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Evidence of negative affective state in Cavalier King Charles Spaniels with syringomyelia

Alastair Cockburn[a,1], Melissa Smith[a], Clare Rusbridge[b,c], Carol Fowler[d], Elizabeth S. Paul[a], Joanna C. Murrell[a], Emily J. Blackwell[a], Rachel A. Casey[a,2], Helen R. Whay[a], Michael Mendl[a,*]

[a] Bristol Veterinary School, University of Bristol, Langford House, Langford, BS40 5DU, UK
[b] School of Veterinary Medicine, University of Surrey, Guildford, GU2 7AL, UK
[c] Fitzpatrick Referrals, Halfway Lane, Eashing, Surrey, GU7 2QQ, UK
[d] Dog Breeding Reform Group, Wotton-under-Edge, GL12 7AX, UK

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ABSTRACT

Syringomyelia is a common and chronic neurological disorder affecting Cavalier King Charles Spaniels. The condition is putatively painful, but evaluating the affective component of chronic pain in non-human animals is challenging. Here we employed two methods designed to assess animal affect – the judgement bias and reward loss sensitivity tests – to investigate whether Cavalier King Charles Spaniels with syringomyelia (exhibiting a fluid filled cavity (syrinx) in the spinal cord of ≥2 mm diameter) were in a more negative affective state than those without the condition. Dogs with syringomyelia did not differ in age from those without the condition, but owners reported that they scratched more ($P < 0.05$), in line with previous findings. They also showed a more negative judgement of ambiguous locations in the judgement bias task ($P < 0.05$), indicating a more negative affective state, but did not show a greater sensitivity to loss of food rewards. These measures were unaffected by whether the dog was or was not receiving pain-relieving medication. Across all subjects, dogs whose owners reported high levels of scratching showed a positive judgement bias ($P < 0.05$), indicating that scratching was not directly associated with a negative affective state. Tests of spontaneous behaviour (latency to jump up to or down from a 30 cm high platform) and physiology (thermography of the eye) did not detect any differences. These results provide initial evidence from the judgement bias task that syringomyelia may be associated with negative affect in dogs, and open the way for further and larger studies to confirm findings and investigate the effects of medication in more detail.

1. Introduction

Syringomyelia is a neurological disorder commonly affecting Cavalier King Charles Spaniels (CKCSs) (Parker et al., 2011; Rusbridge et al., 2006). It involves the formation of syrinxes (fluid filled sacs) in the spinal cord, secondary to an obstruction in the flow of cerebrospinal fluid (CSF) (Rusbridge et al., 2006). In CKCSs, this is usually due to a Chiari-like malformation which is a developmental change to skull and cranial cervical vertebrae morphology characterized by rostro-caudal bony insufficiency (Rusbridge, 2014). A consequence is that the brain and cervical spinal cord are overcrowded in the skull, especially at the cranio-cervical junction, leading to obstruction of the foramen magnum and CSF channels. These obstructions to CSF flow are thought to play a critical role in the aetiology of syringomyelia (Cross et al., 2009; Cerda-Gonzalez et al., 2009; Knowler et al., 2017a,b). In an MRI study of asymptomatic CKCSs, 46% were found to have syringomyelia upon MRI, rising to 70% in dogs aged six years or older (Parker et al., 2011).

Syringomyelia in dogs is thought to cause chronic neuropathic pain (Rusbridge et al., 2006). Reported clinical signs that may indicate pain include frequent scratching of the caudal head and neck area. However 'phantom scratching' towards one shoulder or neck region without skin contact is not necessarily associated with pain (Nalborczyk et al., 2017). Other signs include spinal hyperaesthesia (aversion to being touched especially in the cervical and thoracolumbar regions) and vocalisations resembling "screaming" after sudden head movements, when rising, and when the dogs is lifted under the sternum (Rusbridge

* Corresponding author.
E-mail address: mike.mendl@bris.ac.uk (M. Mendl).
[1] Present address: Green Templeton College, 43 Woodstock Road, Oxford, OX6 2HG, UK.
[2] Present address: Dogs Trust, Clarissa Baldwin Building, 17 Wakley Street, London, EC1 V 7RQ, UK, and The Royal Veterinary College, Hawkshead Lane, Hatfield, Hertfordshire, AL9 7TA, UK.

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and Knowler, 2004). Syringomyelia also occurs in humans, often as the result of a Chiari type-1 malformation similar to that seen in dogs (Todor et al., 2000). 50–90% of human patients report pain as a prominent feature (Todor et al., 2000),with around 40% reporting unpleasant burning, tingling or stretching sensations (Milhorat et al., 1996) that are often "overwhelming and pervasive" (Todor et al., 2000). Similarities in pathogenesis between humans and dogs with syringomyelia, the fact that pain is a central characteristic of the disease in humans, and the nature of the spontaneous behavioural signs seen in dogs, strongly suggest that syringomyelia can be painful in this species. However, not all dogs show these behaviours, even when MRI scans indicate the presence of syringomyelia (Parker et al., 2011), so questions remain as to whether, for example, these dogs are in pain despite not exhibiting any signs. Measures designed to assess affective state may help to address these important uncertainties.

Assessing the affective experience of pain in dogs, or any other non-human species, is far from straightforward because ultimately we cannot be certain about the private subjective experiences or feelings of such species (e.g. see Paul et al., 2005; Mendl et al., 2010a,b). Even in humans we have to rely on the indirect measure of linguistic report as our 'gold standard'. Nevertheless, if we take the 'componential view' that affective or emotional states comprise subjective, behavioural, and neurophysiological elements (e.g. Paul et al., 2005), we are able to measure the latter two components objectively. Many current methods of pain assessment in animals, such as nociceptive threshold testing and reflex responses (Mogil et al., 1999; Roughan and Flecknell, 2001; Sneddon et al., 2003) focus on the sensory and nociceptive aspects of pain (i.e. the detection and encoding of nociceptive stimuli) and how these change in chronic pain conditions (Mogil, 2009), rather than the affective component (i.e. the impact of the noxious stimulus on the animal's emotional state). In clinical practice, pain assessment in dogs is often performed via subjective observation of, or validated scoring systems for, spontaneous behavioural signs thought to be associated with pain (Firth and Haldane, 1999; Brodbelt et al., 1997; Mathews et al., 2001). However, it is unclear whether the observed variability in propensity to display such behavioural signs (Firth and Haldane, 1999) is due to genuine variation in pain experienced, or whether some dogs are merely less likely to display behavioural signs than others.

Measuring the affective component of pain in chronic conditions such as syringomyelia is thus challenging (Mogil and Crager, 2004) but important. Here, we employ two measures that have previously been used to detect changes in animal affective valence (positivity/negativity); judgement bias and reward loss sensitivity. The judgement bias paradigm provides an empirical proxy measure of affective valence by assessing an animal's interpretation of an ambiguous cue (Harding et al., 2004). It is based on findings from human psychology studies (Paul et al., 2005) and theoretical arguments (Mendl et al., 2010a) that individuals in a negative affective state are more likely to make negative ('pessimistic') interpretations of ambiguous stimuli than those in a more positive state, and has successfully detected negative judgement biases in conditions likely to induce negative affect in species including rats (Harding et al., 2004; Burman et al., 2008a; Enkel et al., 2010; Papciak et al., 2013), sheep (Doyle et al., 2011), pigs (Murphy et al., 2015), humans (Paul et al., 2011; Schick et al., 2013; Iigaya et al., 2016) and dogs (Mendl et al., 2010a,b). There is also evidence in dogs that positive judgement biases occur following manipulations designed to induce a more positive affective state (Kis et al., 2015; Karagiannis et al., 2015). In a study of calves, negative judgement biases were seen between 6 and 22 h after disbudding, which is likely to be painful and by which time the effects of local anaesthesia would have worn off (Neave et al., 2013). Here we use the paradigm to investigate whether negative judgement biases are observed in CKCSs with syringomyelia.

We also use a reward loss sensitivity paradigm. Unexpected omission of an expected reward is known to cause behavioural and physiological changes in a wide range of mammalian species (Papini and Dudley, 1997; Papini, 2003), and it is known that humans in a negative affective state show increased sensitivity to loss of reward (Rolls, 2016). Human patients with depression showed increased error-related negativity (brain event-related potentials that occur after an error is made) compared to healthy controls (Chiu and Deldin, 2007), as did people with greater negative affect as assessed by questionnaire (Hajcak et al., 2004). An animal's sensitivity to loss of reward can be measured using the successive negative contrast method (SNC; Flaherty, 1999) by training it to run to a point at which it receives the reward, and then unexpectedly decreasing the amount of reward given. Burman et al. (2008b) found that rats raised in an enriched environment but then housed in a barren environment showed a more prolonged response to the unexpected decrease in food reward (their latency to approach the low reward remained higher for more successive trials) than rats raised and housed in an enriched environment, suggesting that removal of enrichment induced an increased sensitivity to reward loss indicative of a negative affective state. SNC effects have been demonstrated in dogs (Bentosela et al., 2009, but see Reimer et al., 2016) but without studying the effects of putative background affective state on response to a loss of reward. Here we employ a runway task similar to that used for rats to assess whether dogs with syringomyelia show a stronger slowing response to reward loss than control dogs.

We also use tests of physiological change and spontaneous behaviour that may provide further information about nociceptive and/or affective changes. We measure eye temperature as this has previously been used as an indicator of acute pain in other species. Stewart et al. (2008) found that calves dehorned without local anaesthetic initially displayed an initial transient decrease in eye temperature followed by a prolonged increase. Sheep showed increased eye temperature following ischaemic damage to the forelimb (Stubsjøen et al., 2009), and elk showed increased eye temperature following antler removal (Cook et al., 2006). If eye temperature measurement correlates with the presence of syringomyelia or with negative judgement bias, it offers a more convenient proxy measure of pain or distress. Additionally, since owners often describe a reluctance for dogs with syringomyelia to jump up or to climb stairs, we measure the latency for dogs to jump up to and down from a surface in exchange for a reward to assess whether syringomyelia affects the dogs' mobility. We also use owner reports of frequency of scratching performed by dogs in their home environment in order to assess the severity of spontaneous behavioural signs of syringomyelia.

2. Materials and methods

2.1. Animals

Ethics approval was granted by the University of Bristol, UIN number UB/12/010. 27 CKCSs were recruited using Clare Rusbridge's website http://clarerusbridge-news.blogspot.co.uk/. Eligible dogs were purebred Cavalier King Charles spaniels that had a MRI scan of the head and neck in the last two years. Dogs that were known to have other medical conditions causing neurological signs, scratching or pain were excluded, as were dogs with grade III or greater mitral valve disease. It was not possible to exclude dogs with medication (e.g. NSAIDs, corticosteroids, opioid or gabapentin analgesics), since medical treatment is commonly initiated as soon as signs of syringomyelia become apparent. Neither was it possible to withhold medication during the study, as this may exacerbate the dogs' pain or discomfort and thus would be ethically unacceptable.

Dogs were diagnosed with syringomyelia (SM) if their MRI results revealed a fluid-filled cavity (syrinx) within the spinal cord parenchyma with an internal transverse diameter greater than or equal to 2 mm. Of the 27 dogs recruited, 11 were diagnosed with syringomyelia and 16 were free from syringomyelia. 11 dogs (7 diagnosed with SM on MRI and 4 diagnosed as free from SM) were on medication, and 16 (4 diagnosed with SM and 12 diagnosed as free from SM) were not taking medication. This discrepancy is probably because dogs may be put on