Emotional Learning and Memory Deficits in a Neuropathic Pain Rat Model

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INTRODUCTION

Neuropathic pain can lead to depression, insomnia, depressed immune function, changes in eating patterns, and other long-term deleterious effects. In previous studies we have shown that chronic pain patients are impaired on an emotional decision making task, have dorsolateral prefrontal cortex atrophy and show medial prefrontal cortex (mPFC) hyperactivity. Here the hypothesis is that chronic pain produces cortical changes that interfere with cortical networks involved with emotional associative learning. We test this hypothesis by comparing responses on conditioned fear and sucrose reward in neuropathic (spared nerve injury) and inflammatory (carrageenan) rats, along with SHAM controls.

METHODS

Adult Sprague-Dawley rats (250-300 g) were used.

Spared Nerve Injury(SNI)

Tibial and peritoneal branches are cut, leaving the sural branch of the sciatic intact (Decosterd and Woolf, 2000). In SHAM controls the sciatic nerve is exposed but not manipulated.

Carrageenan Treatment

Inflammatory pain was induced in the hind paw by intraplantar injection of Carrageenan solution (100 µg of Carrageenan in 10 µl of saline). Control animals were pricked with a needle, but no solution injected into the paw.

Fear Conditioning

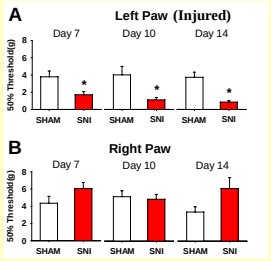
One day before fear conditioning, rats were pre-exposed to the conditioning cages for 20min. Next day, they were placed into the cage, and after an adaptation period they were presented with a 30 s tone. Two minutes later, 5 pairings of a 30 s tone that co-terminated with a 1 s shock (0.8mA), was delivered through stainless steel floor. Each pairing was separated by 2 min. Rats remained in the cage for an additional 2 min, and then returned to their home cage for 15 min. Then returned to the conditioning cage for an extinction trial. After a 2 min adaptation period the rats were presented with 3 x 2 min tone, separated by 2 min. On days 2, 3 and 21, the rats were again tested for extinction.

Sucrose and Water Consumption

Reward behavior and its memory was tested in a two-choice sugar-water task. On day 1, bottle 1 was filled with 20% sucrose water and bottle 2 with water. Rats were placed in the middle of the cage and given 15 min to find the sucrose water. The rats were put back into their home cage for 15 min, and bottle 1 (20% sucrose) was replaced with water. Then rats were place back into the cage for an additional 15 min. Day 2 and 3, both bottle 1 and bottle 2 were filled with water, and rats explored this space for 15 min. Both chambers are dark but each contains sensory cues that rats can use to discriminate between the chambers.

Tactile thresholds

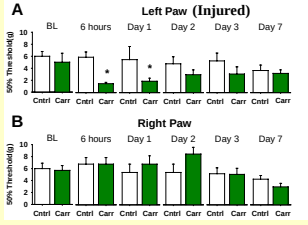
SNI vs. SHAM



Tactile threshold determined by Von Frey filaments for left and right hind paws in both SHAM and SNI rats. Injured paw thresholds are less than uninjured and sham for at least 14 days.

* p<0.05 compared to the SHAM rats.

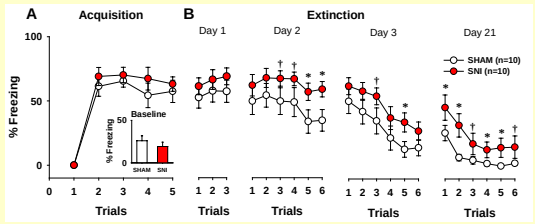
Tactile thresholds carrageenan vs. control



Tactile threshold determined by Von Frey filaments for left and right hind paws in both control and carrageenan rats. Injured paw thresholds are less than uninjured and control animals for up to three days post-injury.

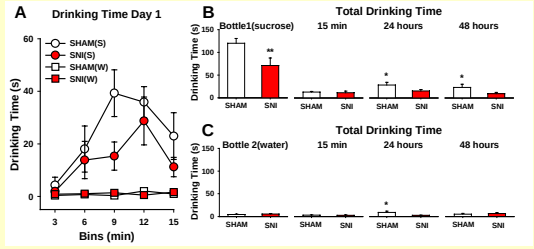
* p<0.05 compared to the control rats.

Extinction of freezing behavior is impaired in SNI rats



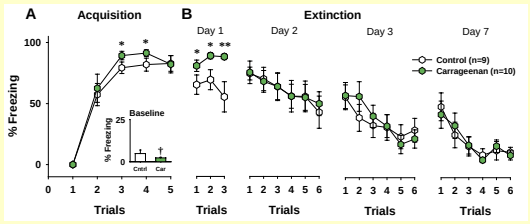
A) Fear conditioning acquisition is not different between SNI (red) and SHAM rats (open circles). Inset: baseline freezing during test tone prior to pairing tone with shock. B) Extinction trials on day 1 (15 minutes after acquisition), day 2 (24 hours after acquisition), day 3 (48 hours after acquisition) and 21 days after acquisition. Extinction is impaired in SNI, especially long-term. * p<0.05, † p=0.08 SNI vs. SHAM.

Sucrose consumption and seeking is impaired in SNI rats



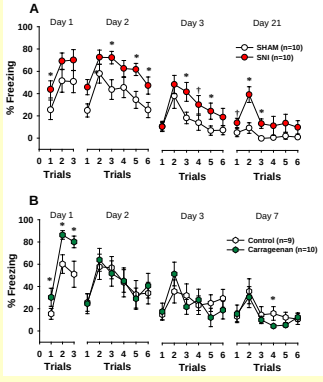
A) Initial sucrose consumption (bottle 1, 20% sucrose) is reduced in SNI (red circles) in contrast to SHAM (open circles). Water consumption (bottle 2, squares) is not different between the two groups. B) Total drinking time at first exposure (first panel, same data as in A), and in subsequent exposure where both bottle are now water. Twenty-four and 48 hours after initial exposure show reduced seeking (for bottle where sucrose was present). C) Total drinking time from bottle 2 (always water) shows minimal difference between the two groups. ** p<0.001 compared to SHAM. *p<0.05 compared to SHAM.

Extinction of freezing behavior is not impaired in Carrageenan treated rats



A) Fear conditioning acquisition is not different between carrageenan treated rats (green) and control rats (white). Inset is baseline freezing. B) Extinction trials on day 1 (15 minutes after acquisition) is different between the two groups but this difference disappears at longer time periods (days 2-7). * p<0.05, † p=0.06 compared to control.

Extinction of freezing to context is impaired in SNI but not carrageenan treated rats



A) Contextual extinction, i.e. extinction trials when the animals are exposed just to the chamber where conditioning was done, is reduced in SNI (red) vs. SHAM (white), for most times tested. B) Contextual extinction is only different at 15 minutes post-conditioning (day 1), in Carrageenan (green) vs. Control rats. * p<0.05 compared to control. † p=0.06 compared to control.

CONCLUSIONS

Our results show that rats with sustained neuropathic pain show exaggerated long-term memory for fear. Behavior akin to chronic pain patients who are dubbed “catastrophizers”. In contrast, rats with sustained inflammatory pain only show short-term exaggerated memory.

Also, rats with neuropathic pain exhibit reduced motivation for reward, and reduced long-term memory for reward.

These behavioral results are the first to demonstrate the cortical impact of neuropathic pain going beyond the classical pain perceptual brain network, and emphasize the need to study interactions between chronic neuropathic pain and cognition.

The results imply that neuropathic but not inflammatory pain specifically modulates fear/reward/hedonics systems in the cortex.