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The impact of pain upon cognition: what have rodent studies told us?

Lucie A. Low[1]
[1]35 Convent Drive, Room 1C-1012, National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD, 20892 USA

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Introduction

Pain interferes with cognition in humans. Acute pain can distract and interrupt task completion, and chronic pain patients experience trouble with attention, memory, and decision-making [23]. While rodent studies are inherently limited in their translational power to humans, rodents can perform complex behavioral tasks that probe facets of cognitive ability, using brain regions analogous to those utilized in humans [7]. These studies are crucial in pain research for uncovering the underlying cellular, molecular and signaling systems that dictate the effects of pain upon brain function. However, rodent studies of cognition demand a deep and clear understanding and appreciation of the potentials and limitations of rodent behavior, how these relate to 'normal' behaviors of the chosen species, and careful interpretation of results to human experience.

This review will discuss how researchers investigate the effects of acute and chronic pain on cognitive processing in rodents. We define the term 'cognitive' as processing required in higher cortical areas such as the prefrontal cortex (PFC), since modalities such as attention, learning, memory, decision-making and risk-taking, all rely heavily on this region [7].

Pain interrupts attention-demanding tasks

In humans, pain can interrupt attention, and direction of attention away from a painful stimulus can decrease its intensity [34]. Ford et al [10] validated the effects of distraction on acute nociception in rats by injecting their hindpaws with 2.5% formalin and then introducing them to novel objects, places or unfamiliar conspecifics. Pain behaviors were decreased in the presence of novelty, but plasma corticosterone was not increased with any distractor, indicating that the decreased pain behavior was not due to stress-induced analgesia. Novelty exposure also reduced serotonin and dopamine metabolite levels in the

Corresponding author: Lucie Low 35 Convent Drive, Room 1C-1012, National Center for Complementary and Alternative Medicine, National Institutes of Health, Bethesda, MD, 20892 USA lucie.low@nih.gov Telephone: +1 (301) 496 2219 Fax: +1 (301) 480 0772.

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medial prefrontal cortex (mPFC), suggesting a role for these neurotransmitters in distraction-induced analgesia.

Operant tasks, where rodents must press a lever or nosepoke into a window, can be used to measure sustained attention (maintained over several seconds). The 5-choice Serial Reaction Time Task (5-CSRTT) is useful for this, and is sensitive to attention, impulsivity, and memory, depending on its configuration. To investigate sustained attention, rats are trained to monitor multiple windows over 5 seconds, one of which lights up when food reward can be earned [2]. Formalin-induced acute pain [4], as well as chronic joint inflammation [28], increased the number of missed trials in rats, but giving an analgesic before the task restored attention only in the acute pain model. This suggests that analgesia reduces the distracting effects of acute pain, whereas chronic pain may have interfered with the brain's processing capability at a more fundamental level – perhaps via gray matter reductions, which are documented in both human pain patients and chronically injured rodents [23,32]. Drawbacks of using the 5-CSRTT include its intensive training regime, and the difficulty in separating food pellet satiety from reduced attention or vigilance.

In humans, the ability to show flexibility in making choices when reward values change can be measured using the Wisconsin Card Sorting Task [11], where participants have to deduce which rules to use to sort decks of cards, as rules 'shift' during the task. It requires ongoing attention and frontal lobe functionality, and in rodents, analogous attentional ability can be measured by 'set-shifting' tasks. For example, rats can learn to associate an odor or a texture with a bowl in which to dig for a treat (a 'set'), but when associations are shifted, animals have to recognize this shift and respond appropriately to find the treat. Leite-Almeida and colleagues trained nerve-injured rats on this task, and showed that they are impaired at shifting associations [17,18]. As in humans, 'set-shifting' tasks require attention, working memory, and visual processing, so do not exclusively measure one cognitive modality. However, the translation of similar tasks from humans to rodents is useful in probing the neurobiological underpinnings of impaired cognition in humans.

Millecamps et al [22] used a non-operant, modified Novel Object Recognition Task (NORT) to investigate visual attention and visuospatial recognition. After 3 days of familiarization to an arena, chronically colitic rats spent no more time exploring a novel shape over familiar ones affixed to the walls, unlike healthy controls. Morphine administration restored exploration levels of the novel object in colitic rats, suggesting the pain state interrupted rats' ability to attend to the environment. This paradigm was recently validated in chronically nerve-injured rats [20]. Six months after a nerve injury, rats were also impaired upon this recognition task relative to controls, showing that disruption on recognition tasks can last for many months after injury.

Learning and Memory are impaired in rodents in a pain state

Chronic pain has robust effects on multiple memory modalities in both rodents and humans [23]. For example, the NORT requires recognition memory in addition to attention, and performance is impaired in chronically nerve-injured mice [16]. Social recognition memory, where active social interaction between pairs of rats decreases as they recognize each other over the course of minutes or hours, is also impaired by chronic constriction injury (CCI) of the sciatic nerve [12]. This is reversed by duloxetine and gabapentin, and as these drugs are commonly used to treat patients, their validation in animal models is particularly useful.

Working memory, which is highly dependent on prefrontal cortical integrity in humans and animals [7] is disrupted in pain states in humans [23]. In mice, working memory can be measured using the 8-arm radial maze, where mice remember prior consistently baited arms on an 8-armed maze and explore unbaited ones to win food rewards. After 3 weeks, nerve-

injured mice are impaired upon this task, and the authors link the memory deficits to the pro-inflammatory cytokine tumor necrosis factor-α(TNF-α), providing a molecular target for future cognitive impairment treatments [31].

Learning and memory are highly dependent on interactions between 'executive' regions such as the prefrontal cortex (PFC) and critical regions for memory such as the hippocampus [6]. While classically conditioned associations between cues and aversive stimuli (i.e. footshock) are not impaired by injury [24,33,36], spatial learning and memory are impaired in both humans and animals in a pain state. For example, Morris Water Maze performance is impaired in nerve-injured rodents [13]. In this test, animals are placed into a circular arena filled with opaque water, with a submerged platform placed in one quadrant. The learning ability of rodents can measured over the course of 4-5 days as animals learn the location of the submerged platform. Spatial memory can be investigated by removing the platform on a 'probe' test day, and counting quadrant crossings as the animal searches for the platform - rats with a spinal nerve ligation took longer to find the platform, inferring impaired memory. While confounds due to motor impairment in injured rodents must be considered when using any locomotor tasks, the ability of this simple test to measure spatial learning and memory enables subtle deficits to be uncovered without the intense and time-consuming training needed for more complex operant tasks.

Spatial working memory is critical in operant tasks where animals must learn to press, or attend to, levers and lights placed in particular positions. For example, delayed non-match to place (DNMTP) tasks are sensitive to spatial learning and memory as well as attention and motivation, making them an attractive option for cognition researchers researching global cognitive impairments. Rodents are trained to press a lever (either left or right, only one is presented) and then nosepoke to a central food panel. After a delay, ranging from 0 to 30s, both levers are presented; the rat must press the lever that was *not* previously presented to receive a pellet, and difficulty increases as the temporal delay before lever presentation is increased. Two months after an injection of Complete Freund's adjuvant (CFA) into the base of the tail, which induces a chronic global inflammatory state akin to arthritis, rats which were previously unimpaired at the DNMTP task begin to make mistakes (pressing the wrong lever), and are more impaired the longer the time delay [5]. Furthermore, chronic morphine administration via subcutaneous pellet helps rescue performance to a certain degree [19], although the sedative effects of morphine are a potential confound on any cognitive task and need to be carefully controlled for.

Pain influences decision-making in rodents

Perhaps the most complex 'executive function' that has been investigated by pain researchers is decision-making. In humans, this can be studied using gambling tasks. The Iowa Gambling task [3], a classic clinical task for patients with prefrontal damage, has been adapted for rodents and re-named the 'rat gambling task' (rGT) [35]. Animals are trained to lever press either of two levers for a food pellet reward 8 out of 10 times. In the 'gambling' portion of the test, each lever is then assigned either as 'low risk' (1 pellet 8 out of 10 times) or 'high risk' (3 pellets 3 out of 10 times). When tested at 5, 21 and 56 days after CFA injection into the ankle, arthritic rats consistently chose the 'high risk' lever instead of learning to choose a more conservative strategy with the 'low risk' lever, as sham controls did [29]. While the human test involves monetary losses but the animal version's 'loss' is a time-out period where no pellets can be won, overall these results are parallel to human studies in chronic pain populations, where 'high risk' strategies are consistently chosen, unlike control populations, who learn to choose the low-risk but consistently rewarded strategy instead [1].

Networks underlying this risk-prone pattern of choices likely rely on multiple brain regions. Lesions of the orbitofrontal cortex (OFC) lead to higher-risk choices [27], and reward magnitude, encoded by firing rates of OFC neurons, drops after injury [26]. The amygdala is also involved when rats perform a gambling task while in an acute pain state. Ji et al [15] saw that increased neuronal activity in the basolateral amygdala (BLA) was accompanied by decreased medial PFC activation that also caused impaired decision-making. During an acute pain phase, the authors suggest that this increased BLA activity excites medial PFC GABAergic interneurons, leading to prefrontal inhibition and faulty decision-making. How or if this mechanism applies in a chronic pain state is yet to be addressed.

Conclusions

The major advantage of back-translating human cognitive tasks into rodents is the potential for discovery of the mechanisms behind the functional impairments. Chronic pain interferes with brain function from molecular to systems levels, with pro-inflammatory cytokines and the resulting neuroinflammation influencing cellular function in higher cortical areas [8-10,13,14,16,21,25,30], and ultimately leading to disruptions in network synchrony between brain regions critical for cognitive functions [6,15], although comprehensive mechanisms for the effects of peripheral injury on cognitive processing remain to be described.

Animal studies of cognition will always necessarily be constrained by the vast differences in brain structure and ability between rodents and humans, and rodent cognition studies require careful planning and interpretation, as few tasks utilize single cognitive modalities and separation of modalities can be complex. However, we can learn a great deal from rodent studies. Understanding *how* the brain is compromised in a pain state will likely lead to new drug targets, as well as the development of tools for prevention and reversal of the toxic effects upon the brain of unrelenting pain.

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