences from drug interactions can lead to supratherapeutic  
124 or subtherapeutic drug concentrations. Some psychotropic medications may affect affect seizure  
125 thresholds. In humans, the highest recognized risk of seizures is reported in bupropion, amoxapine,  
126 clomipramine, maprotiline, chlorpromazine, loxapine, olanzapine, and clozapine (Habibi et al., 2016).  
127 In dogs there are ane Similar research into antidepressant use to treat epileptic dogs with psychiatric  
128 comorbidities is lacking. . On the other hand, as reported for human when veterinarians, general  
129 practitioners as well as neurologists and behaviorists, treat epileptic patients, they should be aware of  
130 cognitive side effects of AEDs. The pharmacological management of the seizure disorder could have  
131 either a negative or a positive effect on psychiatric comorbidities (Hermann et al., 2017; Kanner, 2016).  
132 In dogs, AEDs may affect behavior, including changes in fear/anxiety, abnormal perception, abnormal  
133 reactivity, attachment disorder, demented behavior, and apathetic behavior (Erath et al., 2020; Levitin  
134 et al., 2019; Packer et al., 2016; Shihab et al., 2011).

135

In humans and in dogs there is a possible link between narcolepsy/cataplexy and some behavioral conditions. In humans, narcolepsy and cataplexy (a narcolepsy symptom) can be triggered by laughing and joking and by anger on the other side (Hublin et al., 1994; Anic-labat et al., 1999). Narcolepsy is often comorbid with depression, anxiety, hallucinations, and attention-deficit hyperactivity disorder (ADHD) in humans (Carls et al., 2020; Lopez et al., 2017; Ruoff et al., 2017; Ohayon, 2013; Carls et al., 202), so there is routine screening for psychiatric conditions in patients with narcolepsy (). Children with narcolepsy can display attention problems, behavior resembling hyperactivity, and emotional lability, leading to a misdiagnosis of ADHD in the absence of thorough anamnesis and diagnostics (Scammell, 2015; Thorpy and Krieger, 2014). In dogs, canine narcolepsy/cataplexy may be triggered by vigorous play, the eating of favored foods or other forms of emotional excitement. Progressive lethargy/hypersomnia and disruption of the sleep-wake cycle, has been described in both humans (Thorpy and Krieger, 2014) and dogs (Gulyani et al., 2002; Kaitin et al., 1986; Mari and Shea, 2020; Tonokura et al., 2007; Van Heerden and Eckersley, 1989; Wu et al., 2004) afflicted with narcolepsy. A combination of behavioral therapy (such as psychotherapy and cognitive behavioral treatment) and antidepressant drugs (such as venlafaxine, fluoxetine, imipramine, clomipramine, citalopram and psychostimulants drugs as amphetamines and methylphenidate) are used to treat narcolepsy/cataplexy in humans (Agudelo et al., 2014; Bassetti et al., 2019; Szabo et al., 2019). Imipramine, fluoxetine, clomipramine, dexamphetamine, sulpiride and methylphenidate have been used in veterinary medicine (Babcock et al., 1976; Hendricks and Hughes, 1989; Jeong et al., 2013; Okura et al., 2000; Van Heerden and Eckersley, 1989).

Cooperation between neurologists and behaviorists is also desirable when pain is likely to be involved in a neurological condition. Chiari-like malformation and syringomyelia may lead to some behavioral signs including vocalizations, reduced activity, reduced stairs/jumping ability, touch aversion, altered emotional state, sleep disturbance, head-scratching/rubbing and phantom scratching, which may be the only signs of this neurological disease (Rusbridge et al., 2019). The link between pain and fear and anxiety-related problems is well recognized in humans and pets, as well as its influence on the quality of life (Belshaw and Yeates, 2018; Dodd et al., 2020; Elman and Borsook, 2018; Khan et al., 2020; Lascelles et al., 2019; Lindley, 2012; Mills et al., 2020). Pain is an essential component of many neurological diseases, such as diskospondylitis and meningitis (Lau et al. 2019, Affenzeller et al., 2017). Pain can increase irritability and reduce threshold levels for displaying aggression and may be an early sign that disease is present (Barcelos et al., 2015, Affenzeller et al., 2017, Camps et al., 2012). The pain condition needs to be addressed directly and with behavioral recommendations **as suggested by behavioral medicine specialist**. During the behavioral consultation, signs of pain may be displayed through “adjunctive” behavior including yawning, frequent body stretching, body shaking

170 with or without initial scratching, interrupted body shaking, and excessive licking of others. **This sign**  
171 **are also non specific signs of anxiety and once again a systematic data collection of this signs**  
172 **during behavioral consultation is needed in veterinary.** Assessment of behaviour, in general, is  
173 likely flawed during a routine preventative clinical examination due to the short duration of the visit  
174 and the commonness of behavioral inhibition in dogs during physical exam (Doering et al., 2009).  
175 Consultations in behavioural medicine provide the the dog time to relax, if he can, and for more  
176 comprehensive behavioural expression. In humans, cats and dogs, chronic pain is connected with  
177 changes in the central nervous system (CNS) related to central sensitization (Guillot et al., 2014;  
178 Moore, 2016; Nijs et al., 2019). These changes clinically contribute to the development of allodynia,  
179 hyperalgesia and hypersensitivity in the site of injury and it can then extend to other sites. For this  
180 reason, **it is clinically relevant to prevent or managed the central sensitization in patients with**  
181 **chronic pain with a combination of pharmacological options** (acetaminophen, antidepressant,  
182 opioids, N-methyl-d-aspartate (NMDA)-receptor antagonists) and stress management (Moore, 2016;  
183 Nijs et al., 2019; Pozzi et al., 2006).

184

185

186 **As we described above in different diseases such as epilepsy, narcolepsy, chronic**  
187 **pain/neuropathic pain there is a comorbidity of psychiatric disorder and a synergy between**  
188 **neurologists and behavioral medicine specialists could improve diagnosis and therapy. In order**  
189 **to present a broader view of the link between behavioral medicine and neurology, in this review**  
190 **we focus now on neurological diseases that could display behavioral symptoms and behavioral**  
191 **disorders that could be involved in neurological conditions.** We describe the localization of nervous  
192 system lesions relating to behavioral anomalies and then discuss some diseases in the “gray zone”  
193 between neurology and behavioral medicine. We will conclude by analyzing the differential diagnoses  
194 of the neurological diseases and their relationship with behavioral signs.

195

## 196 **Localization of the nervous system pathology related to behavioral anomalies.**

197 Behavioral responses are affected by interactions between the external environment and the component  
198 of the internal environment of each animal (physiology, neurochemistry, neuroanatomy, and genomic  
199 code). The nervous system allows the individual to respond to internal and external environmental  
200 changes, to motivational states (e.g., anger or thirst), and to pathophysiological states (e.g., pain) Fatjó  
201 and Bowen, 2009). Behavior is the **integration of all organ system responses and in his**  
202 **manifestation are relevant** structures in different areas of the brain, such as prefrontal and temporal  
203 cortices and limbic system. This latter component receives and associates the impulses from the

204 olfactory, optic, auditory, exteroceptive, and interoceptive sensory systems; it is also involved in  
 205 emotional and behavioral patterns.

206

207

208

209 **As you can see below** Table 1 lists broad behavioral signs and associated brain anatomical regions  
 210 putatively involved in their development and/or presentation.

211

212 **Table 1: correlations between behavioral signs and neuroanatomic PATHOLOGY.**

| POSSIBLE<br>BEHAVIORAL<br>SIGNS                    | ANATOMICAL SITE OF PATHOLOGY                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Anxiety, fear and<br/>phobic behavior</b>       | <b>amygdala</b> (Allikmets, 1966)<br><b>hippocampus and piriform lobe</b> (Brini et al., 2004; Fatzer et al., 2000)<br><b>cingulate gyrus</b> (de Lahunta et al., 2014)<br><b>pituitary gland</b> (Briola et al., 2020)<br><b>frontal and temporal lobes and basal nuclei</b> (James et al., 2012; Overall, 2003; Vanhaesebrouck et al., 2012)<br><b>spinal cord and peripheral nervous system</b> (Dodd et al., 2020; Stella et al., 2011)                                                                                                                                                                                                                                                                                                                                                                                                    |
| <b>Aggressive<br/>behavior</b>                     | <b>amygdala</b> (Adamec and Stark-Adamec, 1983; Allikmets, 1966; Andersson and Olsson, 1965; Jacobs et al., 2006, 2003; Kandel et al., 2013; Overall, 1999; Siegel and Shaikh, 1997; Squire et al., 2012)<br><b>cingulate gyrus</b> (de Lahunta et al., 2014)<br><b>hypothalamus</b> (Barrett et al., 1987; de Lahunta et al., 2014; Fatjó et al., 1999; Fonberg, 1971; Fuchs et al., 1985; Inselman and Flynn, 1972; Jacobs et al., 2003)<br><b>pituitary gland</b> (Menchetti et al., 2019)<br><b>frontal lobe</b> (Allen et al., 1974; Foster et al., 1988; Jacobs et al., 2003)<br><b>temporal lobe</b> (Fatjó et al., 1999; Overall, 2003)<br><b>spinal cord, meninges and peripheral nervous system</b> (Affenzeller et al., 2017; Barcelos et al., 2015; Camps et al., 2012; Dodd et al., 2020; James et al., 2012; Mills et al., 2020) |
| <b>Compulsive and<br/>repetitive<br/>behaviors</b> | <b>hippocampus and piriform lobe</b> (Brini et al., 2004)<br><b>thalamus</b> (Gonçalves et al., 2011; Kornegay, 1991)<br><b>pituitary gland</b> (Briola et al., 2020; Menchetti et al., 2019; Puente, 2003)<br><b>basal nuclei</b> (Brundin et al., 1987; Chrisman, 1994)<br><b>frontal lobe</b> (Chrisman, 1994)<br><b>temporal lobe</b> (Chrisman, 1994; de Lahunta et al., 2014; Kornegay, 1991)                                                                                                                                                                                                                                                                                                                                                                                                                                            |

|                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                      | <b>spinal cord and peripheral nervous system</b> (Dodd et al., 2020)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <b>Cognitive dysfunction, memory deficits, dementia, change in learning behavior</b> | <b>hippocampus</b> (Fatzer et al., 2000; Fuller et al., 1957; Kowalska, 2000, 1995; Skelly and Franklin, 2002)<br><b>thalamus</b> (de Lahunta et al., 2014; Gonçalves et al., 2011; Kornegay, 1991)<br><b>hypothalamus</b> (de Lahunta et al., 2014)<br><b>pyriform lobe</b> (Fatzer et al., 2000)<br><b>frontal lobe</b> (Chrisman, 1994; Kornegay, 1991; Overall, 2003)<br><b>temporal lobe</b> (de Lahunta et al., 2014; Foster et al., 1988; Kornegay, 1991; Kowalska, 2000)<br><b>peripheral nervous system</b> (Dodd et al., 2020; Gamble et al., 2020) |
| <b>Reduced activity, altered consciousness: depression or lethargy</b>               | <b>thalamus</b> (Gonçalves et al., 2011; Kornegay, 1991; Motta et al., 2012)<br><b>hippocampus</b> (Fatzer et al., 2000)<br><b>pituitary gland</b> (Menchetti et al., 2019)<br><b>reticular substance</b> (Horwitz, 2015; Motta et al., 2012)<br><b>frontal lobe</b> (de Lahunta et al., 2014; Kornegay, 1991; Motta et al., 2012)<br><b>meninges</b> (Tipold and Schatzberg, 2010; Vandeveld et al., 2012; Webb et al., 2002; Wrzosek et al., 2009)<br><b>spinal cord and peripheral nervous system</b> (Dodd et al., 2020; Stella et al., 2011)             |
| <b>House soiling</b>                                                                 | <b>amygdala</b> (Allikmets, 1966; Overall, 2003)<br><b>hippocampus and pyriform lobe</b> (Brini et al., 2004)<br><b>pituitary gland</b> (Long et al., 2003; Menchetti et al., 2019)<br><b>basal nuclei, thalamus, spinal cord</b> (Fatjó and Bowen, 2009)<br><b>peripheral nervous system</b> (Duh et al., 2018; Fatjó and Bowen, 2009; Stella et al., 2011)                                                                                                                                                                                                  |
| <b>Changes in ingestive behavior</b>                                                 | <b>amygdala</b> (Ballarini, 1990; Fonberg, 1971; Summer and Kaelber, 1962)<br><b>septal nuclei</b> (Hart, 1977)<br><b>hippocampus</b> (Fatzer et al., 2000)<br><b>thalamus</b> (Overall, 2003)<br><b>hypothalamus</b> (Ballarini, 1990; Rodney, 1996)<br><b>spinal cord, meninges and peripheral nervous system</b> (Dodd et al., 2020; Stella et al., 2011; Webb et al., 2002)                                                                                                                                                                               |
| <b>Changes in sexual behavior</b>                                                    | <b>hypothalamus</b> (Hart, 1977, 1974; Rodney, 1996)<br><b>temporal lobe and limbic system</b> (Overall, 2003)                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <b>Changes in sleep behavior</b>                                                     | <b>hippocampus</b> (Kemp and Kaada, 1975)<br><b>hypothalamus</b> (Rodney, 1996)                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

## *Borderline disorders between neurology and behavioral medicine in dogs*

Ogata et al., (2013) reported that compulsive disorders (CD)/obsessive compulsive disorders (OCD) in dogs are associated with structural abnormalities mirroring some of those identified in humans with anxiety disorders, including obsessive compulsive disorders (OCD). Their research found that 8 Doberman Pinschers with either blanket or flank-sucking behavior presented some anatomical differences when compared with controls. These differences, similarly, to humans with OCD included: higher total brain and gray-matter volumes, lower gray-matter densities in the dorsal anterior cingulate cortex and right anterior insula, and higher fractional anisotropy in the splenium of the corpus callosum, than in controls. Anatomical lesions consistent with hydrocephalus were also found in 7 bull terriers out of a sample of 8 displaying abnormal behaviors including tail chasing (TC), unprovoked aggression, and extreme irrational fear (Dodman et al., 1996). In addition, Uccheddu et al., (2018), described a case of TC in a bull terrier with brain atrophy. As suggested by the latter, the practitioners should be aware that in case of atypical, unremitting, or complex TC or other CD/OCD, intracranial structural disorders, such as brain atrophy, should be included in differential diagnoses. In fact, compulsive behaviors such as TC may be primarily behavioral or arise as a result of medical disorders, including neurological ones (e.g., focal seizures or intracranial disease). Impaired responsiveness during TC could be related to a reduced level of consciousness, as often displayed during focal seizures, or it could reflect level of compulsive behavior that limits the dog responsiveness even with a normal level of consciousness (Berendt et al., 2004; Tiira et al., 2012). Treatment with antidepressant drugs is considered the medication of choice for canine CD/OCD (**Overall, 2001; Chutter et al., 2019; Overall and Dunham, 2002**) with behavioral interventions including management and behavioral modification. Particular attention in the behavioral management plan should be paid to those situations that are likely to trigger or exacerbate the TC, such as those that increase the dog's level of arousal, new/unpredictable or restrictive environment, lack of mental or physical stimulation, insufficient interaction with the owner and reactivity to sound (Moon Fanelli et al., 2011; Tiira et al., 2012).

Fly snapping syndrome (FSS) in behavioral medicine has been categorized as a compulsive/obsessive compulsive behavior with the differential diagnosis of epileptoid disorders (as visual cortex epileptiform disturbances, and simple and complex partial seizures), conditions of disorders of the

special senses, neuropathic pain and gastro-intestinal disorders (Overall and Dunham, 2002; Frank et al., 2012; Schneider et al., 2009; Wrzosek et al., 2015). Complete medical and behavioral history, physical examination, neurological examination and deeper analysis (with EEG, BAER, MRI, cerebrospinal fluid examination) should be considered when evaluating dogs with suspected FSS. In a case report of FSS in a dog, thymoma metastases were found in the choroid plexus, leptomeninges, cerebral cortex and hippocampus (Sordé et al., 1994). Thus, a cooperation between neurologists and behaviorists could improve FSS management. However, if no neurological alteration is found, it may be difficult to **to rule out the rarer epilepsies**. In this case, as suggested by Wrzosek et al. (2015), a patient's response to treatment can sometimes provide suggestive evidence of the etiology of a given behavior: for instance, **most of the “fly biting” in Wrozonek study was responsive to SSRIs, which have anti-obsessional effects, thus suggesting the fly biting was an OCD..** Rapid eye movement (REM) sleep disorders may include episodes of violent limb movements, howling, barking, growling, chewing, and have been treated with an AED (potassium bromide) (Schubert et al., 2011)., whereas one case of REM sleep disorder in dogs that mirrored the electroencephalographic signs seen in humans responded to tricyclic antidepressants (Bush et al., 2004).

Bull terriers exhibit a hypokinetic gait with compulsive pacing of variable duration, during which consciousness is apparently altered with the dog remaining conscious of its surroundings. Episodes appear to be triggered by the contact with some surface such as when they walk under particular objects in the home environment. Once recognized, the progression of the episodes increases in frequency in six months and then tends to stabilize even though without remission (Berendt et al., 2004; Lowrie et al., 2015; Moon-Fanelli et al., 2011). Lowrie et al. (2015) argue against seizure activity because of the long duration of tracing-like episode (seizure usually lasts less than 10 minutes) with an immediate recovery after those episodes and no postictal signs. There is also a lack of response to conventional antiepileptic medication. Neurological examinations for the dogs studied were normal: no structural abnormalities were revealed, cerebrospinal fluid analysis and neospora antibody were unremarkable.

### *Borderline disorders between neurology and behavioral medicine in cats*

Other diseases of the “gray zone” between neurology and behavior are two syndromes involved with neuropathic pain: the feline orofacial pain syndrome (FOPS) and the feline hyperesthesia syndrome (FHS). Addressing environmental needs and avoiding triggers could be more important than pharmacotherapy, both for FOPS and FHS (Rusbridge et al., 2020).

279 FOPS is characterized by acute episodes, typically unilateral, of oral and/or tongue discomfort up to  
280 auto-mutilation of the face. Oral lesions may be an important predisposing cause, but environmental  
281 factors such as social conflicts between household cats may exacerbate the condition. Addressing social  
282 factors is crucial, Analgesic drugs, such as nonsteroidal anti-inflammatory drugs, opioids, and  
283 phenobarbital may all help (Rusbridge et al., 2010). FOPS should not be confused with an acute onset  
284 of feline complex partial seizures with orofacial automatism, which are associated with hippocampal  
285 necrosis (FEPSO-HN). Moreover, in FEPSO-HN cats didn't display signs of discomfort or  
286 automutilation of tongue and face and in FOPS cats didn't show seizure-like movement (Brini et al.,  
287 2004; Pakozdy et al., 2011). Oral pain is reported to be involved in several neuropathic conditions in  
288 humans such as burning mouth syndrome, persistent idiopathic facial pain, atypical odontalgia, and  
289 trigeminal neuralgia (REFS) . Diagnosis and management of these diseases may be challenging due to  
290 complex histories, pathophysiology and associated psychosocial co-morbidities, such as depression,  
291 anxiety and post-traumatic stress. Early recognition and a holistic approach to management are central  
292 in limiting the negative psychosocial impact of orofacial pain (De Leeuw et al., 2005; Ghurye and  
293 McMillan, 2017).

294  
295 Finally, feline hyperesthesia syndrome (FHS) is a disorder characterized by involuntary muscle  
296 contractions with skin rippling over the dorsal lumbar area and changes in behavior, such as jumping  
297 and running, excessive vocalizations, tail chasing, and self-trauma. FHS has been associated with  
298 behavioral, dermatological, orthopaedic and neurological conditions (**Overall and Dunham,**  
299 **2002**)Amengual Batle et al., 2019; Rusbridge, 2020). Gabapentin and topiramate, which are used as  
300 antiepileptic drugs with effects on neuropathic pain in small animals, may suggest a role played by the  
301 neuropathic pain in the development of this condition in cats, but gabapentin is also increasingly used  
302 as an anti-anxiety treatment making attribution of effect tricky (**Pankratz et al, 2017; van Haaften et**  
303 **al., 2017; Hudec et al., 2020)**. **As suggested by Overall since 1997integrated multidisciplinary**  
304 **diagnostic pathway could be to be used for the management of clinical cases (Overall and**  
305 **Dunham, 2002; Amengual Batle et al., 2019).** .  
306 and then

307

## 308 **Differential diagnoses of neurological diseases and their relationship with behavioral** 309 **signs**

310 Diseases, including neurological ones, are often defined through the acronym D.A.M.N.I.T- V or  
311 V.I.T.A.M.I.N.-D.: degenerative (D), anomalous (A), metabolic (M), neoplastic (N), inflammatory  
312 (infectious/immune-mediated) (I), idiopathic (I), traumatic (T), and vascular (V) diseases (Garosi,

2004; Bernardini, 2010). Table 2 reflects on these pathological classifications and their effects on behavior.

D: Neurodegenerative diseases are often subtle and progressive and can primarily involve the nervous tissue, the vertebral column, or the intervertebral disc; thus, their consequences on behavior are extremely variable (Bernardini, 2010). In both people with Alzheimer disease and dogs with canine cognitive dysfunction syndrome (CDS) have been identified neurodegenerative abnormalities including cerebrovascular disease, A $\beta$  and hyperphosphorylated microtubule associated protein (TAU) accumulation, oxidative brain damage, neuronal mitochondrial dysfunction, glutamate-mediated excitotoxic neuronal damage, impaired neuronal glucose metabolism, microglial dysfunction, and astrocyte dysfunction. Moreover, neuronal loss and cortical atrophy, infarcts, microhemorrhages and occasionally macrohemorrhages, meningeal thickening, ventricular dilatation and gliosis have been described in several brain regions including cortex, hippocampus, and parts of the limbic system (Dewey et al., 2020, 2019; Mihevc and Majdic, 2019). Canine and feline CDS leads to changes summarized by the acronym DISHAA (Disorientation, altered social Interactions, altered Sleep–wake cycles, House soiling and loss of other learned behaviors, altered Activity levels and increasing Anxiety) (Krug et al., 2019; Landsberg et al., 2010; Landsberg et al., 2011).

A: Regarding congenital anomalies, behavioral changes usually occur in the first few months of life of the animal; however, they could also develop later in life. In particular, the rupture of a precarious balance of the malformation can lead a delayed disease progression (Bernardini, 2010). These diseases, most frequently observed in puppies, need to be differentiated from behavioral changes, such as depression of the puppy and difficulty in learning (Chrisman, 1994; Horwitz, 2015; Overall, 2003). Moreover, congenital anomalies can lead to fear and anxiety, stereotypic and compulsive disorders, seizures, and aggressive behavior (see Table 2).

M: Metabolic and toxic diseases create an imbalance in the normal functioning of the body, which in turn affects the CNS. The symptoms onset may be acute or chronic and the symptoms evolution can be progressive or non-progressive (Bernardini, 2010). As described for fucosidosis by Smith et al. (1996), the late onset of neurological signs, particularly changes in behavior, may result in misdiagnosis as a primary behavior problem or acquired neurologic diseases.

N: Neoplasia in the nervous system can cause long-lasting behavioral changes in individuals with a normal neurological examination (Fatjó et al., 1999). Additionally, owners may attribute more subtle signs of forebrain disease (such as pacing or mentation change) to the normal aging process in a geriatric pet (Snyder et al., 2006). The clinical signs depend on the location of the tumor. Neoplasia of the pituitary gland can lead to compulsive behaviors, obtundation and disorientation, head pressing, star gazing, urinating or defecating in unusual places, aggressiveness, circadian rhythm alteration, lethargy,

347 and anxiety (Briola et al., 2020; Menchetti et al., 2019; Puente, 2003). Neoplasia involving the  
348 hypothalamus can cause drowsiness, inactivity, apathy, drinking/eating behavior change and may  
349 contribute to the display of sexual disorder and aggression (Overall, 2003; Schulman et al., 1992).  
350 Intracranial neoplasia causing apathy and depression, eating and drinking behavior changes are usually  
351 located in the thalamus (Motta et al., 2012; Overall, 2003; Schulman et al., 1992). Neoplasia of the  
352 frontal lobe and basal nuclei can cause apathy, depression, inability to learn and dementia, ritualistic  
353 and compulsive behavior, as well as fear and anxiety (Chrisman, 1994; Motta et al., 2012; Overall,  
354 2003; Schulman et al., 1992). Neoplasia of the pyriform lobe can lead to aggression (Vanhaesebrouck  
355 et al., 2012; Overall, 2003). Neoplasia involving the temporal lobe can lead to sexual behavior disorder  
356 and aggression (Overall, 2003). Neoplasia of the pons can cause apathy and depression (Motta et al.,  
357 2012; Overall, 2003). Neoplasia of the spinal cord with the involvement of the meninges or  
358 surrounding bone structures can cause pain and consequently possible aggression (James et al., 2012).  
359 Neoplasia of the pudendal nerve is related to inappropriate elimination (Overall, 2003).

360

361 I: The onset of inflammatory diseases is generally subacute to acute with a progressive trend in the  
362 absence of therapy. Inflammatory diseases of the nervous system causing behavioral changes are  
363 usually multifocal or diffuse and can affect the brain, spinal cord or meninges. In case of meningitis or  
364 vertebral infections pain and behavioral changes could be the only symptoms in the absence of  
365 neurologic deficit (Bernardini, 2010; Gunn-Moore and Reed, 2011). Indeed, pain-related consequences  
366 due to neurological diseases can lead to aggressive behavior (Affenzeller et al., 2017; Barcelos et al.,  
367 2015; Belshaw and Yeates, 2018; Camps et al., 2012; Lascelles et al., 2019; Mills et al., 2020), noise  
368 hypersensitivity (Fagundes et al., 2018; Lindley, 2012; McPeake et al., 2017), obsessive-compulsive  
369 disorder (Dalgin et al., 2017; Ferreira et al., 2019; O'Hagan, 2006; Zulch et al., 2012), and changing in  
370 learning ability (Worth et al., 2013). As shown in Table 2, other behavioral signs linked to neurological  
371 conditions include inappropriate elimination, depression, reduced activity, somnolence, apathetic  
372 behavior, changes in ingestive behavior, cognitive dysfunction, learning and memory deficits,  
373 dementia, non-specific anxiety/fear and anomalies of sexual behavior.

374 T: Traumas have two major consequences: the vascular one and pain-related one. Vascular  
375 consequences have been described in the section about vascular diseases, and pain-related  
376 consequences in the section regarding the inflammatory diseases.

377 V: Vascular diseases cause acute and non-progressive neurological signs with an onset of 24-72 hours  
378 except for polycythemia, which is a chronic and progressive disease. In particular, behavioral signs  
379 associated with neurovascular diseases include aggression, head pressing, vocalizations, dementia,  
380 disorientation, anorexia, circling, lethargy, depression, fear, anxiety and seizures. (Berg and Joseph,

2003; Bertolini et al., 2007; Garosi et al., 2006; Glass et al., 1998; Gonçalves et al., 2011; Irwin et al., 2007; Long et al., 2003; Overall, 2003; Thomsen et al., 2016; Tieber et al., 2006; Williams et al., 1998).

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**Table 2: Behavioral signs and their possible association with neurological diseases. V = vascular, I = inflammatory/infectious, T = trauma, A = congenital anomalies, M = metabolic-toxic, I = idiopathic, N = neoplasia, D = degenerative. FeLV = feline leukemia virus, FIP = feline infectious peritonitis, FIV = feline immunodeficiency virus infection, FSE = feline spongiform encephalopathy, NME=necrotizing meningoencephalitis, NLE= necrotizing leukoencephalitis, GME=granulomatous meningoencephalitis; n.r.= not reported.**

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| POSSIBLE<br>BEHAVIORAL<br>SIGNS   | UNDERLYING NEUROLOGICAL CONDITIONS                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Anxiety fear and phobic behaviors | <p><b>V:</b><br/><b>cerebrovascular accidents</b> (Overall, 2003).</p> <p><b>I:</b><br/><b>Borna disease</b> (Bernardini, 2010), <b>distemper</b> (Overall, 2003), <b>FIP</b> (Overall, 2003), <b>FIV</b> (Maingat et al., 2009; Phillips et al., 1994), <b>FSE</b> (Demierre et al., 2002), <b>lymphohistiocytic meningoencephalomyelitis</b> (De Risio et al., 2012), <b>rabies</b> (Fogelman et al., 1993; Overall, 2003), <b>toxoplasmosis</b> (Landsberg et al., 2013; Overall, 2003).</p> <p><b>T:</b><br/><b>brain trauma</b> (Overall, 2003).</p> <p><b>A:</b><br/><b>hydrocephalus, Chiari-like malformation and syringomyelia</b> (Rusbridge et al., 2019; Rutherford et al., 2012).</p> <p><b>M:</b><br/><b>cocaine intoxication</b> (Barfield et al., 2007), <b>heavy metal and organophosphates poisoning</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>hepatic encephalopathy</b> (Overall, 2003), <b>hyperthyroidism</b> (Falzone and Lowrie, 2011), <b>hypothyroidism</b> (Overall, 2003), <b>L-2-hydroxyglutaric aciduria</b> (Abramson et al., 2003), <b>lead poisoning</b> (Kowalczyk, 1976; Zook et al., 1967), <b>uremic syndrome</b> (Overall, 2003), <b>neuronal ceroid-lipofuscinosis</b> (Ashwini et al., 2016).</p> <p><b>I:</b><br/><b>idiopathic epilepsy/epileptic partial crisis</b> (Berendt et al., 2004; De Risio et al., 2015; Levitin et al., 2019; Packer and Volk, 2015; Shihab et al., 2011; Watson et al., 2018), <b>feline hyperesthesia syndrome</b> (Landsberg et al., 2013), <b>feline</b></p> |

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|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            | <p><b>orofacial pain syndrome</b> (Rusbridge et al., 2010), <b>interstitial cystitis</b> (Stella et al., 2011).</p> <p><b>N:</b></p> <p><b>frontal lobes, temporal lobes and basal nuclei tumors</b> (James et al., 2012; Overall, 2003; Vanhaesebrouck et al., 2012), <b>pituitary tumor</b> (Briola et al., 2020).</p> <p><b>D:</b></p> <p><b>lumbosacral stenosis</b> (Dodd et al., 2020), <b>Ammon's horn necrosis in cats</b> (Brini et al., 2004; Fatzer et al., 2000), <b>CCDS</b> (Dewey et al., 2019; Mihevc and Majdic, 2019).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Aggressive behavior</b> | <p><b>V:</b></p> <p><b>cerebral hypoxia</b> (Overall, 2003), <b>cerebrovascular accidents</b> (Chrisman, 1994; Overall, 2003), <b>feline ischemic encephalopathy</b> (Overall, 2003).</p> <p><b>I:</b></p> <p><b>Aujeszky disease/pseudorabies</b> (Henke and Vandeveld, 2012; Monroe, 1989), <b>Borna disease</b> (Bernardini, 2010), <b>Cuterebriasis</b> (Overall, 2003; Williams et al., 1998), <b>distemper</b> (Overall, 2003), <b>FeLV</b> (Frank and Dehasse, 2003), <b>FIP</b> (Frank and Dehasse, 2003; Overall, 2003), <b>FIV</b> (Frank and Dehasse, 2003; Maingat et al., 2009; Phillips et al., 1994), <b>FSE</b> (Bernardini, 2010), <b>rabies</b> (Fogelman et al., 1993; Frank and Dehasse, 2003; Odendaal, 1997; Overall, 2003), <b>steroid responsive arteritis-meningitis</b> (Bernardini, 2010; Vandeveld et al., 2012), <b>toxoplasmosis</b> (Frank and Dehasse, 2003; Overall, 2003; Simion et al., 2019), <b>diskospondylitis and chronic pain</b> (Affenzeller et al., 2017; Barcelos et al., 2015; Camps et al., 2012; Mills et al., 2020).</p> <p><b>T:</b></p> <p><b>brain trauma</b> (Overall, 2003).</p> <p><b>A:</b></p> <p><b>Chiari-like malformation and syringomyelia</b> (Rusbridge et al., 2019), <b>hydrocephalus and lissencephaly</b> (Chrisman, 1994; Horwitz, 2015; Overall, 2003), <b>porencephaly</b> (Overall, 2003).</p> <p><b>M:</b></p> <p><b>hepatic encephalopathy</b> (Camps et al., 2019; Overall, 2003), <b>heavy metal and organophosphates poisoning</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>hyper/hypoadrenocorticism</b> (Horwitz, 2015; Overall, 2003), <b>hyperthyroidism</b> (Falzone and Lowrie, 2011; Frank and Dehasse, 2003; Overall, 2003; Simion et al., 2019), <b>hypothyroidism</b> (Beaver and Haug, 2003; Scott-Moncrieff, 2007), <b>thiamine/taurine deficiency</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>uremic syndrome</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>marijuana intoxication</b> (Janeczek et al., 2018), <b>lysosomal storage diseases</b> (Overall, 2003).</p> <p><b>I:</b></p> |

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|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                   | <p><b>idiopathic epilepsy/epileptic partial crisis</b> (Berendt et al., 2004; De Risio et al., 2015; Packer and Volk, 2015; Shihab et al., 2011), <b>feline hyperesthesia syndrome</b> (Amengual Batle et al., 2019; Fatjó and Bowen, 2020), <b>complex regional pain syndrome</b> (Collins et al., 2006).</p> <p><b>N:</b><br/> <b>intracranial tumors: temporal lobes, limbic system, hypothalamus (ventromedial and posterolateral areas in the cat)</b> (Fatjó et al., 1999; Frank and Dehasse, 2003; Overall, 2003), <b>pyriform lobe</b> (Vanhaesebrouck et al., 2012), <b>pituitary neoplasia</b> (Menchetti et al., 2019), <b>neoplasia of the spinal cord with involvement of the meninges</b> (James et al., 2012).</p> <p><b>D:</b><br/> <b>Ammon's horn necrosis in cats</b> (Brini et al., 2004; Fatzer et al., 2000), <b>cerebral atrophy</b> (Uccheddu et al., 2018), <b>polioencephalomalacia of the pyriform lobe and hippocampus</b> (Overall, 2003), <b>lumbosacral stenosis</b> (Dodd et al., 2020).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p><b>Compulsive and repetitive behaviors</b></p> | <p><b>V:</b><br/> <b>cerebrovascular accidents</b> (Gonçalves et al., 2011; Overall, 2003; Thomsen et al., 2016), <b>polycythemia</b> (Bernardini, 2010).</p> <p><b>I:</b><br/> <b>Aujeszky disease/pseudorabies</b> (Monroe, 1989), <b>botulism</b> (Overall, 2003), <b>canine ehrlichiosis</b> (Bernardini, 2010), <b>cuterebriasis</b> (James and Poma, 2010; Williams et al., 1998), <b>FIP</b> (Foley et al., 1998), <b>FIV</b> (Podell et al., 1993), <b>GME</b> (Overall, 2005), <b>neosporosis</b> (Garosi et al., 2010), <b>NME</b> and <b>NLE</b> (Vandevelde et al., 2012), <b>protothecosis</b> (Salvadori et al., 2008), <b>rabies</b> (Overall, 2003), <b>tetanus</b> (Overall, 2003).</p> <p><b>T:</b><br/> <b>frontal lobe trauma</b> (Chrisman, 1994; Overall, 2003), <b>reflex sympathetic dystrophy</b> (LaBarre and Coyne, 1999).</p> <p><b>A:</b><br/> <b>Chiari-like malformation and syringomyelia</b> (Rusbridge et al., 2019; Sparks et al., 2018; Wrzosek et al., 2015), <b>hydrocephalus</b> (Horwitz, 2015), <b>hydranencephaly</b> (Davies et al., 2012), <b>porencephaly</b> (Davies et al., 2012).</p> <p><b>M:</b><br/> <b>bromethalin toxicosis</b> (Dorman et al., 1990), <b>hepatic encephalopathy</b> (Chrisman, 1994; Fernandes et al., 2019), <b>hyperadrenocorticism</b> (Bernardini, 2010), <b>hyperthyroidism/hypothyroidism</b> (Bernardini, 2010), <b>hypocalcemia</b> (Overall, 2003), <b>hypomagnesemia</b> (Bernardini, 2010), <b>L-2-hydroxyglutaric aciduria</b> (Abramson et al., 2003), <b>lead poisoning</b> (Bernardini, 2010), <b>loperamide toxicity</b> (Bernardini, 2010), <b>lysosomal storage diseases</b> (Skelly and Franklin, 2002).</p> <p><b>I:</b></p> |

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|----------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                              | <p><b>idiopathic epilepsy/epileptic partial crisis</b> (Berendt et al., 2004; Wrzosek et al., 2015), <b>feline hyperesthesia syndrome</b> (Amengual Batle et al., 2019), <b>feline orofacial pain syndrome</b> (Pakozdy et al., 2011; Rusbridge et al., 2010), <b>idiopathic ganglioradiculoneuritis/sensory neuropathy</b> (Correard et al., 2016).</p> <p><b>N:</b></p> <p><b>pituitary neoplasia</b> (Briola et al., 2020; Menchetti et al., 2019; Puente, 2003), <b>meningioma of the falx cerebri</b> (Wrzosek et al., 2015), <b>frontal lobes and basal nuclei tumours</b> (Chrisman, 1994; Overall, 2003).</p> <p><b>D:</b></p> <p><b>Ammon's horn necrosis in cats</b> (Brini et al., 2004), <b>CCDS</b> (Dewey et al., 2019; Mihevc and Majdic, 2019), <b>cerebral atrophy</b> (Uccheddu et al., 2018), <b>neuronal ceroid-lipofuscinosis</b> (Ashwini et al., 2016), <b>lumbosacral stenosis</b> (Dodd et al., 2020).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p><b>Cognitive dysfunction, memory deficits, dementia, changes in learning behavior</b></p> | <p><b>V: n.r</b></p> <p><b>I:</b></p> <p><b>canine encephalitozoonosis</b> (Odendaal, 1997), <b>cuterebriasis</b> (James and Poma, 2010), <b>distemper</b> (Overall, 2003), <b>FIP</b> (Foley et al., 1998), <b>FIV</b> (Maingat et al., 2009; Phillips et al., 1994; Sellon and Hartmann, 2012; Steigerwald et al., 1999), <b>FSE</b> (Overall, 2003), <b>mycotic encephalitis</b> (Overall, 2003), <b>rabies</b> (Overall, 2003), <b>spinal problems</b> (Worth et al., 2013), <b>toxoplasmosis</b> (Overall, 2003).</p> <p><b>T:</b></p> <p><b>frontal lobe trauma</b> (Chrisman, 1994; Overall, 2003).</p> <p><b>A:</b></p> <p><b>hydrocephalus</b> (Chrisman, 1994; Horwitz, 2015), <b>Chiari-like malformation and syringomyelia</b> (Rutherford et al., 2012).</p> <p><b>M:</b></p> <p><b>hepatic encephalopathy</b> (Chrisman, 1994; Fernandes et al., 2019), <b>hypocalcemia and hypomagnesemia</b> (Falzone and Lowrie, 2011), <b>L-2-hydroxyglutaric aciduria</b> (Abramson et al., 2003), <b>lead poisoning</b> (Bernardini, 2010), <b>thiamine and taurine deficiency</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>uremic syndrome</b> (Overall, 2003).</p> <p><b>I:</b></p> <p><b>idiopathic epilepsy</b> (Packer et al., 2018, 2016; Watson et al., 2018).</p> <p><b>N:</b></p> <p><b>frontal lobe tumors</b> (Overall, 2005), <b>intracranial neoplasia</b> (Snyder et al., 2006).</p> <p><b>D:</b></p> <p><b>Ammon's horn necrosis in cats</b> (Fatzner et al., 2000), <b>CCDS</b> (Dewey et al., 2019; Mihevc and Majdic, 2019), <b>lysosomal</b></p> |

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|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                               | <p><b>storage diseases</b> (Skelly and Franklin, 2002), <b>lumbosacral stenosis</b> (Dodd et al., 2020; Gamble et al., 2020).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>Reduced activity, altered consciousness: depression or lethargy</b></p> | <p><b>V:</b><br/> <b>cerebrovascular accidents</b> (Berg and Joseph, 2003; Garosi et al., 2006; Gonçalves et al., 2011; Irwin et al., 2007; Thomsen et al., 2016), <b>hemorrhage</b> (Bertolini et al., 2007), <b>feline ischemic encephalopathy</b> (James and Poma, 2010).</p> <p><b>I:</b><br/> <b>angiostrongylosis</b> (Zarelli et al., 2012), <b>Aujeszky disease/pseudorabies</b> (Henke and Vandeveld, 2012), <b>bacterial meningoencephalitis/canine ehrlichiosis/cryptococcosis</b> (Bernardini, 2010), <b>cuterebriasis</b> (Glass et al., 1998; James and Poma, 2010; Williams et al., 1998), <b>distemper</b> (Cantile et al., 1999), <b>FIP</b> (Foley et al., 1998), <b>FIV</b> (Phillips et al., 1994), <b>GME</b> (Vandeveld et al., 2012), <b>hydrocephalus with periventricular encephalitis in dogs</b> (Cantile et al., 1997; Vandeveld et al., 2012), <b>NME</b> (Cantile et al., 2001), <b>neosporosis</b> (Garosi et al., 2010), <b>NLE</b> (Vandeveld et al., 2012), <b>protothecosis</b> (Salvadori et al., 2008), <b>steroid responsive meningitis-arteritis</b> (Lau et al., 2019; Tipold and Schatzberg, 2010; Vandeveld et al., 2012; Webb et al., 2002; Wrzosek et al., 2009), <b>West Nile Virus infection in dogs</b> (Bernardini, 2010).</p> <p><b>T:</b><br/> <b>brain trauma</b> (Overall, 2003).</p> <p><b>A:</b><br/> <b>Chiari-like malformation and syringomyelia</b> (Rusbridge et al., 2019), <b>hydrocephalus</b> (Odendaal, 1997), <b>lissencephaly</b> (Overall, 2003), <b>porencephaly and hydranencephaly</b> (Davies et al., 2012).</p> <p><b>M:</b><br/> <b>bromethalin toxicosis</b> (Dorman et al., 1990), <b>heavy metal poisoning</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>hepatic encephalopathy</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>hyperadrenocorticism</b> (Bennaim et al., 2019; Falzone and Lowrie, 2011; Overall, 2003), <b>hyperkalemia</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>hyperthyroidism</b> (Carney et al., 2016), <b>hypoadrenocorticism</b> (Wood et al., 2007), <b>hypoglycemia and hyperglycemia</b> (Chrisman, 1994), <b>hypothyroidism</b> (Jaggy et al., 1994), <b>L-2-Hydroxyglutaric aciduria</b> (Abramson et al., 2003), <b>lysosomal storage disease</b> (Overall, 2003), <b>tranquilizers poisoning</b> (Chrisman, 1994), <b>marijuana poisoning</b> (Godbold et al., 1979), <b>uremic</b></p> |

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|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|               | <p><b>syndrome</b> (Chrisman, 1994; Falzone and Lowrie, 2011; Overall, 2003), <b>lysosomal storage diseases</b> (Nakamoto et al., 2011).</p> <p><b>I:</b><br/><b>idiopathic Epilepsy</b> (De Risio et al., 2015; Packer and Volk, 2015; Watson et al., 2018), <b>interstitial cystitis</b> (Stella et al., 2011).</p> <p><b>N:</b><br/><b>intracranial tumors: thalamus, frontal lobes, tegmentum of midbrain and pons</b> (Motta et al., 2012; Overall, 2003), <b>cerebellum meningioma</b> (Schulman et al., 1992), <b>pituitary neoplasia</b> (Menchetti et al., 2019).</p> <p><b>D:</b><br/><b>Ammon's horn necrosis in cats</b> (Fatzner et al., 2000), <b>CCDS</b> (Dewey et al., 2019; Mihevc and Majdic, 2019), <b>spongy degeneration of the grey matter</b> (Salvadori et al., 2007), <b>lumbosacral stenosis</b> (Dodd et al., 2020).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| House soiling | <p><b>V:</b><br/><b>pituitary apoplexy</b> (Long et al., 2003).</p> <p><b>I:</b> <b>distemper</b> (Guilford et al., 1990), <b>FIP</b> (Foley et al., 1998), <b>NME</b> (Cantile et al., 2001), <b>neosporosis</b> (Didiano et al., 2020), <b>steroid responsive meningitis-arteritis</b> (Lau et al., 2019).</p> <p><b>T:</b><br/><b>intervertebral disc disease</b> (Bernardini, 2010).</p> <p><b>A:</b><br/><b>hydrocephalus</b> (Horwitz, 2015; Overall, 2003), <b>lissencephaly</b> (Overall, 2003).</p> <p><b>M:</b><br/><b>hepatic encephalopathy</b> (Overall, 2003), <b>hypercalcemia</b> (Overall, 2003), <b>hyperthyroidism</b> (Falzone and Lowrie, 2011; Horwitz, 2015), <b>hypokalemia</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>hyperadrenocorticism/hypoadrenocorticism</b> (Falzone and Lowrie, 2011; Horwitz, 2015; Overall, 2003), <b>diabetes mellitus</b> (Falzone and Lowrie, 2011; Overall, 2003), <b>uremic syndrome</b> (Overall, 2003).</p> <p><b>I:</b><br/><b>neurogenic cystitis/interstitial cystitis</b> (Duh et al., 2018; Stella et al., 2011).</p> <p><b>N:</b><br/><b>neoplasia of the basal nuclei, thalamus, pudendal nerve</b> (Overall, 2003), <b>pituitary neoplasia</b> (Menchetti et al., 2019).</p> <p><b>D:</b><br/><b>Ammon's horn necrosis in cats</b> (Brini et al., 2004), <b>CCDS</b> (Dewey et al., 2019; Mihevc and Majdic, 2019), <b>neurodegenerative conditions of the basal nuclei, thalamus, pudendal nerve</b> (Overall, 2003).</p> |

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|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Changes in ingestive behavior</b></p> | <p><b>V:</b><br/><b>feline ischemic encephalopathy</b> (Glass et al., 1998).<br/><b>I:</b><br/><b>Aujeszky disease</b> (Monroe, 1989), <b>cuterebriasis</b> (Glass et al., 1998; James and Poma, 2010), <b>FIP</b> (Foley et al., 1998), <b>FSE</b> (Bernardini, 2010; Demierre et al., 2002), <b>hydrocephalus with periventricular encephalitis in dogs</b> (Vandeveldt et al., 2012), <b>NME</b> (Cantile et al., 2001), <b>rabies</b> (Odendaal, 1997; Overall, 2003), <b>steroid responsive arteritis-meningitis</b> (Lau et al., 2019; Webb et al., 2002).<br/><b>T:</b><br/><b>n.r.</b><br/><b>A:</b><br/><b>hydrocephalus</b> (Odendaal, 1997).<br/><b>M:</b><br/><b>canine encephalitozoonosis</b> (Odendaal, 1997), <b>diabetes</b> (Overall, 2003), <b>hepatic encephalopathy</b> (Overall, 2003), <b>hyperadrenocorticism</b> (Bennaim et al., 2019; Overall, 2003; Wood et al., 2007), <b>hypoadrenocorticism</b> (Bernardini, 2010), <b>hyperthyroidism</b> (Carney et al., 2016; Horwitz, 2015; Overall, 2003), <b>hypoglycemia</b> (Overall, 2003), <b>lead poisoning</b> (Kowalczyk, 1976), <b>thiamine deficiency</b> (Odendaal, 1997), <b>marijuana intoxication</b> (Janeczek et al., 2018).<br/><b>I:</b><br/><b>idiopathic epilepsy</b> (De Risio et al., 2015; Packer and Volk, 2015), <b>interstitial cystitis</b> (Stella et al., 2011).<br/><b>N:</b><br/><b>intracranial tumors: thalamus, ventromedial and posterolateral hypothalamus of cats</b> (Overall, 2003).<br/><b>D:</b><br/><b>Ammon's horn necrosis in cats</b> (Fatzner et al., 2000), <b>lumbosacral stenosis</b> (Dodd et al., 2020).</p> |
| <p><b>Anomalies of sexual behavior</b></p>  | <p><b>V:</b><br/><b>n.r</b><br/><b>I:</b><br/><b>Rabies</b> (Odendaal, 1997).<br/><b>T, A:</b><br/><b>n.r</b><br/><b>M:</b><br/><b>hypothyroidism</b> (Beaver and Haug, 2003).<br/><b>I:</b><br/><b>n.r.</b><br/><b>N:</b><br/><b>tumors of temporal lobe, limbic system, and hypothalamus</b> (Overall, 2003).<br/><b>D:</b><br/><b>n.r</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

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## Conclusions

There is a strong link between neurology and behavior both in humans and in pets. This implies that the associations should be considered to understand the pathophysiology and to improve the diagnosis and treatment of several diseases. In particular, neurology and behavior could be connected in four different ways. i) Several neurological diseases are associated with behavioral signs that can be the first and the only symptoms of the neurological disorder. ii) Comorbidity between neurological and psychiatric disorders occurs. iii) Some conditions can be considered “borderline” between neurology and behavioral medicine. iv) Some behavioral conditions may trigger or exacerbate neurology disease and vice-versa. An interdisciplinary approach to those disorders that lie at the intersection between neurology and behavior could lead to their early detection in patients. In addition, an interdisciplinary approach strongly decreases the possibility of misdiagnosis and unrecognition, that are usually responsible for an increase of the symptom burden and a delay in effective treatment (Bassetti et al., 2019; Hermann et al., 2017; Lopez et al., 2019; Tait et al., 2017). After the detection of these conditions that overlap between neurology and behavior, when appropriate treatment should be comprised of a combination of neurological and behavioral treatments, both in humans, dogs and cats. In treating these behaviors, we should be aware of the interaction between the drugs prescribed in neurology and those prescribed in behavioral medicine. **Moreover we should also be aware that no drugs used in either field are sufficiently specific to confirm a diagnosis or mechanism affected.** Hingray et al., (2020) suggest Epi-Psy (in short for epilepsy-psychiatric) as an effective discipline to improve the management of this condition and the welfare of patients. A multidisciplinary and then interdisciplinary approach would be an interesting challenge for veterinary behavioral medicine, considering its bond (often underestimated) with many other branches of veterinary medicine, especially neurology. On the research side, there are still undiscovered areas of interaction between neurology and behavior, and many other studies are needed to shine light on this area. On the consultation side, this multidisciplinary approach should be encouraged and strengthened. For instance, at least a neurological examination should be covered in the routine tests of the behavioral visits. **At the same time the neurology visit should always include a behavior assessment with short standardized questionnaires as the ones provide by AAHA.** Currently, a neurological disease with behavioral changes should lead to a behavioral consultation. The patient would benefit from the synergy between medical therapy and behavior modification.

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426 responsibility for manuscript preparation. Chiara Mariti assisted with development and drafting the  
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431 Conflict of interest

432 The authors have no conflict of interest to declare

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