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REVIEW

Cognitive Dysfunction in Cats: Update on Neuropathological and Behavioural Changes Plus Clinical Management

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Abstract

Cognitive dysfunction syndrome (CDS) is an established condition in cats that shares many similarities with human Alzheimer's disease (AD), where cognitive decline ultimately results in dementia. Cats with CDS display behavioural abnormalities, including excessive Vocalisation, altered Interaction with owners (increased affection/attention), altered Sleep-wake cycles, House-soiling, Disorientation (spatial and/or temporal), alterations in Activity, Anxiety, and/or Learning/memory deficits (i.e., VISHDAAL). These cats develop neuropathologies, such as accumulation of β-amyloid and hyperphosphorylated tau deposits. Because of its similarities to those in the brains of people with cognitive impairment and AD, the domestic cat could be a natural model for human dementia studies. It is important to diagnose CDS promptly in cats, ruling out other causes for these behavioural changes, to provide effective management. Interventions include environmental enrichment (e.g., easy access to key resources, calming pheromones), dietary supplementations (e.g., Senilife, Aktivait for cats, SAMe), specific diets (e.g., containing antioxidants, medium-chain triglycerides) and, potentially, medication (e.g., selegiline or propentofylline). This article reviews the literature about CDS in cats, its causes, neuropathology, clinical signs, diagnosis and potential management options. By doing so, it furthers our understanding of this condition and allows improved health, welfare and quality of life of affected cats.

KEYWORDS
behaviour, amyloid-β, cognitive dysfunction syndrome, diagnosis, management, tau deposits

INTRODUCTION

Thanks to advances in veterinary medicine, improvements in veterinary nutrition, and changes in the way we manage our pets (e.g., indoor living), the life expectancy of pet cats is increasing, with a reported median longevity of 14 years.[1] When classifying cats by age, they are considered to be 'mature' at 7–10 years of age; 'senior' at 12–14 years of age; and become 'geriatric' or 'super senior' at 15 years of age.[2,3] The most common age-related neurological changes include deterioration of cognition (ultimately resulting in dementia), motor performance, and visual and auditory decline.[4–6]

BEHAVIOURAL CHANGES IN ELDERLY CATS

Since behavioural changes in aged pets often appear before other signs of illness, they can be useful early indicators of a decline in health and welfare. There are many potential causes of these behavioural changes, as diverse as cognitive dysfunction syndrome (CDS), hypertension, hyperthyroidism, pain (commonly associated with osteoarthritis), and separation anxiety, to name but a few causes, so it is important that our elderly cats get a full clinical examination, to determine the cause of their specific behavioural changes (see section on Diagnosis). It is essential to identify these behavioural changes early, in order to provide the most effective interventions. In a questionnaire-based study, 36% of owners of cats aged 7–10 years reported that their cats had developed age-related behavioural problems, including house-soiling and alterations in their activity levels, with the percentage of affected cats increasing to 88% in cats aged between 16 and 19 years.[7] Since some of these changes can be subtle or misinterpreted as 'normal ageing', cat owners often need assistance in identifying and reporting them to their veterinary surgeon.[8] This is made worse when owners are reluctant to take their elderly cats to

the veterinary clinic. Many owners and cats find clinic visits stressful (getting the cat into its basket, driving it to the practice, and coping with the consultation).[9] In addition, many owners worry that little can be done to help improve their cat's quality of life, so euthanasia may be suggested.[10] Veterinarians need to be aware of these concerns and counsel owners about how best to reduce this stress (e.g., giving gabapentin or trazadone to the cat before travel),[11,12] and making sure that owners know there are many potential interventions that can help elderly cats to have a better quality of life.

BEHAVIOURAL CHANGES IN CATS WITH CDS

Cognitive dysfunction syndrome (CDS) describes the age-related decline in cognitive abilities, characterised by certain behavioural changes that cannot be attributed to any other medical condition.[13,14] Although CDS in cats is a well-established condition, much of its pathophysiology has been extrapolated from findings in other species,[15] mainly dogs with CDS and people with Alzheimer's disease (AD), so our understanding of CDS in cats is less detailed.

The prevalence of the signs of CDS varies by species: for pet cats, around 28% of cats between 11 and 14 years of age develop at least one behavioural problem related to CDS, with this increasing to 50% in cats over 15 years of age.[14,16]

The major signs of CDS in cats and dogs have previously been summarised by the acronym DISHAAL, which stands for: spatial or temporal Disorientation; alterations in Interactions between the pet and its owners or other pets; alterations in the Sleep-wake cycle; House-soiling; alterations in Activity levels; Anxiety; and Learning and memory.[8,17] While DISHAAL does recognise many of the major behavioural changes reported in cats with CDS, it fails to emphasise the importance of excessive vocalisation, especially at night, which is often the most common finding, especially in the oldest cats. In the prevalence study mentioned above,[14] altered interactions with the family (especially increased attention seeking) was the most common behavioural change in cats aged from 11–14 years, while alterations in the activity levels and excessive vocalisations were the most common signs in cats aged over 15 years. A study of 100 cats with behavioural abnormalities (7–11 years old), found 36% of them vocalised excessively, especially at night, and 48% presented with house-soiling.[8] In another study of 100 cats, 61% of cats between 12 and 22 years of age vocalised excessively, with 31% vocalising mostly at night. In the same study, 27% of cats presented with house-soiling and 22% were disorientated.[15] Additional studies further emphasise the importance of increased vocalisation in cats with CDS, while also trying to determine the likely cause. In our most recent study of more than 850 cats of 11 years of age or more, almost 60% of cats were reported to vocalise excessively, particularly at night, and 50% were more affectionate towards their owners, demanding more attention[18] (Figure 1).

In a detailed study of 37 cats with CDS where owners reported increased vocalisation, 67% vocalised more at night and 64% vocalised more during the day. When asked to suggest the likely main cause of their cats increased vocalisation, 41% suggested disorientation, 41% suggested attention seeking (i.e., wanting affection and attention from their owner) and 16% that their cat was looking for food. The owners also reported that 67.5% of cats were more affectionate[19] (Figure 2). These studies show that most of the behaviours detailed in the acronym DISHAAL can in themselves cause increased vocalisation; 'alteration in the Interactions between the pet and its owners', 'Anxiety' (e.g., causing attention seeking), 'spatial or temporal Disorientation' and 'deficits in Learning and memory' (e.g., causing a cat to forget that they have been fed), and 'alterations in the Sleep-wake cycle' likely to play a role in night crying. However, while these findings clearly support that increased vocalisation is part of CDS, the acronym DISHAAL does not recognise the importance of increased vocalisation within the acronym itself, with the V of Vocalisation being given prime position.

Given that cats with CDS present differently to dogs with CDS, for whom the DISHAAL acronym was originally developed,[8,17] the authors believe that a different acronym is needed for cats. They propose the new feline acronym of VISHDAAL. VISHDAAL describes the behaviours seen in cats with CDS: excessive Vocalisation; alterations in Interactions (e.g., increased affection); changes in the Sleep-wake cycle; House-soiling; Disorientation; alterations in Activity levels; Anxiety; and Learning and memory. The behaviours included in this new acronym are more specific to cats and are listed in order of prevalence, as supported by the aforementioned studies.

COGNITIVE DECLINE IN CATS WITH CDS

While cognition in humans is composed of multiple features such as learning, memory, executive function (the processes to manage resources in order to achieve a goal, for example, planning, reasoning and problem solving), attention, language, psychomotor and spatial abilities, it is less well understood in pets, especially cats. There is limited evidence assessing cognitive decline in cats with CDS. Since changes in cognition may initially be subtle in pets affected by CDS, and their recognition may present a challenge for their owners, laboratory-based protocols have been developed to try to assess and measure cognitive function in dogs and cats.[8,14]

A neuropsychological test, originally created for dogs to assess cognitive function, has been remodelled for use in cats. The cats were divided into three groups: 1) young adults aged 3.0–3.8 years; 2) mature cats aged 7.7–9.0 years; and 3) senior cats aged 10.5–15 years. The cats were put through a battery of cognitive tasks,

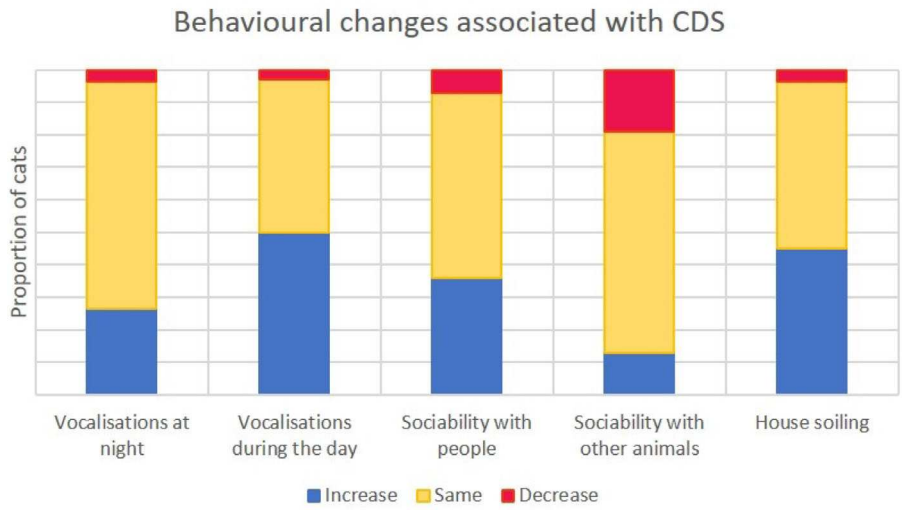
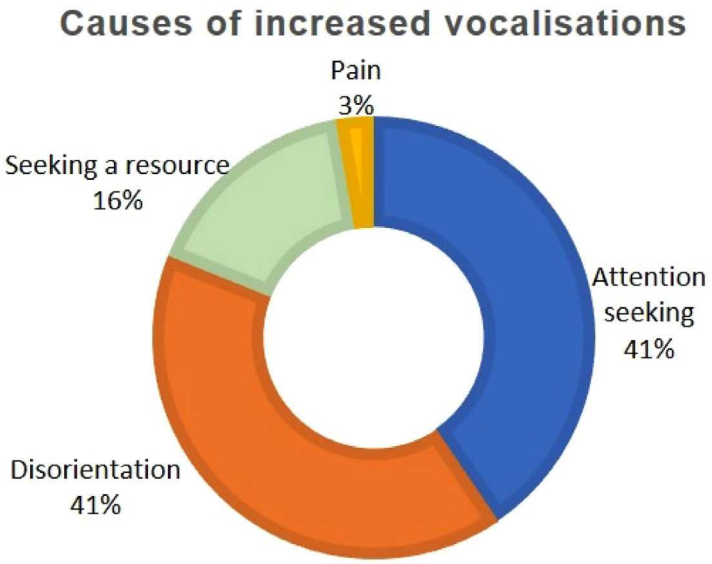


FIGURE 1 Some of the behavioural changes that are associated with CDS. In a study conducted by the authors, cat owners reported whether each of the age-related behaviours increased, decreased, or remained the same, when compared to when their cats were younger. Graph modified and used with permission from Sordo et al. 2020[18]

FIGURE 2 Main causes of increased vocalisations in cats with CDS, as reported by their owners. Graph modified and used with permission from Cerna et al. 2020[19]



including a T-maze and matching tasks. The results showed an age-dependent decline in both discrimination and reversal learning*, as well as significant differences between groups during the matching tasks, suggesting that the older the cat, the more severe the cognitive decline they may develop.[20,21] *(Reversal learning is tested when the cat is first trained to remember under which shaped pot food is hidden (discrimination learning). Once the cat has learned this, the food is then hidden under a different-shaped pot, challenging the cat to reverse or inhibit what they previously learned during the discrimination phase)

CAUSES OF CDS

The exact cause of CDS remains unknown; however, several alterations in the brain are believed to be involved in its development, including oxidative damage, vascular changes (see vascular pathology) and compromised cerebrovascular blood flow.

There is normally a balance between the production and removal of free radicals within the body such that oxidative damage is limited. However, factors such as stress, ageing or disease can alter this balance, reducing their elimination and promoting an excess of free radicals which may damage the brain.[13] This oxidative damage is believed to occur in cats, dogs and other species.[14,22]

With age, the blood flow to and within the brain can be compromised by changes to the vessels themselves, systemic hypertension, heart disease, anaemia, alterations in blood viscosity and/or hypercoagulability, all of which exacerbate neuronal hypoxia.[13,14]

CHANGES IN THE BRAIN WITH CDS

It is useful to compare changes seen in cats and humans. With ageing, the brains of cats and humans suffer several anatomical and physiological changes, ultimately associated with the development of

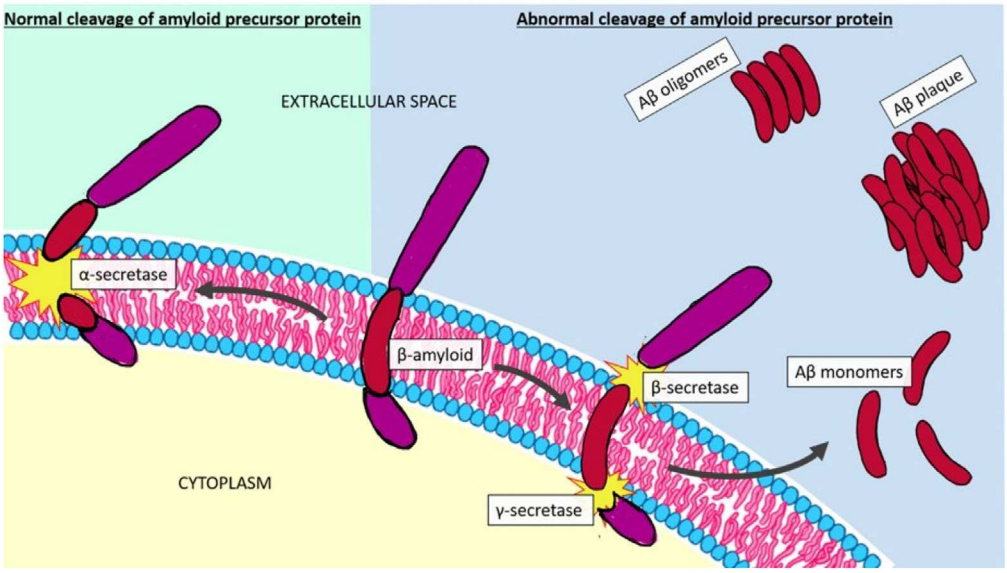


FIGURE 3 Normal and abnormal cleavage of the amyloid precursor protein leading to the accumulation of amyloid-β

dementia.[23,24] These changes include gradual atrophy of the cerebral cortex and basal ganglia; region-specific neuronal loss; increased ventricular size; vascular and perivascular changes; lipofuscin accumulation; amyloid-β (Aβ) deposition and tau hyperphosphorylation (see below), amongst others.[14,24,25] In old cats, brain atrophy, neuronal loss, increased ventricular size and widened sulci have all been described, although these changes are usually less pronounced than in people,[15] and as yet, have not been directly associated with cognitive dysfunction.[14,26,27]

Brain atrophy and neuronal loss

The cerebella of aged cats[26] have a reduced number of Purkinje cells and other neurons. In cats, this neuronal loss is more evident within the molecular layer of the cerebellum in animals of 12–13 years of age, compared with 2–3 year old cats.[26]

The initial changes in the caudate nucleus, which include neuronal loss and reduced numbers of synapses,[28,29] appear in cats as young as 6–7 years of age.[5,29] However, these changes are typically more evident in cats over 10 years, when compared with cats between 1 and 3 years of age.[30] They are believed to cause impairments in motor function and the inability to habituate to repeated stimuli in older cats[31–33]; hence, elderly cats can be repeatedly scared by common noises.

The cholinergic system (which regulates attention and higher-order cognitive processing) and the locus coeruleus (which is the main site for norepinephrine/noradrenaline synthesis in the brain, and responsible for promoting arousal at times of stress) are both affected in humans with AD.[34–36] The loss of cholinergic neurons may directly impair cognition.[35,36] Cats aged 15–18 years show myelin disruption, axonal degeneration, and a marked reduction in both the size of cholinergic neurons and the dendritic length in the locus coeruleus, when compared with cats aged 2–3 years.[37] These abnormalities, as well as other neuronal deficits, may cause the alterations in the sleep-wake cycle of affected cats.[37,38]

The hippocampus (an essential area for learning and memory) is also affected. Neuronal loss is seen in cats over 14 years of age, being most severe when both Aβ plaques and hyperphosphorylated tau deposits are present.[39]

Amyloid-β

In humans, amyloid-β (Aβ) cleavage peptides have amino acid sequences of different lengths (Aβ1-42 and Aβ1-40).[40] The aggregation of these proteins is neurotoxic and associated with cognitive impairment and dementia (Figure 3).[40]

Oligomers of Aβ are thought to be the most toxic conformation, resulting in synaptic dysfunction in AD.[41] These Aβ oligomers have been found in the brains of cats over 8 years of age[39]; however, the relationship between these oligomers and behavioural abnormalities remains unclear.

Unlike humans, Aβ deposits in the brains of cats are made predominantly of the peptide Aβ1-42[42,43] and are almost only detectable using certain antibodies, for example, anti-Aβ17-24 (4G8) or Aβ1-42[43]; furthermore, since Aβ in cats do not bind to amino acid residues 1–16 of Aβ (e.g., 6E10),[43] it is possible that Aβ in cats is formed by a cleaved Aβ protein (i.e., amino acid residues 17–42). The lack of Aβ1-40 in cats may be due to its higher solubility and rapid turnover, which impedes its accumulation in the brain.[42,44,45] Interestingly, Aβ1-40 deposition has been reported within blood vessels in cats, associated with cerebral amyloid angiopathy.[46]

Cats over 10 years of age have been shown to aggregate Aβ.[42,43,46–48] However, these accumulations have a more diffuse distribution than those

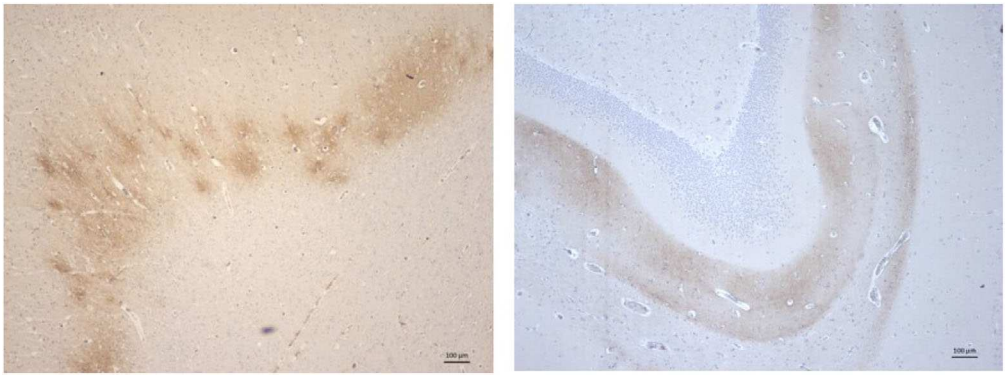


FIGURE 4 Diffuse deposits of amyloid-β (anti-beta amyloid 1-42 mOC64) in the parietal cortex of a 20-year-old cat (left) and in the hippocampus of a 15-year-old cat (right)

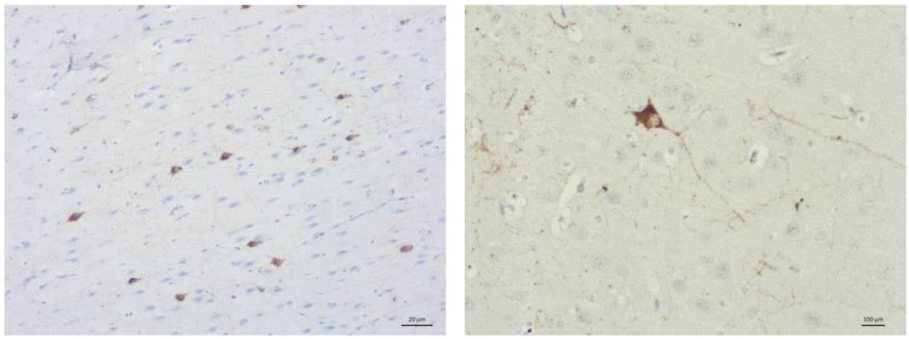


FIGURE 5 Hyperphosphorylated tau immunolabelling (phosphor-tau antibody AT8) in the rostral cortex of a 15-year-old cat (left) and in the parietal cortex of a 16-year-old cat

in humans[14,39,42,43,46,48] (Figure 4). Interestingly, only intracellular Aβ has been reported in the cerebellum of cats, unlike in humans, there are no extracellular plaques.[39,43]

While there are similarities between the Aβ plaque-like deposits seen in cats and those in humans, the Aβ plaque-like deposits in cats are less mature than those in humans with AD; the Aβ plaques in AD have dense cores, which are not seen in the other species.[14,42,46] The pattern and distribution of Aβ in cats with CDS are perhaps more similar to those seen in healthy, non-demented, aged human brains, rather than humans with AD.[14,42,43,46,47] However, cats with Aβ deposits can display abnormal behaviours, such as confusion, excessive vocalisation and wandering,[42,48] although the severity of these behaviours, as yet, does not seem to be well correlated with the extent of Aβ deposition.[43]

Tau pathology

Cats produce a number of different tau isoforms similar to those in humans with AD.[39,43,48] While some studies found no evidence of neurofibrillary tangles (NFTs) in the brains of old cats,[46,49] others found occasional immunostaining for hyperphosphorylated tau deposits, which are an early stage of NFT[39,43,48] (Figure 5). It has been suggested that instead of NFT, cats show a pre-tangle formation.[43,48] As there is only evidence of hyperphosphorylated tau in a small number of cats so far, an association between NFTs and CDS cannot yet be established.[14,39,48] Interestingly, intraneuronal hyperphosphorylated tau is also found in kittens during early postnatal development[50] and as a result of ischaemia and seizures.[43,48]

Vascular pathology

Several vascular and perivascular changes have been associated with neuropathological ageing and CDS in cats. These include micro-haemorrhages, infarcts, a non-lipid variety of arteriosclerosis, and the accumulation of amyloid-β in plaques and sometimes around blood vessels in the brain.[13,14,42]

Cerebral amyloid angiopathy occurs when Aβ accumulates around the meninges and blood vessels.[51,52] It is believed to be a major cause of vascular dysfunction and cognitive decline in humans[53–55]; however, it can also be found in the brains of healthy, non-demented people, suggesting that this pathology is not specific to AD.[51] In cats, there is controversy regarding the existence of cerebral amyloid angiopathy. Some studies have found this in aged cat brains,[3,42,43,46,48] while some have not.[39]

DIAGNOSIS

The diagnosis of CDS is challenging, especially as the clinical signs involve behavioural changes, which can be nebulous and complicated to investigate.

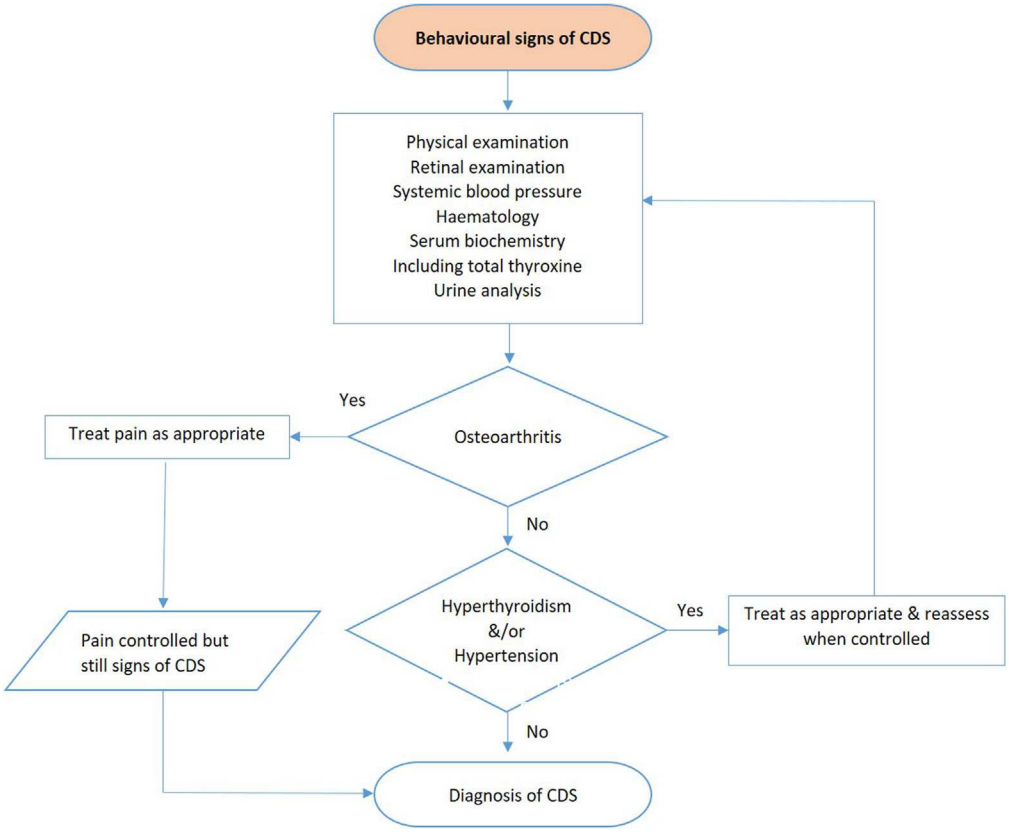


FIGURE 6 Diagnosis of CDS. Veterinarians have to undertake a complete examination of the cat and rule out other potential causes of behavioural changes. Diagram modified and used with permission from Cerna et al. 2020[19]

TABLE 1 Diagnosis of CDS can only be made by ruling out other potential causes of the behavioural changes

Potential causes for behavioural changes
• Hypertension
• Pain (e.g., due to osteoarthritis or other musculoskeletal problems, gastrointestinal, pancreatic or dental disease, etc.; pain may be a more insidious cause of behavioural changes in cats than previously considered [56–58], for this reason, an analgesia trial may be needed to determine whether or not it is playing a role in the behavioural alterations)
• Chronic diseases (e.g., liver or kidney failure)
• Endocrine disorders (e.g., hyperthyroidism or diabetes mellitus)
• Infectious diseases (e.g., toxoplasmosis, feline immunodeficiency virus [FIV], feline leukaemia virus [FeLV], urinary tract infections)
• True behavioural problems (e.g., separation anxiety)
• Neoplasia (e.g., meningioma)
• Inflammatory diseases

Before making a diagnosis of CDS it is necessary to rule out other potential causes of the behavioural changes.[8,14,15] These include pain, hypertension, chronic, endocrine and infectious diseases (Table 1).

Of note, some of these conditions may exacerbate the clinical signs of CDS, such as pain, hyperthyroidism, hypertension, and chronic kidney disease, and since elderly cats are more likely to have a number of concurrent interacting conditions, this can complicate both diagnosis and treatment.[59]

Veterinary surgeons have to conduct a complete evaluation of the cat, assessing its history for medical and behavioural problems, performing a full physical examination (including determining systemic blood pressure), undertaking blood and urine analysis (as needed), and pursuing further diagnostics in many cases (Figure 6). Only then can the veterinary surgeon identify any underlying cause(s) for the behavioural signs. Elderly cats frequently have a number of concomitant interacting conditions, so it can be difficult to establish exactly what role CDS may be playing. However, it is necessary to identify all contributing disorders in order to allow for accurate intervention.[8] Veterinarians need to educate owners on how to recognise and monitor changes in their cat's behaviour, and to report not only any further changes in these behaviours, but also any changes in their cat's body weight, food/water consumption, and urine/faeces production.[59]

MANAGEMENT

Although CDS cannot be cured, appropriate management can reduce its clinical impact, and improve the cats' quality of life. Since it is stressful when a loved cat becomes disoriented and confused—and increased vocalisation at night (i.e., night-crying) can cause broken nights—improving the cat's quality of life can also help the owner, and preserve the cat-owner bond. Potential interventions include environmental enrichment/modification, dietary supplementations, specific diets and medication. Interventions will need to be tailored to each individual cat, its behavioural changes as suggested by the authors' recent study[19]

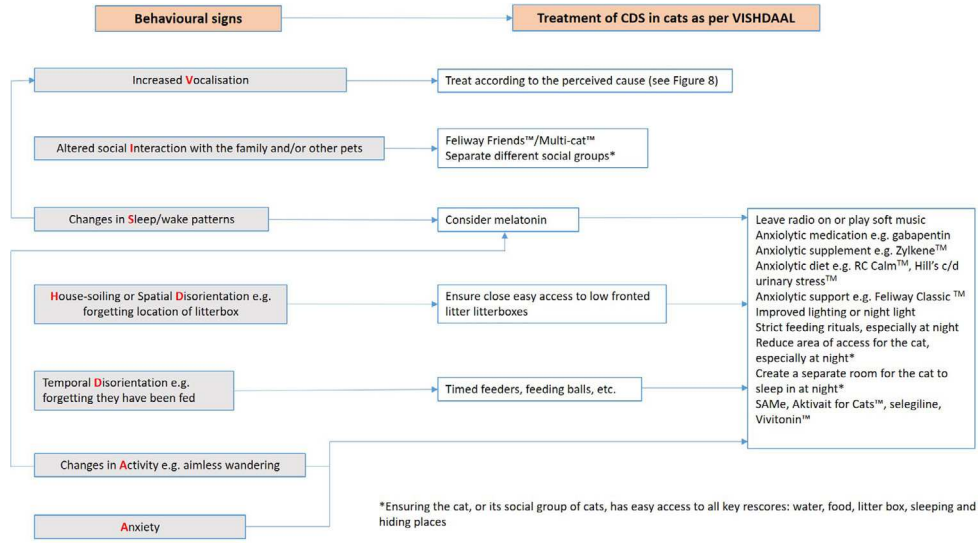


FIGURE 7 Treatment of CDS according to the behavioural changes displayed by the cat

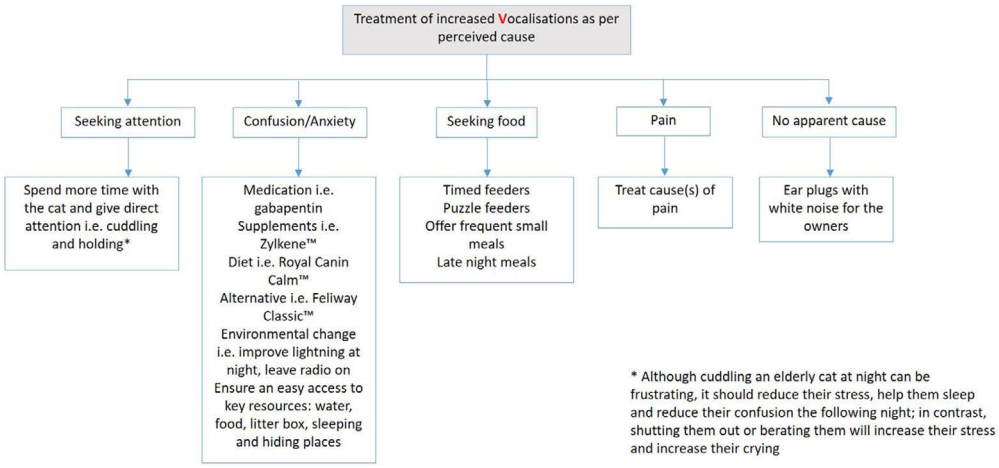


FIGURE 8 Treatment of increased vocalisations as per perceived cause. Diagram modified and used with permission from Cerna et al. 2020[19]

(Figures 7 and 8), and any concomitant illnesses. Unfortunately, as yet, there is little information to indicate which interventions are most likely to help in specific cats, leading to trial and error, which is not ideal in cats that are easily frustrated. More work is urgently needed in this area.

Environmental enrichment/modification

Environmental enrichment provides mental stimulation and increases activity levels; it enhances the growth and survival of neurons, and improves cognition.[14,60] Environmental enrichment can be synergistic with antioxidant-enriched diets.

Poor environmental stimulation increases the risk of developing CDS in later life; it can also cause frustration in cats that have already developed CDS, aggravating it.[61] Environmental enrichment is recommended for all young cats, especially if they have no access outside. Environmental enrichment includes activities and objects that promote play, exploration, hunting, climbing, and perching behaviours, and includes novel ways to obtain food or treats.[8]

However, in older cats with significant to severe CDS, environmental changes can potentially have a negative effect, leading to confusion. These animals cannot cope with changes (e.g., environment, daily routine, diet) and become stressed, thus, exacerbating CDS (e.g., anorexia, hiding, house-soiling).[17,62,63] It is the best for these cats to keep changes to a minimum or to reduce the size of their environment to minimise stress, while ensuring that their key resources are all within easy reach (i.e., food, water, litter box, resting/sleeping places, and escape routes and/or a safe place to hide).[61] Where changes have to be made, for example, where they may improve the cat's quality of life, they need to be made slowly; reassuring the cat frequently, to ensure it does not become too stressed. Since osteoarthritis is very common in older cats, these resources need to be on all floors of the home that the cat can access; raised food bowls can help, as can low fronted litterboxes, etc. The application of synthetic feline pheromone diffusers may help

to reduce anxiety (Feliway Classic; Ceva Animal Health Ltd., Zenifel; Virbac UK)[64] and reduce conflict with other cats (Feliway Friends; Ceva Animal Health Ltd.).

Environmental needs will differ for each cat. Cats that cry for food may be helped by introducing an automatic feeder timed to give many small meals throughout the night, scatter feeding, forage feeding, or being given a feeding ball at night. Cats which cry for their owner's attention may need positive affirmation and reassurance (often at night). In one of the author's (Gunn-Moore) experience, plus evidence from discussion groups showed that while cuddling an elderly cat at night can be frustrating, it will reduce their stress, helping them sleep and so reduce their confusion the following night; in contrast, shutting them out or shouting at them will increase their stress, and so increase their crying. Cats which cry when they wake up confused and disorientated may be helped by having a night-light, leaving a radio on to play soft music or a speech radio station, plugging in synthetic pheromone dispensers (e.g., Feliway Classic), or reducing the area the cat has access to so it cannot get lost so easily.[19] Ultimately, the cat may need to have a room of its own to sleep in, with all of its key resources, including a warm comfortable bed (e.g., a heat pad under a snuggle bed plus a blanket).[59,65] A strict night-time routine with a warm meal, warm bedding and a cuddle before shutting the door at night may help them to settle. Adding a 'kitty camera' can help to reduce owner stress as they can then check on the cat, without waking it up.

Dietary supplements

S-adenosyl-l-methionine (SAMe) (NoviSAMe; generic SAMe) helps to maintain the fluidity of cell membranes and enhances the production of the antioxidant glutathione,[66] and when given to elderly cats, there was an improvement in cognitive tests, including object discrimination and reversal learning; the effects were most evident in cats with mild CDS, suggesting that it is more likely to help early in disease.[67]

While proprietary dietary supplements, such as Senilife (CEVA Animal Health),[8,68] and Aktivait (VetPlus),[69] have been shown to reduce signs of CDS in dogs, there is little evidence of their efficacy in cats. Senilife contains *Gingko biloba*, D- α -tocopherol, vitamins B6 and E, and resveratrol, amongst other components. Although it is labelled for use in cats, no trials have yet been performed in this species.

Aktivait contains omega-3, fish oils, vitamins E and C, L-carnitine, alpha-lipoic acid, and phosphotidylserine, amongst other compounds. It is important to highlight that products developed for dogs are not always safe for cats, for example, Aktivait as it contains alpha-lipoic acid which is toxic in cats.[70] A feline-safe version of Aktivait has been commercially released; however, trials still need to determine its efficacy.

Complementary remedies such as melatonin, plug-in pheromones[8,15] (Feliway Classic and/or Friends aka MulticatCeva Animal Health Ltd.), suntheanine (Pet Remedy and/or Anxitane Virbac), milk protein hydrolysate (Zylkene Intervet Schering Plough)[71], essential oils (e.g., lavender)[8,15,17] and amino acid/herbal combinations (e.g., Help My Pet—Nerves, VetPartners Limited), may help in re-establishing the sleep-wake cycles and reducing anxiety.

Specific diets

Diets high in fruits, vegetables, nuts and whole grains, as well as vitamins C, E and B_{12}, may potentially improve cognition and delay the development of dementia in humans; deficiency in these vitamins is a risk factor for strokes, brain ageing and dementia.[72] Diets enriched with antioxidants are known to decrease oxidative damage, while other compounds, such as alpha-lipoic acid, L-carnitine and omega-3 fatty acids, may have a positive effect in the management of dementia as they enhance the health of the cell membranes and mitochondrial function.[73]

Developing diets to reduce the signs of CDS in cats has proved to be challenging. Some of the compounds used in diets designed for dogs with CDS, for example, alpha-lipoic acid, are toxic in cats,[70] and the effect of diets enriched with MCTs is as yet unclear, as MCTs are unpalatable to cats.[61] Nevertheless, it is believed that MTC consumption may improve feline metabolism.[74]

While no specific diet has been designed for cats with CDS, some diets have shown positive effects. Commercial diets containing fish oils, antioxidants and other supplements (Feline Mature Adult 7+ Hill's Pet Nutrition); and others containing antioxidants, essential fatty acids and dried chicory root (Nestlé Purina Pro Plan Age 7+ Nestlé Purina Pet Care) have been associated with increased longevity compared with non-supplemented diets.[75,76] Another study by Nestlé Purina showed that the brain function of middle-aged and older cats improved significantly when fed a diet supplemented with fish oils, antioxidants, arginine, and vitamin B.[77] A separate study demonstrated that activity levels in aged cats increased when fed with a diet containing tocopherols, vitamin C, beta-carotene, and L-carnitine, amongst other ingredients.[78] Finally, a two-month long questionnaire-based study showed that CDS signs improved in around 70% of the cats that were fed a diet containing antioxidants, essential fatty acids, chondroprotectants, L-carnitine, and lysine, designed to help osteoarthritis (Prescription Diet Feline j/d Hill's Pet Nutrition) (Hill's Pet Nutrition, data on file, 2008).

Diets have been supplemented with milk protein hydrolysate (i.e., α-casozepine) to reduce anxiety (Royal Canin Calm Royal Canin; Hill's Urinary Support Hill's Pet Nutrition). Both diets also contain additional L-tryptophan, to reduce anxiety. A 2017 study reported that cats fed Royal Canin Calm showed reduced fear and anxiety when placed in an unfamiliar location.[79] These diets may potentially reduce anxiety in cats with CDS. Hill's Urinary Support may be of particular use in cats with CDS plus urinary problems, for example,

struvite or oxalate urolithiasis, or feline idiopathic cystitis (FIC – which is significantly affected by stress).[80,81]

Drug treatments

Selegiline (Selgian Ceva Animal Health Ltd.; Anipryl Zoetis) and propentofylline (Vivitonin MSD Animal Health) are licensed in various countries to treat the clinical signs of CDS in dogs.[82–85] Selegiline has undergone many studies, although all in dogs.[82,83,85] It is an inhibitor of monoamine oxidase B, which has a neuroprotective effect as it reduces the production of free radicals and stimulates the production of enzymes that eliminate these free radicals. Propentofylline has neuroprotective properties and increases the blood flow to the heart and brain.[8] Despite these drugs having been shown to have positive effects in dogs with CDS,[86,87] they are not licensed for use in cats; however, positive effects have been anecdotally reported.

Anxiety and altered sleeping patterns are common features in pets with CDS. Antidepressants/anxiolytics, such as fluoxetine (i.e., Prozac), have been used to treat the signs of CDS in pet cats.[61] Other anxiolytics, such as trazodone, gabapentin, benzodiazepines (e.g., alprazolam, diazepam, clonazepam, and lorazepam), or buspirone can be considered.[8,61] However, diazepam in tablet form is not recommended as it may cause acute fulminant liver failure in cats,[88] and care should be taken when combining drugs, such as selegiline, fluoxetine, gabapentin and others that may affect the concentration of serotonin as they could induce serotonin syndrome, seen as pyrexia, agitation, increased reflexes, tremor, sweating, dilated pupils, and diarrhoea. Melatonin may help to restore the sleep cycles.

Given that cats with CDS have reduced numbers of cholinergic neurons,[37] drugs that enhance cholinergic transmission might improve the signs of CDS, such as cholinesterase inhibitor donepezil (Aricept; Pfizer),[89] which is used in people with AD[90]; however, these have not been tested in cats.

It has been suggested that by blocking the specific receptor AT_1, the renin-angiotensin system (RAS) might be inhibited; thus, cognitive function may improve.[91,92] Telmisartan (Semintra; Boehringer Ingelheim) blocks the AT_1 receptor of RAS and partially activates peroxisome proliferator-activated receptor gamma (PPARγ), which regulates neurological disease by preventing inflammation and reducing the accumulation of Aβ plaques in the brain.[93–95] In rodents, telmisartan has been shown to: 1) inhibit inflammation, therefore reducing brain injury after the induction of ischemia[95]; 2) improve post-stroke effects[96]; 3) reduce the death and injury of neurons after glutamate-induced toxicity, which is an important neurotransmitter that, if released in excess, causes neurotoxicity, neuronal death and apoptosis[97]; 4) protect against oxidative damage caused by glucose administration[98]; 5) protect against nutrient deprivation-induced neuronal death[99]; 6) restore cognitive functions after chronic stress-induced cognitive impairment[100]; and 7) prevent cognitive decline.[94,101] A study to assess the efficacy of Telmisartan (Semintra; Boehringer Ingelheim) in cats with CDS is currently being performed by the authors. In addition, there are two ongoing studies aimed to assess the efficacy of telmisartan in treating human patients with AD.[102]

CONCLUSION

As a result of ageing, ever more cats are being recognised with behavioural changes suggestive of CDS, including increased vocalisation and house-soiling, amongst other signs. However, CDS can be challenging to diagnose; it is a diagnosis of exclusion and many other medical disorders can cause similar behavioural changes. It is essential that veterinary surgeons undertake a full assessment of affected cats and educate owners on how to recognise the clinical signs of CDS. Although CDS cannot be cured, there are several interventions that can help to improve the health, welfare and quality of life of the affected cats. The brains of cats with CDS show neuropathological changes similar to those found in the brains of humans with AD and dogs with CDS; these similarities suggest that the domestic cat could be a natural model for AD.

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CONFLICT OF INTEREST

The authors declared no potential conflict of interests with respect to the research, authorship, and/or publication of this article.

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REFERENCES

1. O'Neill DG, Church DB, Mcgreevy PD, Thomson PC, Brodbelt DC. Longevity and mortality of cats attending primary care veterinary practices in England. J Feline Med Surg. 2015;17:125–33.
2. Vogt AH, Rodan I, Brown M, Brown S, Buffington CAT, Forman MJL, et al. AAFP-AAHA feline life stage guidelines. J Am Anim Hosp Assoc. 2010;46:70–85. https://doi.org/10.5326/0460070.
3. Vite CH, Head E. Aging in the canine and feline brain. Vet Clin North Am: Small Anim Pract. 2014;44:1113–29. https://doi.org/10.1016/j.cvsm.2014.07.008.
4. Harrison J, Buchwald J. Eyeblink conditioning deficits in the old cat. Neurobiol Aging. 1983;4:45–51.
5. Levine MS, Lloyd RL, Fisher RS, Hull CD, Buchwald NA. Sensory, motor and cognitive alterations in aged cats. Neurobiol Aging. 1987;8:253–63.
6. Harrison J, Buchwald J. Auditory brainstem responses in the aged cat. Neurobiol Aging. 1982;3:163–71.
7. Landsberg GM. Behavior problems of older cats. In: *Schaumburg I (ed)*: *Proceedings of the 135th Anual Meeting of the*

American Veterinary Medical Association San Diego, CA, 1998 1998, pp. 317-20.
8. Landsberg GM, Nichol J, Araujo JA. Cognitive dysfunction syndrome. a disease of canine and feline brain aging. Vet Clin North Am: Small Anim Pract. 2012;42:749–68.
9. Sparkes A, Manley DS. From small acorns… the new cat friendly clinic/cat friendly practice programmes. J Feline Med Surg. 2012;14:180–1. https://doi.org/10.1177/1098612X12439264.
10. Miele A, Sordo L, Gunn-Moore DA. Feline Aging: Promoting Physiologic and Emotional Well-Being. Vet Clin North Am: Small Anim Pract. 2020;50:719–48.
11. Van Haaften KA, Forsythe LRE, Stelow EA, Bain MJ. Effects of a single preappointment dose of gabapentin on signs of stress in cats during transportation and veterinary examination. J Am Vet Med Assoc. 2017;251:1175–81. https://doi.org/10.2460/javma.251.10.1175.
12. Stevens BJ, Frantz EM, Orlando JM, Griffith E, Harden LB, Gruen ME, et al. Efficacy of a single dose of trazodone hydrochloride given to cats prior to veterinary visits to reduce signs of transport- and examination-related anxiety. J Am Vet Med Assoc. 2016;249:202–7. https://doi.org/10.2460/javma.249.2.202.
13. Landsberg G, Araujo JA. Behavior problems in geriatric pets. Vet Clin North Am: Small Anim Pract. 2005;35:675–98.
14. Gunn-Moore D, Moffat K, Christie L-A, Head E. Cognitive dysfunction and the neurobiology of ageing in cats. J Small Anim Pract. 2007;48:546–53. https://doi.org/10.1111/j.1748-5827.2007.00386.x.
15. Landsberg GM, Denenberg S, Araujo JA. Cognitive dysfunction in cats: a syndrome we used to dismiss as 'old age'. J Feline Med Surg. 2010;12:837–48.
16. Moffat K, Landsberg G. An investigation of the prevalence of clinical signs of cognitive dysfunction syndrome (CDS) in cats. J Am Anim Hosp Assoc. 2003;39:512.
17. Landsberg GM, Hunthausen W, Ackerman L. The effects of aging on the behavior of senior pets. Handbook of Behavior problems of the dog and cat. 2nd ed ed. Oxford: Saunders, 2003, pp. 269-304.
18. Sordo L, Breheny C, Halls V, Cotter A, Tørnqvist-Johnsen C, Caney SMA, et al. Prevalence of disease and age-related behavioural changes in cats: past and present. Vet Sci. 2020;7:1–19.
19. Cerna P, Gardiner H, Sordo L, Tørnqvist-Johnsen C, Gunn-Moore DA. Potential causes of increased vocalisation in elderly cats with cognitive dysfunction syndrome as assessed by their owners. Animals. 2020;10:1092. https://doi.org/10.3390/ani10061092.
20. Milgram NW, Landsberg GM, De Rivera C, et al. Age and cognitive dysfunction in the domestic cat. In: *Proceedings of the ACVB/AVSAB Symposium* St. Louis, 2011 2011, pp. 28-9.
21. Cotman CW, Head E. The canine (dog) model of human aging and disease: dietary, environmental and immunotherapy approaches.J Alzheimer's Dis. 2008;15:685–707.
22. Head E, Liu J, Hagen TM, Muggenburg BA, Milgram NW, Ames BN, et al. Oxidative damage increases with age in a canine model of human brain aging. J Neurochem. 2002;82:375–81.
23. Scheff SW, Price DA, Schmitt FA, Mufson EJ. Hippocampal synaptic loss in early Alzheimer's disease and mild cognitive impairment. Neurobiol Aging. 2006;27:1372–84.
24. West MJ, Coleman PD, Flood DG, Troncoso JC. Differences in the pattern of hippocampal neuronal loss in normal ageing and Alzheimer's disease.Lancet (London, England). 1994;344:769–72.
25. Juraska JM, Lowry NC. Neuroanatomical changes associated with cognitive aging. Curr Top. Behav. Neurosci. 2012;10:137–62.
26. Zhang C, Hua T, Zhu Z, Luo X. Age related changes of structures in cerebellar cortex of cat.J. Biosci. (New Delhi, India). 2006;31:55–60.
27. Dobson H, Denenberg S. Ageing and imaging based neuropathology in the cat. In: *Programs and abstracts of the 17th Congress of ESVCE and 1st Congress of ECAWBM* Avignon, 2011 2011.
28. Levine MS, Adinolfi AM, Fisher RS, Hull CD, Guthrie D, Buchwald NA. Ultrastructural alterations in caudate nucleus in aged cats. Brain Res. 1988;440:267–79.
29. Levine MS, Lloyd RL, Hull CD, Fisher RS, Buchwald NA. Neurophysiological and morphological alterations in caudate neurons in aged cats. Brain Res. 1987;401:213–30.
30. Levine MS, Adinolfi AM, Fisher RS, Hull CD, Buchwald NA, Mcallister JP. Quantitative morphology of medium-sized caudate spiny neurons in aged cats. Neurobiol. Aging 1986;7:277–86.
31. Levine MS, Hull CD, Villablanca JR, Buchwald NA, Garcia-Rill E. Effects of caudate nuclear or frontal cortical ablation in neonatal kittens or adult cats on the spontaneous firing of forebrain neurons. Brain Res. 1982;4:129–38.
32. Levine MS, Hull CD, Buchwald NA, Villablanca JR. Effects of caudate nuclei or frontal cortical ablations in kittens: motor activity and visual discrimination performance in neonatal and juvenile kittens. Exp Neurol. 1978;62:555–69.
33. Villablanca JR, Olmstead CE, Levine MS, Marcus RJ. Effects of caudate nuclei or frontal cortical ablations in kittens: neurology and gross behavior. Exp Neurol. 1978;61:615–34.
34. Muir JL. Acetylcholine, aging, and Alzheimer's disease. Pharmacol Biochem Behav 1997;56:687–96.
35. Bartus R, Dean R, Beer B, Lippa A. The cholinergic hypothesis of geriatric memory dysfunction. Science. 1982;217:408-14.
36. Coyle J, Price D, Delong M. Alzheimer's disease: a disorder of cortical cholinergic innervation. Science. 1983;219:1184–90.
37. Zhang J-H, Sampogna S, Morales FR, Chase MH. Age-related changes in cholinergic neurons in the laterodorsal and the pedunculo-pontine tegmental nuclei of cats: a combined light and elecetron microscope study. Brain Res. 2005;1052:47–55.
38. Chase MH. Sleep patterns in old cats. In: Chase MH, editor. Sleep disorders: basic and clinical research. New York: Spectrum Publications, Inc.; 1983, pp. 445-8.
39. Chambers JK, Tokuda T, Uchida K, Ishii R, Tatebe H, Takahashi E, et al. The domestic cat as a natural animal model of Alzheimer's disease. Acta Neuropathol Commun. 2015;3:78.
40. Gravina SA, Ho L, Eckman CB, Long KE, Otvos L, Younkin LH, et al. Amyloid β protein (Aβ) in Alzheimer's disease brain biochemical and immunocytochemical analysis with antibodies specific for forms ending at Aβ40 or Aβ42 (43). J. Biol. Chem. 1995;270:7013–6.
41. Glabe CG. Common mechanisms of amyloid oligomer pathogenesis in degenerative disease. Neurobiol Aging. 2006;27:570–5.
42. Cummings BJ, Satou T, Head E, Milgram NW, Cole GM, Savage MJ, et al. Diffuse plaques contain C-terminal A beta 42 and not A beta 40: evidence from cats and dogs. Neurobiol Aging. 1996;17:653–9.
43. Head E, Moffat K, Das P, Sarsoza F, Poon WW, Landsberg G, et al. Beta-amyloid deposition and tau phosphorylation in clinically characterized aged cats. Neurobiol. Aging. 2005;26:749–63.
44. Wisniewski T, Lalowski M, Bobik M, Russell M, Strosznajder J, Frangione B. Amyloid Beta 1–42 deposits do not lead to Alzheimer's neuritic plaques in aged dogs. Biochem J. 1996;313:575–80.
45. Hyman BT, Marzloff K, Arriagada PV. The lack of accumulation of senile plaques or amyloid burden in Alzheimer's disease suggests a dynamic balance between amyloid deposition and resolution. J Neuropathol Exp Neurol. 1993;52:594–600.
46. Nakamura S-I, Nakayama H, Kiatipattanasakul W, Uetsuka K, Uchida K, Goto N. Senile plaques in very aged cats. Acta Neuropathol. 1996;91:437–9.
47. Brellou G, Vlemmas I, Lekkas S, Papaioannou N. Immunohistochemical investigation of amyloid beta-protein (Abeta) in the brain of aged cats. Histol Histopathol. 2005;20:725–31.
48. Gunnmoore D, Mcvee J, Bradshaw J, Pearson G, Head E, Gunnmoore F. Ageing changes in cat brains demonstrated by beta-amyloid and AT8-immunoreactive phosphorylated tau deposits. J Feline Med Surg. 2006;8:234–42.
49. Kuroki K, Uchida K, Kiatipattanasakul W, Nakamura S-I, Yamaguchi R, Nakayama H, et al. Immunohistochemical detection

of tau proteins in various non-human animal brains. Neuropathology. 1997;17:174–80.
50. Riederer BM, Mourton-Gilles C, Frey P, Delacourte A, Probst A. Differential phosphorylation of tau proteins during kitten brain development and Alzheimer's disease. J Neurocytol. 2001;30:145–58.
51. Selkoe D, Bell D, Podlisny M, Price D, Cork L. Conservation of brain amyloid proteins in aged mammals and humans with Alzheimer's disease. Science. 1987;235:873–7. https://doi.org/10.1126/science.3544219.
52. Selkoe DJ. Alzheimer's disase: genotypes, phenotype, and treatments. Science. 1997;275:630–1.
53. Attems J. Sporadic cerebral amyloid angiopathy: pathology, clinical implications, and possible pathomechanisms. Acta Neuropathol. 2005;110:345–59.
54. Attems J, Jellinger KA, Lintner F. Alzheimer's disease pathology influences severity and topographical distribution of cerebral amyloid angiopathy. Acta Neuropathol. 2005;110:222–31.
55. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. Cold Spring Harbor Perspec Biol. 2011;1:a006189.
56. Slingerland LI, Hazewinkel HAW, Meij BP, Picavet Ph, Voorhout G. Cross-sectional study of the prevalence and clinical features of osteoarthritis in 100 cats. Vet J. 2011;187:304–9.
57. Lascelles BDX, Dong Y-H, Marcellin-Little DJ, Thomson A, Wheeler S, Correa M. Relationship of orthopedic examination, goniometric measurements, and radiographic signs of degenerative joint disease in cats. BMC Vet Res. 2012;8:10.
58. Enomoto M, Lascelles BDX, Gruen ME. Development of a checklist for the detection of degenerative joint disease-associated pain in cats. J Feline Med Surg. 2020;22:1137–47. https://doi.org/10.1177/1098612X20907424.
59. Gunn-Moore DA. Cognitive dysfunction in cats: clinical assessment and management. Top Companion Anim Med. 2011;26:17–24. https://doi.org/10.1053/j.tcam.2011.01.005.
60. Head E. Combining an antioxidant-fortified diet with behavioral enrichment leads to cognitive improvement and reduced brain pathology in aging canines: strategies for healthy aging. Ann N Y Acad Sci. 2007;1114:398–406.
61. Gunn-Moore D. Cognitive dysfunction in the cat. In: Little SE and August JR, editors August´s consultation in feline internal medicine, Volume 7. St. Louis: Elsevier, 2016, pp. 977-85.
62. Houpt KA, Beaver B. Behavioral problems of geriatric dogs and cats. Vet Clin North Am: Small Anim Pract. 1981;11:643–52. https://doi.org/10.1016/S0195-5616(81)50076-3.
63. Landsberg GM, Deporter T, Araujo JA. Management of anxiety, sleeplessness and cognitive dysfunction in the senior pet. Vet Clin North Am: Small Anim Pract 2011;41:565–90.
64. Griffith CA, Steigerwald ES, Buffington CAT. Effects of a synthetic facial pheromone on behavior of cats. J Am Vet Med Assoc. 2000;217:1154–6.
65. Ellis SLH, Rodan I, Carney HC, Heath S, Rochlitz I, Shearburn LD, et al. AAFP and ISFM feline environmental needs guidelines. J Feline Med Surg. 2013;15:219–30.
66. Bottiglieri T. S-Adenosyl-L-methionine (SAMe): from the bench to the bedside - molecular basis of a pleiotrophic molecule. Am J Clin Nutr. 2002;76:1151S-7S.
67. Araujo JA, Faubert ML, Brooks M, Landsberg GM, Lobprise H. NOVIFIT (NoviSAMe) tablets improve executive function in aged dogs and cats: implications for treatment of cognitive dysfunction syndrome. Intern J Appl Res Vet Med. 2012;10:90–8.
68. Araujo JA, Landsberg GM, Milgram NW, Miolo A. Improvement of short-term memory performance in aged beagles by a nutraceutical supplement containing phosphatidylserine, Ginkgo biloba, vitamin E, and pyridoxine. Can Vet J. 2008;49:379–85.
69. Heath SE, Barabas S, Craze PG. Nutritional supplementation in cases of canine cognitive dysfunction-a clinical trial. Appl. Anim Behav Sci. 2007;105:284–96. https://doi.org/10.1016/j.applanim.2006.11.008.
70. Hill AS, Werner JA, Rogers QR, O'neill SL, Christopher MM. Lipoic acid is 10 times more toxic in cats than reported in humans, dogs or rats. J Anim Physiol Anim Nutr 2004;88:150–6.
71. Meyer HP, Bečvářová I. Effects of a urinary food supplemented with milk Protein hydrolysate and L-tryptophan on feline idiopathic cystitis - results of a case series in 10 cats. Int J Appl Res Vet Med 2016;14:59–65.
72. Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, et al. Dietary patterns and risk of dementia: the three-city cohort study. Neurology. 2007;69:1921–30.
73. Butterfield DA, Castegna A, Pocernich CB, Drake J, Scapagnini G, Calabrese V. Nutritional approaches to combat oxidative stress in Alzheimer's disease. J Biochem 2003;14:444–61.
74. Trevizan L, De Mello Kessler A, Bigley KE, Anderson WH, Waldron MK, Bauer JE. Effects of dietary medium-chain triglycerides on plasma lipids and lipoprotein distribution and food aversion in cats. Am J Vet Res. 2010;71:435–40.
75. Cupp CJ, Jean-Phillipe C, Kerr WW, Patil AR, Perez-Camargo G. Effect of nutritional interventions on longevity of senior cats. Int J Appl Res Vet Med 2006;4:34–50.
76. Cupp CJ, Kerr WW, Jean-Philippe C, Patil AR, Perez-Camargo G. The role of nutritional interventions in the longevity and maintenance of long-term health in aging cats. Int J Appl Res Vet Med 2008;6:69–81.
77. Pan Y, Araujo JA, Burrows J, De Rivera C, Gore A, Bhatnagar S, et al. Cognitive enhancement in middle-aged and old cats with dietary supplementation with a nutrient blend containing fish oil, B vitamins, antioxidants and arginine. Br J Nutr. 2013;110:40–9.
78. Houpt K, Levine E, Landsberg G, et al. Antioxidant fortified food improves owner perceived behaviour in the aging cat. In: *Proceedings of the ESFM Conference* Prague, Czech Republic, 2007 2007.
79. Landsberg G, Milgram B, Mougeot I, Kelly S, De Rivera C. Therapeutic effects of an alpha-casozepine and L-tryptophan supplemented diet on fear and anxiety in the cat. J. Feline Med. Surg. 2017;19:594–602.
80. Naarden B, Corbee RJ. The effect of a therapeutic urinary stress diet on the short-term recurrence of feline idiopathic cystitis. Vet Med Sci. 2019;6:32-8. https://doi.org/10.1002/vms3.197.
81. Westropp JL, Kass PH, Buffington CAT. Evaluation of the effects of stress in cats with idiopathic cystitis. Am J Vet Res. 2006;67:731–6. https://doi.org/10.2460/ajvr.67.4.731.
82. Ruehl WW, Bruyette DS, DePaoli A, Cotman CW, Head E, Milgram NW, et al. Canine cognitive dysfunction as a model for human age-related cognitive decline, dementia, and Alzheimer's disease: clinical presentation, cognitive testing, pathology and response to l-deprenyl therapy. Prog Brain Res. 1995;106:217–25.
83. Campbell S, Trettien A, Kozan B. A noncomparative open-label study evaluating the effect of selegiline hydrochloride in a clinical setting. Vet Ther: Res Appl Vet Med. 2001;2:24–39.
84. Parkinson FE, Rudolphi KA, Fredholm BB. Propentofylline: a nucleoside transport inhibitor with neuroprotective effects in cerebral ischemia. Gen Pharmacol. 1994;25:1053–8.
85. Milgram NW, Ivy GO, Head E, Murphy MP, Wu PH, Ruehl WW, et al. The effect of l-deprenyl on behavior, cognitive function, and biogenic amines in the dog. Neurochem Res. 1993;18:1211–9.
86. Landsberg G. Therapeutic options for cognitive decline in senior pets. J. Am. Anim. Hosp. Assoc. 2006;42:407–13.
87. Studzinski CM, Araujo JA, Milgram NW. The canine model of human cognitive aging and dementia: pharmacological validity of the model for assessment of human cognitive-enhancing drugs. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 2005;29:489–98.
88. Center SA, Elston TH, Rowland PH, Rosen DK, Reitz BL, Brunt JE, et al. Fulminant hepatic failure associated with oral administration of diazepam in 11 cats.J Am Vet Med Assoc. 1996;209:618–25.
89. Araujo JA, Greig NH, Ingram DK, Sandin J, De Rivera C, Milgram NW. Cholinesterase inhibitors improve both memory and complex learning in aged Beagle dogs.J Alzheimer's Dis. 2011;26:143–55.

90. Doody RS. Current treatments for Alzheimer's disease: cholinesterase inhibitors. J Clin Psychiatry. 2003;64(Suppl 9):11–17.
91. Fogari R, Mugellini A, Zoppi A, Derosa G, Pasotti C, Fogari E, et al. Influence of losartan and atenolol on cognitive function in very elderly hypertensive patients. J Hum Hypertens. 2003;17:781–5.
92. Papademetriou V. Hypertension and cognitive function. Blood pressure regulation and cognitive function: a review of the literature. Geriatrics. 2005;60:20–2.
93. Camacho IE. Peroxisome-proliferator-activated receptor gamma induces a clearance mechanism for the amyloid-beta peptide. J Neurosci. 2004;24:10908–17.
94. Tsukuda K, Mogi M, Iwanami J, Min Li-J, Sakata A, Jing F, et al. Cognitive deficit in amyloid-beta-injected mice was improved by pretreatment with a low dose of telmisartan partly because of peroxisome proliferator-activated receptor-gamma activation. Hypertension. 2009;54:782–7.
95. Pang T, Wang J, Benicky J, Sánchez-Lemus E, Saavedra JM. Telmisartan directly ameliorates the neuronal inflammatory response to IL-1b partly through the JNK/c-Jun and NADPH oxidase pathways. J. Neuroinflammation 2012;9:1–19.
96. Kasahara Y, Taguchi A, Uno H, Nakano A, Nakagomi T, Hirose H, et al. Telmisartan suppresses cerebral injury in a murine model of transient focal ischemia. Brain Res. 2010;1340:70–80.
97. Wang J, Pang T, Hafko R, Benicky J, Sanchez-Lemus E, Saavedra JM. Telmisartan ameriolates glutamate-induced neurotoxicity: roles of AT(1) receptor blockade and PPARγ activation. Neuropharmacology. 2014;79:249–61.
98. Eslami H, Sharifi AM, Rahimi H, Rahati M Protective effect of telmisartan against oxidative damage induced by high glucose in neuronal PC12 cell. Neurosci Lett. 2014;558:31–6.
99. Pang T, Sun Li-X, Wang T, Jiang Z-Z, Liao H, Zhang L-Y. Telmisartan protects central neurons against nutrient deprivation-induced apoptosis in vitro through activation of PPARγ and the Akt/GSK-3β pathway. Acta Pharmacol Sin. 2014;35:727–37.
100. Wincewicz D, Braszko JJ. Telmisartan attenuates cognitive impairment caused by chronic stress in rats. Pharmacol Rep. 2014;66:436–41.
101. Mogi M, Li J-M, Tsukuda K, Iwanami J, Min Li-J, Sakata A, et al. Telmisartan prevented cognitive decline partly due to PPAR-gamma activation. Biochem Biophys Res Commun. 2008;375:446–9.
102. de Barros A Telmisartan, https://alzheimersnewstoday.com/telmisartan/ Accessed 25 February 2019.

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