12 Physiological and Pathological Causes of Behavioural Change

Introduction

Overt behaviour is the consequence of a cat perceiving some change in its environment, evaluating this change, deciding on an appropriate response and the response being generated through the motor systems of the brain to the elements of the skeletal system that control activity. Hence, although behaviour occurs as a consequence of changes in the external environment, the responses generated also depend on internal variations in the processing of information. These processes are susceptible to alteration due not only to normal physiological variations but also to pathological changes. Interpretation of behaviour, therefore, requires an understanding of how the generation of behaviour is modulated by factors influencing the internal state, as well as how responses are generated to events in the external environment.

Pathological changes can be the sole cause of behavioural change – indeed, behavioural signs such as lameness are common first indicators of disease in veterinary medicine. In some cases complex behavioural signs, such as aggressive behaviour towards an owner, can occur entirely as a consequence of pathological events, such as focal seizures. Although such events are rare, their characteristics need to be distinguished from behaviours generated in response to external stimuli when investigating the cause of undesired behaviours. However, physiological or pathological changes more commonly modify cats' behaviour rather than solely cause it. This is through alterations in one or more of the following: (i) perception of external events; (ii) the motivation to show a response; (iii) the threshold at which a response is shown; and (iv) the manner in which a response is generated. Understanding the way that behaviour develops in individual cats, therefore, requires both an understanding of how behaviour is modulated through learning (see Chapter 3, this volume) and how disease can modify such processes. The physical examination of cases by a veterinary surgeon is therefore important before investigating individual cases of undesired behaviour (Fatjó and Bowen, 2009).

In addition to disease processes being important factors in the development of undesired behaviours, cats' responses to their environment can also influence the onset or development of disease. For example, stress can influence susceptibility to infectious disease, or the shedding of infectious agents from animals with carrier status (e.g. Addie *et al*., 2009). Stress caused by environmental factors also influences immune functioning and the onset of bouts of chronic diseases such as feline idiopathic cystitis (Seawright *et al*., 2008).

Since it is impractical to consider all possible medical causes of behavioural change here, we will use a functional approach to consider how disease processes may alter the motivation for behavioural responses in the cat, modify their occurrence or generate new responses. First, we consider how physiological or pathological changes may alter an individual cat's relative motivation to show behaviour, hence changing its frequency or timing. Next, we examine how normal behavioural responses to external events can be modified by internal factors, and where behaviours are generated by disease states. Finally, we give examples of how individual responses to the environment can influence the onset of disease in the cat.

Effects on Motivation to Show Normal Behaviour

Increased or decreased motivation to show normal responses, or the initiation of new behaviours, can all occur in association with physiological and pathological changes. Normal physiological variations that may influence the initiation of behaviour include the fluctuation of female reproductive hormones over the oestrous cycle in entire females. For example, profound changes in the behaviour of entire queens occur with the oestrous cycle, notably related to mate seeking (see Chapter 8, this volume), and this may or may not be seasonal depending on regional photoperiods (Faya *et al*., 2011).

Disease processes can also modify the initiation of behaviour by altering underlying motivation. For example, a cat's motivation to acquire food may be increased by endocrine disorders such as hyperthyroidism (Salisbury, 1991). In such cases, behaviours aimed at obtaining food, such as vocalizing or rubbing around the owner, occur more frequently or in different spatial or temporal contexts. Similarly, conditions decreasing appetite may reduce food-soliciting behaviours towards the owner. Excessive eating or drinking caused by a medical condition will inevitably lead to a higher frequency of toileting behaviour. Hence a cat with a condition causing polydipsia (excessive drinking) may potentially show signs of inappropriate urination, because access to toileting sites becomes limiting with the increased need to eliminate. Similarly in conditions affecting metabolic rate or body temperature, cats may show altered motivation to seek sources of heat (e.g. in hyperthyroidism) or cool locations (e.g. fever). In some cases such changes can lead to the onset of undesired behaviours, perhaps in combination with situational factors. For example, a cat in a household with others that are not socially compatible may only be able to access a litter box intermittently, but concurrent disease-induced polyuria may bring about a change to an 'inappropriate' toileting site due to insufficient access for toileting needs.

Pain is one of the most common reasons for cats to alter their motivation to show behaviours. For example, cats may have a reduced desire to play or interact when suffering from joint pain, and this may be the first sign of which owners are aware in the development of osteoarthritis in older cats (Lascelles and Robertson, 2010). Pain may also lead to context-specific responses: for example, a cat with a bite abscess on the tail base may avoid being stroked by its owners, perhaps by moving away or even showing aggression to stop owner contact. Pain is processed through a network of structures known as the 'pain matrix' (Jones *et al*., 2003). The system has two parallel pathways, one of which (the medial pathway) is involved in the emotional component (i.e. sensation) of pain; the other (lateral) pathway is involved in discriminating the particular details of the stimulus (i.e. type of sensation, location, intensity and duration). Both pathways involve the thalamus and pass through to the insular and somatosensory cortices, respectively (Kulkarni *et al*., 2005). On contact with a painful stimulus, the areas of the brain associated with fear and anxiety are activated (Rainville, 2002); this is obviously adaptive as it enables the animal to learn the salient aspects of an environment that lead to a paineliciting outcome.

Altered motivation to groom areas of the body is also a common result of conditions causing irritation to the skin, and thus activation of mechanoreceptors (see Chapter 2, this volume). A range of conditions including parasite infestation and atopic, infectious or autoimmune-mediated skin disease can result in a cat showing increased grooming, biting or other skin-directed behaviour.

In cases of general illness or infection, animals commonly show what are termed 'sickness behaviours' (Johnson, 2002), which have a range of functions such as conserving energy or promoting defensive mechanisms in the body such as fever (Broom, 2006). Response to infection is mediated by the release of cytokines, which have a direct effect on the brain, leading to increased sleep and reduced activity. Cytokines are also suggested to influence activation of the hypothalamo–pituitary–adrenal axis and hence modulate behavioural responses (McCann *et al*., 2000). Reduced motivation to be active or interact socially may also occur with sensory deficits, such as loss of sight (Turner, 2004).

Modulation of Existing Responses to External Events

In many cases, changes in internal state through physiological variation or disease do not lead to the initiation of a behaviour, but modify existing behavioural responses to external events. These effects can occur through the input of sensory information to the brain, the evaluation of information or in the generation of a motor response.

Modulation of sensory information inputting the brain

Information entering the brain is generated in the sensory organs such as the retinal cells in the eye, the nasal epithelium or the sensory receptors in the skin (see Chapter 2, this volume). Conditions that influence the relative activation of these organs by external stimuli, or the passage of impulses along the sensory nerves to the sensory cortices of the brain, will influence the extent to which cats respond to external events. For example, Siamese cats have an abnormal development of sensory input from the retina to the lateral geniculate nucleus, which means that their capacity to use stereoscopic vision to determine depth (see Chapter 2, this volume) is limited, and it is believed that the development of a squint in some individuals is to enable some overlap of visual fields (Hubel and Wiesel, 1971; Chapter 2, this volume). While the plasticity of the sensory cortex enables most Siamese to respond apparently normally to external events, reduced or absent binocular capability is likely to modify when and how individual cats respond to events, and potentially influence their hunting ability. Perception of olfactory information is dependent on the integrity of the nasal epithelium, and chronic damage from infectious upper respiratory tract disease can influence the relative perception of scents in the environment (Scherk, 2010), influencing a range of scent-related behaviours such as toileting and social interaction (see Chapters 5 and 8, this volume).

Modulation of sensory information from the integument is another example of where abnormalities can influence the extent to which cats perceive external stimuli. Changes in the relative activity of peripheral mechanoreceptors can result in either altered sensation (dysaesthesia) or exaggerated response to stimulation (hyperaesthesia) (Rizzo *et al*., 1996). These changes in relative activation of sensory neurons arise as a result of changes in neuronal conduction properties with variation in sub-type of sodium ion channels in the nerve membrane (Waxman *et al*., 2000). Damage to a peripheral sensory nerve may result, for example, in relative hyperpolarization, such that the threshold of activation by touch sensation is reduced (Matzner and Devor, 1992). These changes in peripheral nerve activation thresholds following damage are one potential underlying cause for behavioural changes in cats sometimes described as 'hyperaesthesia syndrome' or 'hyperkinesis' (Shell, 1994), where cats present with twitching or rippling skin and may jump around to groom intensely, as if responding to severe irritation, following only a mild touch sensation.

Factors influencing processing and evaluation of sensory information

Behaviour arising as a consequence of external changes can also be modulated by factors that influence how information is centrally processed or appraised. Normal physiological changes can influence these processes, such as fluctuations in reproductive hormones, since sex steroids act as modulatory neurotransmitters across many regions of the brain (Rupprecht and Holsboer, 1999). For example, evidence from other species suggests that changes in oestrogen may have profound effects on the activity of a range of different neurotransmitters at the cellular level, resulting in an increased chance of behavioural responses to external events and a reduced threshold of response to painful stimuli (Aloisi and Bonifazi, 2006).

Pathologies can also influence how sensory information is evaluated, and change either the threshold for the behaviour or the degree of behavioural response. Endocrine abnormalities can have a profound effect on responses to external events, as well as a range of physical signs. In Cushing's disease, for example, overproduction of glucocorticoids may ultimately reduce the production of corticotrophin-releasing factor in the hypothalamus due to negative feedback, resulting in an animal that is unresponsive to external events and lethargic. Corticosteroids are also commonly used in the treatment of various medical conditions in cats, and evidence from human patients suggests that iatrogenic steroids may also have effects on mood and behaviour (Brown and Chandler, 2001).

Diseases that influence the breakdown and metabolism of dietary components can also have an influence on the threshold of response generation in the brain. The most common examples are cases where either hepatic (liver) or renal (kidney) function is compromised, resulting in a reduced ability to remove by-products of digestion from the circulation and excrete these via the urine. The behavioural and neurological consequences of such diseases are commonly termed ‘encephalopathies’. The effects on brain function can arise through the build-up of compounds that are neurotoxic, or alternatively can be caused by the relative unavailability of amino acids necessary for neurotransmitter turnover. For example, increased ammonium salts in the circulation as a result of hepatic insufficiency cannot be metabolized to urea in the central nervous system, and are instead converted to glutamine, which ultimately leads to an excess of this amino acid in the brain (Albrecht *et al*., 2007). Since glutamine is the precursor for the excitatory neurotransmitter glutamate, this may explain transient decreases in the threshold of responding (for example, increased aggression) associated with encephalopathies. In addition, chronic low-grade hyperammonaemia has been associated with memory deficits and difficulty in adapting to new environments in both humans and rats (Apelqvist *et al*., 1999). Because increased levels of ammonia, and hence increased glutamine and glutamate, occur as a protein meal is digested and the by-products circulate in the bloodstream, behavioural signs associated with hyperammonaemia will often occur temporarily, associated with feeding. Ultimately, increasing levels of glutamine result in cerebral oedema (Albrecht *et al*., 2007) and more obvious neurological symptoms, such as loss of motor coordination, depression, hysteria, pacing, circling, seizures and, ultimately, coma and death.

Alterations of normal behaviour can arise as a consequence of disorders of the central nervous system. The specific effects of lesions on behaviour will relate to the specific area of the central nervous system affected. For example, lesions affecting the pineal gland may influence the sleep–wake cycle (Uz *et al*., 2003). In older cats, behavioural changes in response to external events are commonly caused by a range of clinical conditions including osteoarthritis, systemic hypertension (often secondary to chronic kidney disease or hyperthyroidism), hyperthyroidism or sensory deficits (Gunn-Moore, 2011). In some cases such changes may result from reduced motivation to show new behaviours, for example due to pain, as discussed earlier. There is also a tendency across species for cognitive ability to decline with increasing age. For example, in both humans (Cherry and Park, 1993) and dogs (Christie *et al*., 2005) the ability to perform allocentric tasks (i.e. requiring reference to external landmarks) declines with age. However, in a proportion of cats more profound changes in cognitive ability and behaviour are associated with specific pathological changes analogous to Alzheimer’s disease in people, known as ‘cognitive dysfunction’ (Landsberg *et al*., 2010). Associated alterations in response to external events might include reduced social interaction with owners or, alternatively, increased dependency on owner attention and presence, loss of previously learnt associations, altered or ‘mixed-up’ responses to previously learnt cues (e.g. change in toileting substrate preference) or general disorientation.

Influences on motor outputs and initiation of behaviour

Disease processes may also modify behavioural responses to external events by altering the output of motor information from the brain and the activation of peripheral muscles via neuromuscular junctions. Changes in this element of the pathway may influence the cat’s ability to show a desired behaviour, or alter the form of the behaviour. A cat’s ability to show a response may be influenced by diseases affecting the motor cortex of the brain or spinal cord. For example, spinal damage can influence the motor control of elimination, potentially resulting in urination or defecation in undesired locations. Control of toileting can also be influenced by conditions affecting the gastrointestinal or urinary tract. Diseases causing inflammation in the bowel, or those affecting absorption, will potentially influence both the frequency and urgency of defecation.

Feline idiopathic cystitis (FIC), also known as idiopathic feline lower urinary tract disease (iFLUTD), is the most common medical cause of abnormal urination in the cat, and hence is an important differential diagnosis to consider when investigating cats presenting with inappropriate elimination (Buffington *et al*., 1997). FIC is termed ‘idiopathic’ when there is no obvious physical cause to account for the condition, and is diagnosed by excluding other causes of lower urinary tract inflammation (such as urinary tract infection, urethral strictures, neoplasia or urolithiasis) (Kalkstein *et al*., 1999). Inappropriate elimination may be the first presenting sign of FIC, and is thought to occur because the cat associates the pain of urination with the specific location in which it has previously urinated. In addition, the condition causes increased frequency and urgency of urination. Because the signs of the condition are commonly present during bouts of 3 or 4 days, affected cats may show repeated changes in the location of urination for several days in a row. Pain on urination can also cause the cat to appear distressed and vocalize before and during urination, and abdominal pain may make cats reluctant to be handled, either moving away or showing aggression as an avoidance response. Male cats may also change their posture from a squat to standing up, as squatting, which bends the urethra, may cause further discomfort (Seawright *et al*., 2008).

The ability of cats to show desired behavioural responses can also be influenced by diseases affecting movement, such as degenerative joint disease (e.g. osteoarthritis), neuropathies of motor nerves (e.g. diabetic polyneuropathy), disorders of the neuromuscular junction (e.g. myasthenia gravis) or problems with muscular functions (e.g. myopathies associated with feline leukaemia virus).

Behaviours Occurring Entirely as a Result of Disease Processes

In some cases behavioural signs in cats are generated entirely as a result of a disease process, and occur unrelated to external events (Reisner, 1991). In general these types of behaviour are less common than where pathology acts to modify behavioural responses to external events. Abnormalities that can generate a response may occur in any part of the process by which a normal response is generated (i.e. sensory input to the brain, the processing of information in the central nervous system or the output of information from the motor cortex).

The generation of abnormal sensory information will create similar behavioural responses to sensory inputs based on actual external stimuli. For example, in addition to dysaesthesic and hyperaesthesic responses in peripheral sensory nerves (described previously), paraesthesic responses can occur, whereby spontaneous activity is generated in the nerve without any mechanical stimulation of the corresponding receptors. This abnormal or ectopic impulse generation is also commonly called sensory neuropathy. Because these abnormal inputs are processed as if they arise in response to normal external events, the reaction of the cat is appropriate to irritation or pain arising from the source (i.e. grooming, scratching or attempting to bite at the affected part of the body). In some cases these responses can be extreme and cause both cat and owner considerable distress. The tail is a common target for such behaviour, possibly because the sensory nerves in the tail are more susceptible to damage (e.g. through bite injuries or the tail being caught in a doorway). A cat may repeatedly and persistently attack its tail to the extent that it becomes damaged and requires repeated medical or surgical intervention. Depending on the origin of the sensory damage, and the extent to which sensitization of the response has occurred, the behaviour can even continue following amputation of part or all of the tail. An abnormal pain sensation in the face and mouth region has also been described, particularly in oriental breeds. Although there may be multiple possible factors involved in the development of this condition, damage to the facial nerves, such as the trigeminal nerve, is likely to be an important factor. Cats suffering from this condition show signs varying in severity; in the most extreme cases cats can cause considerable self-damage by clawing at their own face in an apparent attempt to alleviate the pain (Rusbridge *et al*., 2010).

Spontaneous activity through ectopic activity in nerve cells also occurs in the brain. Spontaneous depolarization shifts or repetitive discharge from hyperexcitable collections of neurons in the brain are expressed as epileptic seizures. In the typical ‘grand mal’ seizure, this activity spreads across the whole brain. However, the spread of electrical activity can also be localized, influencing only one part of the brain. The behavioural response arising from these focal seizures will depend on the part of the brain that is affected and the extent to which it spreads (Dahl, 1999). Hence, a focal seizure in the visual cortex is likely to result in a cat responding as if it has seen something (i.e. a ‘visual hallucination’). The response will often be identical to that as would occur if the animal had seen a ‘real’ stimulus, since activation of this brain region will lead to the generation of the same behavioural response as if the activation was due to inputs via the optic nerve. Hence, cats may appear to pounce on or chase objects which are not there. Seizure activity localized to the limbic part of the brain, responsible for the generation of emotional responses, can result in sudden unprovoked behavioural responses indicative of extreme emotional disturbance. For example, cats may suddenly run off and hide, or show extreme aggression to the nearest person, object or other animal. Where the focus of focal seizures is the motor cortex, resulting behaviours are often rather more fixed in form, rather than the more ‘goal-oriented’ and variable behaviours associated with sensory focal seizures.

Seizure activity develops over time through the process of ‘kindling’, whereby spontaneous activity in one area gradually results in the ‘recruitment’ of neighbouring cells (Bertram, 2007). In the early stages, seizure activity may therefore result in relatively mild signs which are often disregarded. For example, humans with seizures in the limbic part of the brain may initially report mild ‘feelings’ occurring spontaneously, which develop over time into more obvious seizures with clear behavioural indicators (Bertram, 2007). The plasticity of the brain, and susceptibility of cells to repeated electrical stimulation, means that behavioural changes may be used to identify early seizure activity (Shihab *et al*., 2011). The other factor to consider with epilepsy is the effect of seizures on behaviour occurring between the episodes. Because the action of the seizures themselves is to partially ‘remodel’ areas of the brain, the response of the animal to normal stimuli in the interictal (between seizure) period can also be affected (Adamec, 2003).

Persistence of Behavioural Outcomes of Disease

When evaluating the behaviour of an individual animal, it is important not only to consider currently occurring physiological or pathological impacts on behaviour, but to investigate the potential impact of historical effects. In many cases, behavioural changes can arise as a consequence of a previous condition that has been resolved, but where the behavioural response has been retained through learning. For example, male cats with FIC may stand to urinate in order to facilitate the passage of inflammatory material, or due to urethral spasm. However, where these individuals learn that this posture eases the pain associated with elimination, they may continue to show this posture even after resolution of the disease. Similarly, avoidance responses learnt when a cat was in pain may be retained after resolution of the painful lesion. Where aggression to an owner stroking the caudal dorsum effectively prevents contact on the tail base, a cat may continue to respond aggressively after resolution of a tail base abscess because it has not had the opportunity to learn that contact in this area is no longer painful. Behaviours originating for medical reasons can also become reinforced and established for other reasons. For example, grooming behaviour initiated because of an irritating lesion could become reinforced by the owner paying the cat attention when the behaviour is shown. This type of reinforcement is particularly likely where cats highly value owner attention, as response from the owner will be a valued outcome.

Environmental Stressors in Disease Aetiology

It is increasingly recognized in human medicine that psychological stressors impact extensively on somatic disease (Nater *et al*., 2006). Similarly, in veterinary medicine, the influence on disease processes of environment, and individual responses to environmental change, have gained in recognition (Casey, 2010). However, much still needs to be investigated to elucidate the relationship between stress exposure and disease susceptibility. It is unclear, for example, why some individuals appear to be more susceptible to somatic disease than others exposed to similar environments. In addition, it is not known why different individuals exposed to the same stressors develop conditions involving different body systems. However, it is likely that some individuals are predisposed to vulnerability, such that co-occurrence with extreme environments leads to dysregulated stress responses, resulting in disease. Further research is needed to investigate the nature of this vulnerability, and how it interacts with stressors that lead to such consequences.

In cats, FIC is the condition that is most widely recognized as associated with exposure to stress (Seawright *et al*., 2008). Indeed, differentiating cases of FIC from inappropriate elimination can be complicated, as exposure to events that cats find aversive is an important ‘flare factor’ in the multifactorial aetiology of this condition (Cameron *et al*., 2004), and hence similar factors can lead to both inappropriate elimination and FIC. Other chronic conditions in which stress exposure is considered a factor in humans include irritable bowel syndrome (Murray *et al*., 2004) and chronic skin disease (Kimyai-Asadi and Usman, 2001), both of which are anecdotally also relevant in cats. The hyperaesthetic sensory responses, as described earlier, are also postulated to have environmental stress as an aetiological factor.

In addition to chronic disease conditions, where clinical signs appear to be exacerbated or precipitated by stressful events, acute stress can have important impacts on susceptibility to infectious disease. For example, the high level of stress experienced by many cats when entering a boarding or rescue cattery, associated with loss of predictability and change in environmental cues, leads to an increased susceptibility to infectious disease, at the same time as they are brought into the proximity of other cats, thus increasing the probability of contact with infectious agents.

Conclusions

Important welfare implications arise from the appropriate recognition of the influences of disease on behaviour. Behavioural signs may be the first indicators of disease and enable the early treatment of potentially serious medical conditions. In addition, the recognition of confounding disease processes will ensure that behavioural interventions are considered that take these into account, and better inform prognosis when treating undesired behaviours. Furthermore, where stress is likely to impact on disease risk, interventions to reduce exposure to stressors can have important health impacts.

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In considering the relationship between pathological disease or physiological variation and behavioural signs it is important to consider not only those behaviours that are directly caused by pathologies, but also those where changes in internal state may modify existing responses. In addition, it is imperative to adopt a rational, functional approach and consider those aspects of normal response generation where pathology could be having an effect. For example, where a cat is observed attacking its tail, the important factors to investigate and differentiate from behavioural causes will range from conditions that cause irritation of the skin right through to those that might be generating an abnormal motor response.

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