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·Minireview·

# Behavioral assessments of the aversive quality of pain in animals

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**Abstract:** Animals and humans share similar mechanisms of pain detection and similar brain areas involved in pain processing. Also, they show similar pain behaviors, such as reflexed sensation to nociceptive stimuli. Pain is often described in sensory discrimination (algosity) and affective motivation (unpleasantness) dimensions. Both basic and clinical findings indicate that individuals with chronic pain usually suffer more from pain-associated affective disturbances than from the actual pain sensations *per se*. Although the neural systems responsible for the sensory component of pain have been studied extensively, the neural mechanisms underlying negative affective component are not well understood. This is partly due to the relative paucity of animal paradigms for reliable examination of each component of pain. In humans, the experience of pain and suffering can be reported by language, while in animals, pain can only be inferred through physical and behavioral reactions. Animal behaviors, cognitive psychology and functional brain imaging have made it possible to assess pain affection and pain memory in animals. Animals subjected to either neuropathic injury or inflammatory insult display significant conditioned place aversion to a pain-paired environment in behaviors. The present review aims to summarize the common methods of affective unpleasantness assessment in rats.

**Keywords**: pain-related negative affect; unpleasantness; conditioned place avoidance; pain

## 1 Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage[1]. In humans, the experience of pain and suffering is often reported by language, while in animals, pain is judged through physical and behavioral reactions. The division of pain perception by Melzack and Casey into sensory-discriminative and affective-motivational components has had a profound and long-lasting impact on pain research for years[2]. Affect is a psychophysical construct that specifically refers to a subjective emotional state, and it ultimately depends upon introspection and verbal report for validation. Since it is hard to separate affect from motivation of pain in animals, it is reasonable to bundle the 2 different concepts of pain in designing animal experiments to uncover the underlying mechanism. However, this bundle is difficult to be clearly differentiated from a sensory-discriminative process. Rainville *et al.* have found that different types and locations of stimuli produce variable ratios of unpleasantness to algosity magnitude, which supports the concept that different and possibly overlapping circuits mediate the 2 primary dimensions of pain[3]. Unpleasantness is further divided into primary and secondary pain unpleasantness. Primary unpleasantness is directly associated with stimulus, while

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secondary pain unpleasantness is an unpleasant experience reflecting a higher level of process that has a highly variable relationship with stimulus intensity and is largely determined by memories and contextual features[4]. Primary unpleasantness and algosity are 2 distinct stimulus-bound qualities of pain. At the level of neural mechanisms, they are carried out through supraspinal circuits that are partly separate and parallel.

Whether animals can feel unpleasantness of pain has been a controversial issue for many years. Through a combination of animal behavior observation, cognitive psychology and functional brain imaging, the assessment of pain affection and pain memory in animals has become possible. Animals and humans share some similarities in mechanisms of pain detection and in brain areas involved in pain processing. They may also exhibit similar pain behaviors[5]. It is accepted that postero-medial thalamus and cortical regions such as cingulated gyrus and insular cortex, are involved in unpleasantness production[6,7]. Clinically, persistent pain is frequently associated with psychological and emotional dysfunction[6,8]. Some patients with chronic pain are probably suffering from depression and may even commit suicide. Intense affective component of pain is an obvious characteristic which is distinct from the sensation to other stimuli in humans. The neural circuits and the mechanisms of the negative affective component of pain have been elucidated using conditioned place avoidance (CPA) tests[9]. Excitotoxic lesions in the anterior cingulate cortex (ACC), central amygdaloid nucleus, basolateral amygdaloid nucleus (BLA), or bed nucleus of the stria terminalis (BNST) can suppress intraplantar formalin-induced aversive responses[10-14]. Glutamatergic transmission within the ACC and BLA via NMDA receptors is shown to play a critical role in the affective component of pain[12]. In BNST especially its ventral part, noradrenergic transmission via beta-adrenergic receptors is demonstrated to be important for pain-induced aversion[13]. Since persistent pain is frequently associated with psychological and emotional dysfunctions, studies on the neural circuits and the molecular mechanisms involved in the affective component of pain in animals may provide considerable hints for the treatment of chronic pain. In the present review, the methods of affective unpleasantness assessment in rats are summarized, to facilitate better understanding of pain etiology and provide efficient ways for assessment and treatment of pain.

## 2 Behavioral assessment of the aversive quality of pain in rats

**2.1 Vocalization response test** Among various behaviors displayed by rats, vocalization consists of an extensive pattern of vocal emission in the audible and the ultrasonic frequency ranges. Audible and ultrasonic vocalizations occur in several behavioral contexts. Ultrasonic vocalization occurs in infant rats in response to thermal and tactile stimuli when separated from the nest[15,16]. It has also been used to address the emotional-affective responses to painful stimuli in arthritic, formalin and muscular pain models[17-23]. More specifically, long-pulse calls (22-28 kHz) are associated with behaviors exhibited under stressful and/or painful situations[18,20]. To study the relevance of ultrasonic vocalization with different states of pain, audible and ultrasonic vocalizations were measured simultaneously in response to innocuous or noxious stimulation[17-23]. The recording apparatus consists of a condenser microphone and a bat detector, which are used for recording audible (audible range: 20 -16 kHz) and ultrasonic [ultrasonic range: (25±4) kHz] vocalizations, respectively. The microphone and the bat detector are placed on a platform in front of the animal at a fixed distance. The recorded signals are filtered, amplified and fed into a personal computer. Experiments need to be performed in a quiet environment and appropriate filtering levels are used to avoid recording any background noise. The frequencies of audible and ultrasonic vocalizations increase with the elevation of mechanical stimuli intensity that is, the greater the intensity of mechanical stimuli, the higher the vocalization frequency. Meanwhile, although ultrasonic vocalization has been used to address the emotional-affective responses to painful stimuli in arthritic, formalin and muscular pain models[17-23], it is reported that ultrasonic vocalization does not provide any more information than does audible vocalization for assessing responses to painful procedures in some cases[24,25]. Thus, the use of ultrasonic vocalization responses with different fre-

quencies to evaluate pain-related affection is still in debate at present. However, the measurement of audible and ultrasonic vocalizations is easy and convenient for assessing primary pain unpleasantness, but not for the assessment of secondary pain unpleasantness. More recently, ultrasonic vocalizations (37-50 kHz) have been considered as an indicator of ongoing pain in mice[26]. Thus, the ultrasonic vocalization is reconsidered for assessing pain sensation and unpleasantness in animals.

**2.2 Formalin-induced conditioned place avoidance (F-CPA) paradigm** F-CPA combines the hindpaw formalin model with the place-conditioning paradigm. It directly reflects the affective component of pain in the rat, concomitantly with "acute" formalin-induced nociceptive behaviors (such as paw lifting, licking, and flinching) that reflect the intensity and localization of the nociceptive stimulus[9].

A standard place-conditioning apparatus consists of 3 compartments: 2 "conditioning" compartments (formalin treatment is paired with one of these compartments) and one "neutral" compartment, each being characterized by distinct visual and olfactory stimuli. Of the 2 conditioning compartments, one has horizontal stripes on the walls and an odor of 1.0% acetic acid, whereas the other has vertical stripes and a standardized cinnamon scent. The neutral compartment is characterized by uniformed wall color and absence of distinctive odor. The neutral compartment has 2 doors, each linking a conditioning compartment. These doors are closed during conditioning to constrain the animal within a single conditioning compartment.

F-CPA was firstly used by Johansen *et al.*[9] to reveal the contribution of the ACC to the affective component of pain in rodents. Numerous human and animal studies have indirectly indicated the involvement of the ACC neurons in the affective consequences of nociceptive stimulation. Destruction of neurons originating from the rostral, but not from caudal of the ACC, can reduce formalin-induced conditioned place avoidance but not acute pain-related behaviors. These results provide evidence that neurons in the ACC are essential for the nociceptive stimulation-induced aversiveness.

Using F-CPA paradigm, the roles of the ACC and amygdala in formalin-induced acute pain responses and affective pain processing were examined. No significant changes in formalin-induced acute nociceptive behaviors are found in rats with ACC lesion or amygdala lesion, while the magnitude of F-CPA is reduced in these rats. These results further support the different neural substrates underlying pain affection and pain sensation[10,11,27]. In addition, there have been tons of literatures indicating that glutamatergic transmission via NMDA receptors in the BLA plays a crucial role in pain-induced aversion using F-CPA paradigm[28]. NMDA NR2A and NR2B receptors in the rostral anterior cingulate cortex (rACC) are also critically involved in pain-related aversion in rats[29]. Besides, our previous work showed that both NMDA and AMPA receptors underwent plastic changes in animal models of neuropathic pain, indicating that those plastic changes of glutamate receptors are likely to contribute to pain-related affection[30,31]. In addition to its well-characterized effects on the sensory component of pain, morphine also influences the affective component of pain through an inhibitory effect on intra-BLA glutamatergic transmission[28]. Since the glucocorticoid receptors are abundant in the ACC and amygdala[32], they may have great influences on the ACC- and amygdala-dependent aversive learning and memory. It is suggested that corticosterone secretion by the adrenal cortex may play a role in chemical somatic noxious stimuli-induced avoidance learning and aversive memory, but not in sensory discrimination of noxious stimulation[33].

Apart from the typical F-CPA paradigm, other chemicals that cause pain sensory responses can also induce CPA in rats. For example, intraperitoneal injection of acetic acid, a kind of visceral noxious stimulus, can induce CPA[12,13]. Formalin and acetic acid induce pain behaviors probably through different mechanisms, but they both can induce CPA. Intraplantar injection of formalin as a chemical somatic noxious stimulus can increase *c-Fos* mRNA expression in the BLA, but not in the central nuclei of the amygdala (CeA), while intraperitoneal injection of acetic acid as a chemical visceral noxious stimulus induced *c-Fos* mRNA expression highly in the CeA but hardly in the BLA. Activation of distinct amygdaloid nuclei could contribute differentially to formalin and acetic acid-induced negative affection, but not to sensory components of pain. The formalin-induced CPA can

be abolished by the lesion of the BLA or the CeA, while acetic acid-induced CPA can be abolished by CeA lesion, but not by BLA lesion. On the other hand, lesion of the BLA or the CeA fails to attenuate the intraplantar formalin injection- or intraperitoneal acetic acid injection-produced nociceptive behaviors[12]. However, both acetic acid- and formalin-induced CPA can be suppressed by bilateral BNST lesions[13].

Recently, Johansen *et al.*[9] have combined the formalin test with a place conditioning paradigm to examine the affective and sensory components of pain. However, the formalin model is not an optimal model due to its biphasic nature. The formalin model has been described as a persistent model of pain, however, it may also result in behavioral sequelae and changes in gene expression or cell function that are reported to occur in man suffering from chronic pain[34]. Furthermore, it is difficult to discern whether the aberration in affective state resulting from this model is primarily due to the phase I direct effect that formalin has on nociceptors or due to the phase II inflammatory effect. Therefore, some other modified CPA paradigms appear consequently. Until now, F-CPA paradigm fits for acute pain models, such as carrageenan and formalin models[9,12,13].

**2.3 Paradigm of modified CPA coupled with novel objects** The paradigm of modified CPA coupled with novel objects, which incorporates both the sensory and the motivational affective aspects of pain, can address the shortcomings of CPA paradigm to some extent. In this paradigm, rats subjected to inflammatory- and neuropathic-like pain show a prolonged negative association (for up to one month) with the pain-associated environment enriched with novel objects, after a number of conditioning sessions[35].

Most notably, Roth-Isigkeit *et al.* have found that children suffering from chronic pain are less able to pursue hobbies, attend school or meet friends[36]. Accordingly, Hummel *et al.* used novel objects to determine whether animals would interact less frequently with natural reinforcers in the presence of pain, just similar to the human condition[35]. Their findings showed a reduced number of novel object contacts during painful conditioning sessions for both neuropathic and inflammatory rodent models.

Furthermore, the study of Hummel *et al.* has also shown how this pain-induced aversion is attenuated by a non-analgesic, non-rewarding dose of morphine[35]. Thus, this paradigm is not only a useful methodology for modeling the sensory and affective components of pain, but also a novel strategy for gaining better insight into the pharmacology of pain-ameliorating therapies for treating pain-related affection. In short, this paradigm of modified CPA with novel objects can be used in neuropathic pain models and carrageenan inflammatory model[35].

**2.4 Place escape/aversion paradigm (PEAP)** It is hypothesized that animals would quickly avoid a preferred test location associated with the application of a mechanical stimulus to the hyperalgesic paw. Based on this, the PEAP method was firstly demonstrated by the group of Fuchs using L5 spinal nerve ligation and complete Freund's adjuvant inflammatory models[37]. The apparatus is a shuttle box consisting of 2 components: a black one that the rats prefer, and a white one. Unrestricted movement is allowed throughout the box.

The advantage of the present behavioral paradigm is that the aversive nature of neuropathic and inflammatory pain conditions in animals is measured by examining the avoidance of a preferred location[37-41]. In CPA paradigms, the unconditioned stimulus administration is applied during a period of animal confinement to a specific location in the test chamber, after (i.e., 24 h later) which the animals are tested in the absence of unconditioned stimulus to see if they will avoid the specific location to which they were previously confined. In the PEAP experiment, a single test session is used and behavioral test is always performed in the presence of unconditioned stimulus, without a training process. The behavioral paradigm allows animals to choose an environment associated with the application of a mechanical stimulus to the hyperalgesic paw or the non-operated contralateral paw.

Of primary interest is that animals still demonstrated a preference for mechanical stimulus administration to the nonafflicted paw rather than to the afflicted one. In other words, the animals performed a purposeful behavioral response to avoid mechanical stimulation of the afflicted paw, when allowed to choose where the noxious mechanical stimulus was administered. It is hypothesized that lower von Frey

forces and less frequent stimulation would reduce the amount of time spent in the light area of the chamber. In other words, the association between chamber location and paw stimulation would not be as great as that with a lower von Frey monofilament force or less frequent stimulation.

Fuchs *et al.* also demonstrated that the ACC contributes to the affective component of pain. After electrical stimulation of nerve-injured rats, the aversive quality of noxious cutaneous hindpaw stimulation was attenuated[7]. It has also been found that $GABA_A$ but not $GABA_B$ receptors in the rostral ACC selectively modulate pain-induced escape/avoidance behavior[7,42]. In short, the PEAP can be used in neuropathic pain models and complete Freund's adjuvant inflammatory model[37-41,43].

## 3 Conclusion

The above mentioned behavioral methods for assessing pain affective component are dependent on spinal and brainstem or cerebral processing of nociception. Since aversive response is reflected by the escape from one component of the shuttle box, the motor function of rats in the operation group must be intact. Methods listed above are commonly used in basic pain research, but for a specific pain model, there should be an appropriate measurement method (Table 1). For example, the study on pain aversion affect caused by pathological neuropathic pain, a common method in clinic, should choose modified CPA paradigm or PEAP, while F-CPA only fits acute pain, such as carrageenan and formalin models[9,12,13]. Ultrasonic vocalization has been used to address the emotional-affective responses to painful stimuli in arthritic, formalin and muscular pain models[17-23]. Most of such behavioral paradigms use a negative reinforcement strategy whereby the subject learns to perform a behavior that terminates the pain stimulus or supplies an analgesic.

It should be noted that behavioral studies assume that manipulations to limbic system structures that alter ongoing and stimulus-evoked behavior reflect the changes in affective/motivational processing[44,45]. Behavioral tests that measure ongoing and stimulus-evoked behaviors are likely to examine both sensory and affective/motivational processes. Consequently, it is difficult to determine whether attenuation of ongoing and stimulus-evoked behavior as measured using a withdrawal responses is due to the alteration of sensory and/or affective/motivational processing. Similarly, the failure to attenuate ongoing or stimulus-evoked behavior does not necessarily mean that there is no alteration of affective processing. Thus, more behavioral paradigms are required to test the reality of pain-affective aversion.

**Table 1. Behavioral assessments of pain-related affection in rats**

| Measurement | Animal models | Advantages |
|---|---|---|
| Vocalization response test | Arthritic, formalin and muscular pain[15-26] | Test primary pain unpleasantness |
| F-CPA paradigm | Acute pain models,such as formalin, complete Freund's adjuvant models[9-13,27,28,30-32,44] | Test affective and sensory pain together |
| Modified CPA coupled with novel objects paradigm | Neuropathic pain models and carrageenan inflammatory model[35] | Test pain-related affection under neuropathic pain and inflammatory pain states |
| Place escape/aversion paradigm | Neuropathic pain models and complete Freund's adjuvant inflammatory model[37-42] | Test pain-related affection under neuropathic pain and inflammatory pain states |

OPA: conditioned place avoidance. F-CPA: formalin-induced conditioned place avoidance.

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## 动物痛厌恶情绪的行为学检测

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**摘要**：动物和人有着类似的痛感知机制和参与疼痛加工的大脑脑区。他们也会表现出相似的痛行为，譬如对伤害性刺激的反射性感觉。疼痛常用感觉(感觉质量)维度和情感动机(不愉快)维度来描述。基础和临床研究都显示，慢性痛患者经常遭受比实在的痛感觉更多的、与疼痛有关的情绪痛苦。虽然介导痛感觉的神经机制已经被广泛研究，但是痛负面情绪的神经机制还没有得到很好的了解，这主要归因于目前相对模糊的检测疼痛不同成分的行为学方法。人可以用语言来表达疼痛和痛苦的经历，而动物只能依靠其行为学反应来体现疼痛。动物行为学、认知心理学和脑功能成像技术使得检测动物的痛情绪和痛记忆成为可能。遭受神经病理性痛或炎性痛伤害后，动物会在行为上表现出对痛配对环境的条件位置性躲避。本文主要对目前常用的大鼠痛厌恶情绪的检测方法进行综述。

**关键词**：痛厌恶情绪；不愉快；条件位置逃避；疼痛