Feline cognitive dysfunction syndrome

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Introduction

Cognitive dysfunction is a condition of the older cat, and so of growing importance to the practitioner as the feline population demographic ages. In the USA, there has been a 15% increase in the number of cats over 10 years old within the last 20 years, and more than 18 million cats in the USA are now 12 years or older (1), whereas in the UK there are an estimated 2.5 million senior cats, about 30% of the owned population; across Europe, the total is around 20 million (30% of the pet cat population) (2). Accordingly, there is a need for the veterinary profession to focus more attention on quality of life issues and not simply accept certain changes as inevitable. Unfortunately, there is no consensus at which a cat becomes physiologically senior, since individuals may age at different rates. A pragmatic way to classify older cats is to consider those between 7-10 years old as “middle-aged”, those between 11-14 years old as “senior”, and those over 15 years old as “geriatric”. When it comes to brain deterioration, 50% of cats have signs of dementia at 15 years of age; in humans, approximately 50% of 85 years old have such signs (3-5). In this article, for the sake of simplicity, the term “senior” refers to all older cats.

KEY POINTS

- **Cognitive dysfunction syndrome (CDS) is a condition of the older cat and is of growing importance to the practitioner as the feline population demographic ages.**
- **CDS must be distinguished from other age-related changes which may cause superficially similar signs.**
- **CDS cannot be cured, but its progress can be slowed, and clinical signs may be improved with medical and behavioral intervention.**
- **There is a need for the veterinary profession to focus more attention on quality of life issues and not simply accept certain changes as inevitable.**

Cognitive dysfunction syndrome (CDS) is a specific disorder affecting both older dogs (in whom it is well studied as a model of human Alzheimer’s dementia) and cats. CDS needs to be distinguished from other age-related changes (which can cause superficially similar signs) as its neurological features indicate specific interventions which can be unhelpful or even contra-indicated in the management of some of its differentials. Although behavior is controlled by the brain, it is important to appreciate that not all age-related behavior problems are due to poor brain function; behavioral problems in senior individuals can reflect age-related deterioration in a wide range of

tissues. For example, house-soiling may start because of the pain associated with arthritis when trying to access a litter tray. Irritability manifested as aggressive behavior may result from general discomfort (*e.g.*, dental pain), or metabolic diseases such as hyperthyroidism, and increased anxiety may be a sign of chronic kidney disease. These changes may be the first overt sign of the more remote problem and are therefore important in enabling an early diagnosis. To accept such alterations in the senior cat as "inevitable effects of aging" is to disregard the care of patients, and this article aims to provide an overview of brain aging, and especially feline CDS, whilst offering guidance to the practitioner on diagnosis and potential treatment options.

Aging and CDS

Neuropathology of age-related brain changes

The association between neuropathology and age-related behavioral disorders in cats is not well defined. However, as with humans and dogs, there are changes in cat brain anatomy and physiology, such as cerebral atrophy, resulting in increased ventricular size, widening of sulci ***(Figure 1)*** and atrophy of the cholinergic system in the locus ceruleus which may explain disruption of the sleep-wake cycle (6). Abnormal mitochondria, large vacuoles and accumulation of lipofuscin have been observed ultrastructurally, with fewer microfilaments on dendrites in this area (7).

Brain aging and CDS are not the same, and the former does not necessarily result in the latter; CDS has specific pathological features. Aβ plaque formation, which is thought to be involved in brain aging and Alzheimer's disease in humans, has been found in the brain of cats as well (3), but the distribution is different and the association between Aβ deposition and CDS in senior cats (unlike Alzheimer's in humans or CDS in dogs) has not been confirmed. One study of three aged cats with abnormal behavior demonstrated senile plaques in the brain (8), and whilst one paper reported that these plaques were more common in cats with behavioral disorders (9), another study of cats with well documented CDS failed to demonstrate a correlation between behavioral changes and Aβ formation (3). Hyperphosphorylated tau fibrils, another feature of human Alzheimer's, can also be found in cats with senile plaque formation, but the association between it and CDS has yet to be established (3,9).

Behavioral changes during aging

As a cat ages, many behavioral alterations may occur that are often overlooked or viewed as inevitable age-related changes. Owners appear to seek help largely for those changes that impact on their own quality of life, *e.g.*, when a cat soils in the house or is aggressive, but other changes may occur more frequently ***(Table 1)***, and many common changes may therefore go unreported by owners unless they are specifically raised by the veterinarian. One survey suggested 75% of owners will report signs of CDS when specifically asked about them, but only 12% volunteer this information (10), and many cases go undiagnosed; one study found 14% of animals aged 8-19.75 years had CDS but the diagnostic prevalence was only 1.9% (11). In cats aged 11-21 years, it has been found that 36% exhibited behavioral signs that could not be attributed to any underlying medical disease (12); between 11-14 years of age the most common alteration was in social alteration, while in those > 15 years old the most frequent change was excessive vocalization and altered activity levels.

Diagnosis of behavioral problems

General approach

The diagnosis of feline CDS is often a diagnosis of exclusion, inferred *ante-mortem* in older cats when there has been a decline in a particular cluster of behaviors

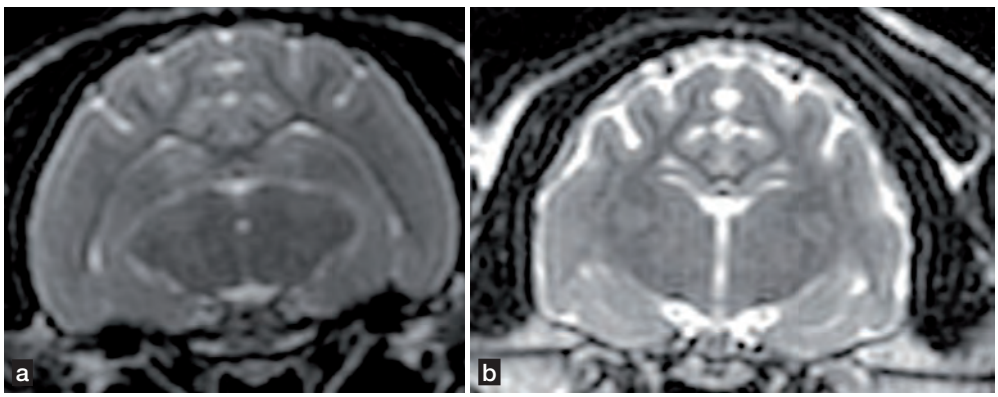

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Figure 1. Transverse MRI sections from 1-year-old **(a)** and 13-year-old **(b)** cats. The CSF appears white. In the older cat, the ventricles are enlarged, but cortical atrophy has caused the sulci to increase in size, and are therefore more prominent as a result.

Table 1. Comparisons of behavioral problems as reported by owners of senior cats to three referral practices and more generally (VIN - Veterinary Information Network - data) (13).

Behavioral referral practices (83 cats, aged > 10 years)	VIN boards (100 cats, aged 12-22 years)
House soiling (elimination and marking) 73%	Excessive vocalization 61% (night vocal 31%)
Intercat aggression 10%	House soiling (elimination and marking) 27%
Aggression to humans 6%	Disorientation 22%
Excessive vocalization 6%	Aimless wandering 19%
Restlessness 6%	Restlessness 18%
Overgrooming 4%	Irritability/aggression 6%
	Fear/hiding 4%
	Clinging attachment 3%

associated with cognitive ability that cannot be attributed to any related medical conditions. These signs typically include disorientation or confusion, alterations in social relationships (following the owner more or social withdrawal), a change in activity, alterations in the sleep-wake cycle, inappropriate vocalization, a decline in learning and memory, a change in interest in food, and decreased grooming activity (14). When a senior cat is presented with behavioral problems, two main differential categories must be excluded: firstly, environmental changes that affect the cat's behavior, *e.g.* a new baby or pet, a house move etc.; and secondly (and more difficult to exclude), other medical problems. During aging, cats are likely to develop an increasing number of both intra- and extra-cranial health problems, but it can be particularly difficult sometimes to diagnose what role, if any, they play in the cat's behavior. Intra-cranial differentials include pathologies such as forebrain meningiomas and vascular accidents which can cause either sensory deficits or motor control problems. Extra-cranial differentials include a range of metabolic disorders, especially those affecting liver or kidney function, endocrine problems such as hyperthyroidism, and various conditions which compromise cardiorespiratory and circulatory function. Perhaps most important are causes of pain such as arthritis or periodontal disease. Periodontal disease may occur in over 60% of cats older than 3 years (15) and osteoarthritis may be present in 70-90% of cats over 10 years of age (14). The latter may not present as an obvious lameness, but instead as abnormal elimination habits, poor grooming and/or aggressive behavior (16). It is also important to realize that other behavioral problems, such as anxiety, may coexist alongside CDS and any concurrent medication for other conditions may also impact on behavior.

Approach to feline CDS

It is suggested that the acronym DISHA, which is used to describe the cardinal signs of CDS in dogs, can also be applied to cats. DISHA refers to:

- **D**isorientation
- **I**nteraction alterations with owners and other pets
- **S**leep-wake cycle changes
- **H**ousesoiling
- **A**ctivity level alterations (decreased or increased)

However, other signs such as excessive vocalization, altered response to stimuli, reduced self-hygiene and alteration in appetite may also be important to the diagnosis of feline CDS (13), but these changes are reported quite frequently in senior cats with other conditions and so the diagnosis is based on careful evaluation of these signs in the context of the individual. It is unreasonable to expect exclusion of all other medical options before suggesting a diagnosis of CDS.

When spatial disorientation is reported (*e.g.*, where the cat is trapped in a corner or stares at a wall), neurologic disorders such as sensory deficits, pain and disrupted motor functions must be ruled out. Disorientation was reported in 22% of senior cats in general practice (13) and is often taken as a strong indicator of potential CDS, as few common medical conditions will result in similar behavior, especially if other neurological deficits are absent.

A cat may show altered social interactions such as irritability or wanting to be near people or other cats, with aggressive behavior occurring in ~6-10% of senior cats (13), but before suggesting these signs are associated with CDS, medical conditions relating to pain and sensory deficits should be ruled out, alongside specific behavioral conditions such as attention seeking or social conflict in the home.

An abnormal sleep-wake cycle, with the cat waking up, vocalizing and disturbing the owner during the night, may also be the result of pain, sensory deficit and hypertension and is the most common owner-reported problem (61% of cases (13)). A cat with painful joints due to osteoarthritis may avoid resting in the same position for a long period of time and will no longer sleep through the night. This is an obvious welfare concern, and so the evaluation of painful medical conditions (*e.g.*, with radiographs or a trial with a short analgesia course) should be a priority if alterations in the sleep-wake cycle are thought to be a sign of CDS.

House soiling (*i.e.*, urine or feces outside the litter tray) is a major reason for owners seeking help from their veterinarian; 27% of senior cats presented with behavioral problems show this sign (13). Whilst house soiling by senior cats may be caused by many of the same conditions that affect younger cats (*e.g.*, cystitis, colitis, litter tray aversion, scent marking etc.), the likelihood that painful conditions can alter use of a litter box is greater in older animals; *e.g.*, osteoarthritis may limit the potential to climb a staircase to access a tray sited in an upper room. For this reason, investigation of litter tray and changes to the environment are essential when considering the potential significance of house-soiling to CDS, and while CDS may well cause house soiling it does not exclude concurrent medical or behavioral issues.

Senior cats can be expected to decrease their activity level due to chronic pain and musculoskeletal weakening, and it is important to appreciate that a CDS related change in activity will often coexist alongside decreased activity due to other conditions, and in these cases both must be recognized and addressed accordingly. Senior cats may also increase their activity level, in the form of repetitive activity, aimless wandering or restlessness for many reasons. These behaviors can be elicited by painful, metabolic or behavioral conditions such as anxiety as well as being specifically evoked by CDS. Increased or decreased activity level is present in 20% of senior cats in first opinion practice (13), and decreased activity in itself as an aid to diagnosing CDS is generally low as it has so many other explanations; on the other hand, increased activity levels are perhaps more indicative of potential CDS, especially when the form of increased activity is carefully examined, any pain has been controlled and hyperthyroidism ruled out.

Other behaviors that are described in senior cats include excessive vocalization, altered response to stimuli, decreased self-hygiene and altered appetite and may be linked to both age-related extra-cranial medical changes and CDS. Pain, sensory deficits and hypertension are particularly important to evaluate alongside CDS. Excessive vocalization is one of the most common owner complaints, with 61% of elderly cats showing this sign in first opinion practices (13), and if painful conditions can be excluded it is one of the more useful signs in the diagnosis of CDS. CDS-related changes may also result in specific anxiety problems as well as temperament alterations.

Often, CDS is characterized by a steady progression, and so evaluating any recent change can be useful. A simple standard questionnaire that covers the points raised above may be useful in this regard.

Treatment options

CDS cannot be cured, but its progress can be slowed and clinical signs may be improved with medical and behavioral intervention. Early diagnosis and treatment are important not only for the improvement of the cat's quality of life, but for the owners' too. Options include behavioral measures, pharmacotherapy, and nutritional supplements, and along with other general measures for aging may work synergistically to improve a senior cat's welfare. Where CDS is accompanied by anxiety, appropriate psychoactive medication should be considered and/or pheromonatherapy; the latter may be particularly useful when there are medical contra-indications to the use of drugs and when the primary signs relate to disorientation.

Pharmacotherapy

Selegiline and propentofylline are licensed in some countries for CDS and age-related changes in dogs, and can be used in cats, but the potential benefits (which can be very large) need to be weighed against the risks. Selegiline, a monoamine oxidase B inhibitor, is said to help ameliorate signs such as disorientation, excessive vocalization, decreased affection and repetitive activity, with a recommended dose of 0.5-1.0 mg/kg q24H (17). The most common adverse effects are gastrointestinal signs,

but are rarely significant in otherwise healthy animals, and in the authors' opinion it is the drug of first choice in cats with clear signs of CDS. Propentofylline, a xanthine derivative which increases cerebral blood flow, has been used to treat older dogs suffering from dullness and lethargy, and anecdotally has been reported to be effective in aged cats as well at 12.5 mg (quarter of a 50 mg tablet) per cat q24H (18).

Products that enhance cholinergic activity or which increase acetylcholine secretion may also have beneficial effects in cats with CDS, but their efficacy, pharmacokinetics and toxicity have yet to be established (7), and so their use is perhaps best left to specialists. Given the evidence for reduced cholinergic activity in the brains of cats with CDS, it is better to avoid anticholinergic drugs (*e.g.*, atropine, scopolamine, trihexyphenidyl and propantheline).

Nutritional and dietary therapy

There are few scientific studies on dietary treatment options for cats with CDS, and so many decisions are based on an adaptation of interventions used in other species. Dietary management with vegetables, nuts, whole grains and vitamins E and C can reduce the risk of cognitive decline and dementia in humans, and various dietary products containing antioxidants, fish oils and other nutritional supplements are promoted for use in cats with age-related problems. There is no peer-reviewed literature to support their value, but they may be useful adjuncts in certain situations. A preliminary study involving 46 cats on a diet supplemented with tocopherols, carnitine, vitamin C, beta-carotene, docosahexaenoic acid, methionine and cysteine reported that owners perceived improved behavior compared to subjects on a control diet (19), but it remains uncertain which of the many ingredients may actually be effective. Another supplement containing choline, phosphatidylcholine, methionine, inositol, vitamin E, zinc, selenium, taurine and other B vitamins was reported to improve confusion and appetite in 9 out of 21 cats (20). Theoretically, diets supplemented with medium-chain triglycerides may benefit aged cats but have not been evaluated in feline CDS (21). Peer-reviewed efficacy studies on even the commercially available supplements for senior cats are sadly lacking, with claims based on purely theoretical grounds and anecdote. These include herbal and nutritional supplements (such as those based on ginkgo biloba, pyridoxin, vitamin E and resveratrol), and a specific feline supplement containing phosphatidylserine, omega-3 fatty acids, vitamins E and C, L-carnitine, coenzyme Q and selenium. Note that some canine products containing alpha-lipoic acid should be avoided, because the ingredients used may be toxic to cats. However, at least one product for cats, based on S-adenosylmethionine, has been shown in a placebo-controlled laboratory test to be associated with better performance in a learning task in aged subjects (22).

Environmental modification

Environmental enrichment plays a specific role in maintaining the cognitive functioning of cats, but it is important to ensure that the animal maintains control over its environment. Excessive psychological demand will antagonize the improvement sought from enrichment, so the introduction of any new potential stressors such as environmental changes must be managed with care. The aim should be to maintain the general environmental context of the cat, while introducing new, low intensity, interesting stimuli. A young kitten to "brighten up the old cat" is not recommended. Some cats with CDS may have difficulty in coping with environmental changes or learning new routines, and so alterations may need to be quite limited and focused, with essential changes made very gradually. Some cats, especially those who get easily disoriented, can benefit from a restructuring of their environment to simplify their core area by providing everything that the cat needs (food, litter box, resting area, etc.) in a single room (14). It is also important to maintain a structured daily routine to assist temporal orientation.

Cats should have sufficient outlets and scope for maintaining their normal behavioral patterns. Plans may be required to ensure sufficient play for the cat, *e.g.*, using toys rather than social "rough-and-tumble" games. Alternative activities like hide-and-seek activities or reward-based training, and new forms of object play (*e.g.*, food manipulating toys and hanging food toys) can provide useful mental stimulation if they are not frustrating. For this reason, electronic games like laser mice and hunting on a computer screen are not recommended, as there is often no physically satisfying outlet for the cat at the end.

General adaptations

Medical conditions, and especially painful degenerative conditions, become more frequent as a result of aging, and owners should facilitate the compensations required as a result to protect their cat's welfare by modifying the domestic environment accordingly. Senior cats may be less comfortable about going outside or upstairs, and there may be an increased risk of elimination in the house

if a downstairs litter tray is not provided in an appropriate, easily accessible location. Low-sided trays on every floor accessed by the cat are recommended and should be in suitably private areas. Providing a ramp up to any cat-flap or favored area may help an animal access it more easily ***(Figure 2)***. Readily accessible food and water are also essential, and improved access may be preferred rather than relocating the feeding station. If a new location is to be used, it is worth providing several bowls initially in more easily accessible areas to see which are preferred by the cat to minimize the stress of the change.

Prognosis and long-term outlook

Early diagnosis is most important to slowing the rate of change due to CDS (which cannot be cured), and routine screening of older cats for potential signs should be the norm, with the veterinarian taking a proactive role in this regard and raising client awareness about the substantial potential to maintain a good quality of life as the cat ages. Expensive diagnostic procedures (*e.g.*, MRI) are rarely justifiable when a rational methodological approach is used in a way that focuses on welfare and risk management to identify and support cats with possible CDS.

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Figure 2. Steps and other innovations can help older cats to continue to access preferred places, such as raised areas, as they age.

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