



## Chronic administration of phencyclidine produces decreased sensitivity to mechanical stimulation in the absence of altered affective behavior: Implications for pain processing in schizophrenia

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### ABSTRACT

Patients with schizophrenia have been shown to display decreased sensitivity to pain, which can severely compound the impact of injuries and illnesses. Alterations in the sensory and affective systems of pain processing have been proposed as mechanisms, but the unique contribution of each of these systems has not been elucidated. The aim of this study was to investigate these two components of pain using the NMDA receptor antagonist, phencyclidine (PCP), an established animal model of schizophrenia. Animals underwent L5 spinal nerve ligation surgery in order to provoke a condition of ongoing pain responding, followed by treatment with 2.58 mg/kg of PCP, or saline, and 20 mg/kg of the atypical antipsychotic clozapine, or vehicle, in a block design. Responses to mechanical stimuli were assessed to determine changes in sensory processing, and affective pain processing was examined with the place escape avoidance paradigm. The results showed animals receiving PCP exhibited decreased sensitivity to mechanical stimulation and unaltered behavior in the avoidance paradigm. These findings corroborate and strengthen the human literature investigating schizophrenia and alterations in pain perception. More importantly, the differential findings between the tests of sensory and affective pain processing provide a novel means of understanding schizophrenia-related pain insensitivity.

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Research and clinical reports indicate that people with schizophrenia experience decreased pain sensitivity relative to the normal population [6,12]. This pain insensitivity results in unreported injuries and wounds, which in turn further increases the fiscal and emotional costs associated with this disorder. For example, Fishbain [15] described case reports of patients with schizophrenia who presented in emergency rooms with symptoms of severe psychosis. Two to eight days after being admitted for psychiatric care, these patients began to complain of slight pain. Examinations revealed one patient suffered a femur fracture and another had a perforated ulcer, which led to that patient's death.

Researchers have attempted to better understand schizophrenia-related pain insensitivity and have found changes in pain perception across a wide array of measurements, including increased pain perception thresholds, decreased postoperative pain medication, and lower visual analogue scale scores following surgery [21], increased threshold to thermal stimuli [19], and

decreased sensitivity to electrical [6] and mechanical stimulation. Animal research has been used in an attempt to better understand the mechanisms of this insensitivity; however, there is a paucity of research of this nature and the results are equivocal. Becker et al. [5] found increase in tail root stimulation thresholds for animals treated with the NMDA receptor antagonist ketamine, but only for singly housed animals. Fiore et al. [14] used prenatal injections of methylazoxymethanol acetate to cause brain abnormalities that are thought to model schizophrenia and reported decreased pain sensitivity. In contrast, Al Amin et al. [1] used neonatal ventral hippocampal lesions to model schizophrenia and found mechanical hypersensitivity.

Currently, it is unclear if people with schizophrenia have an altered nociceptive system, disallowing them from perceiving pain normally, or if there are changes within brain structures which would alter the affect associated with the perceived pain [17]. This point is highlighted by the observation that patients with schizophrenia show changes in activation or volume of key brain areas involved in processing emotion during fMRI scans [4].

The aim of this experiment was to determine if changes in pain perception related to schizophrenia are associated with alterations to both the sensory and affective components of pain in an animal model. Currently, phencyclidine (PCP) is a widely accepted

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model of schizophrenia. It reliably produces positive symptoms such as increased locomotor activity and atypical grooming [3,29] and negative/cognitive symptoms such as impaired social interaction [11,18], and has adequate face, construct, and content validity [16]. Seventy-two hours following a final dose of PCP, differences in responses to somatosensory testing using mechanical pressure were assessed. Differences in the affective component of pain were also assessed using an avoidance paradigm.

Ninety-six adult male Long Evans rats (Charles River) were used for this study. All animals were singly housed with free access to food and water in a temperature controlled room on a 12 h light/dark cycle (7 am–7 pm). Humidity levels were maintained at approximately 60%. To monitor health and administer the correct dosage of drugs, animals were weighed daily. Prior to the beginning of the experiment, animals were randomly assigned to the various treatment conditions. All procedures were approved by the Institutional Animal Care and Use Committee for the University of Texas at Arlington and adhered to the guidelines set forth by the Committee for Research and Ethical Issues of the International Association for the Study of Pain [31].

A neuropathic pain condition was induced in half of all animals ( $n=48$ ) by utilizing tight ligation of the L5 spinal nerve. Animals were first anesthetized using isoflurane (3% induction, 2% maintenance) and then were placed in a prone position. The left paraspinal muscles were separated from the spinous process at the L4–S2 levels. The L6 transverse process was then carefully removed with a small rongeur to visually identify the L4–L5 spinal nerves. The L5 spinal nerve was isolated and tightly ligated with 6–0 silk thread. For the sham group ( $n=48$ ), which served as a control group, surgery was performed as described above except the L5 nerve was only isolated and was not ligated. The muscle layer was sutured and the skin incision was closed with wound clips. An antibacterial solution was applied to the surgical site. Animals were allowed to recover for 3 days prior to being exposed to phencyclidine.

Phencyclidine (PCP) (Sigma Aldrich, St. Louis, MO) was dissolved in normal saline and injected i.p. at a dosage of 2.58 mg/kg. Control animals received saline in similar volumes. Phencyclidine was given according to the dosing schedule described by Cochran et al. [11]. For this protocol, animals were injected once daily for five consecutive days. Injections then occurred three times per week for the following 3 weeks.

The antipsychotic drug clozapine (Sigma Aldrich, St. Louis, MO) was dissolved in 2% glacial acetic acid and buffered to a pH of 5.3–6.0 using NaOH, and then was given s.c. at a dosage of 20 mg/kg [11] once a day beginning just prior to the sixth dose of PCP [11]. Control animals received equivalent volumes of vehicle.

To measure mechanical threshold levels, animals were placed within a Plexiglas enclosure (20 cm × 10.5 cm × 40.5 cm) and allowed to habituate for 15 min. The enclosure was positioned on top of a mesh screen in order to administer mechanical stimuli to the plantar surface of both hind paws. The withdrawal threshold was then determined using methods previously described [7]. Briefly, monofilaments of various increasing forces were applied to the hind paws and withdrawal responses were noted. Using the following formula:  $[X_{th}]_{log} = [vFr]_{log} + ky$ , where  $[vFr]$  is the force of the last von Frey used,  $k = 0.2492$  and is the average interval (in log units) between the von Frey monofilaments, and  $y$  is a value that depends upon the pattern of withdrawal responses, animals that failed to respond to the highest force monofilament were determined to have a ceiling mechanical paw withdrawal response of 424.30 mN. Mechanical paw withdrawal threshold testing was performed across three trials, and the withdrawal values were averaged over these trials to determine the mean mechanical paw withdrawal threshold for each animal.

At the end of the experiment (Day 32), animals were tested in the place escape avoidance paradigm (PEAP). The paradigm consists of

a 60 cm × 30 cm × 30 cm Plexiglas chamber, half of which is painted white (light side) and half is painted black (dark side), positioned on a wire mesh stand that is 30 cm off the table surface. During the 30 min testing session, animals were allowed unrestricted access to both sides of the chamber. Testing began immediately by applying suprathreshold mechanical stimulation (476 mN von Frey monofilament) to the plantar surface of the hindpaws every 15 s. If the animal was in the preferred dark side of the chamber at the 15 s interval, the hind paw ipsilateral to L5 ligation was stimulated; if the animal was in the non-preferred light side of the chamber, the hind paw contralateral to injury was stimulated. The experimenter recorded where the animal was located during stimulation, and upon testing completion, found the mean percentage of time spent in each side of the chamber. It is expected with this test that animals will come to avoid to the dark side of the chamber to avoid stimulation of the injured paw. The PEAP test has been utilized extensively to study the affective component of pain and the role of the anterior cingulate cortex in pain processing [22].

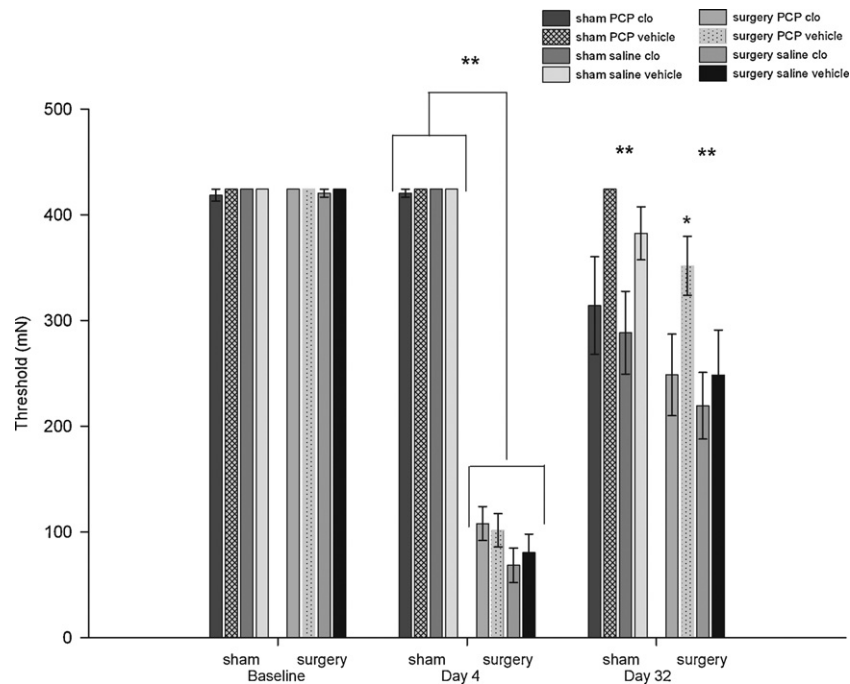
On Day 0, baseline measurements were obtained for mechanical paw withdrawal threshold (MPWT) responding. The following day (Day 1), animals underwent L5 ligation surgery and were then allowed to recover for the following three days. On Day 4, animals were again tested for MPWT responding. Immediately following this testing, animals received the first injection of PCP, or saline. Phencyclidine injections then occurred on Days 5–8, and Days 11, 13, 15, 18, 20, 22, 25, 27, and 29. Beginning just prior to the PCP injection on Day 11, animals were injected with clozapine, or vehicle. Antipsychotic treatment then occurred daily until Day 29. On Day 32, MPWT and PEAP testing occurred.

In addition to sensory testing, all animals were monitored for changes in behavior. Depending on the dose and length of time PCP is administered, positive, negative, and cognitive symptoms have been observed [18], but a chronically administered regimen appears to best model the human condition, especially the neurological aspects of this disease [11]. That being said, a chronically administered, low dose regimen of PCP does not fully model all of the behavioral characteristics of schizophrenia, including changes in motivation and locomotion [18]. As a result, the observable behavior of PCP-treated animals was not different from that of control animals.

Data were analyzed with a repeated measures mixed analysis of variance (ANOVA) for each of the dependent variables (mechanical paw withdrawal threshold testing, place escape avoidance paradigm testing, and weight) using time as the repeated measure and surgery (sham, surgery), condition (saline, PCP), and drug (vehicle, clozapine) as the independent variables. Significant effects were further examined using the Tukey HSD test for post hoc comparisons. The significance level was set at  $p < .05$  for all tests.

As expected, Fig. 1 shows that animals receiving surgery displayed a significant change in paw withdrawal thresholds ( $p < .001$ ), with L5 ligated animals having increased sensitivity to mechanical stimulation when measured on Day 4 ( $p < .001$ ), and this sensitivity remained on Day 32 ( $p < .001$ ). Unexpectedly, clozapine treatment itself also altered MPWT measurements ( $p < .001$ ), with post hoc analyses showing clozapine-treated rats were more sensitive to mechanical stimulation on Day 32 ( $p < .001$ ). Most importantly however, it can be seen that PCP treatment changed mechanical threshold values ( $p < .05$ ), with post hoc analyses showing that all animals treated with PCP showed less sensitivity to mechanical stimulation on Day 32 ( $p < .05$ ).

In Fig. 2, the motivational/affective behaviors of animals can be seen. The analyses for the place escape avoidance paradigm revealed that surgery animals spent more time in the light side of the chamber than sham animals, and this effect became evident 20 min into the test ( $p < .05$ ). Surprisingly, PCP and clozapine treatment did not alter PEAP behaviors.



**Fig. 1.** Mean ( $\pm$ SEM) mechanical paw withdrawal thresholds (MPWT) for all animals ( $n = 12$ ). Twenty-four hours following baseline measurement of MPWT, animals underwent L5 spinal nerve ligation or a sham procedure. Following recovery from surgery, animals were again tested for MPWT on Day 4. As can be seen, L5 ligation induced a significant decrease in thresholds to mechanical stimulation compared to sham animals. Beginning on Day 4, animals were administered phencyclidine (PCP), with the addition of clozapine (clo) starting on Day 11. Animals were tested for MPWT a final time on Day 32. On this test day, PCP treated animals showed less sensitivity to mechanical stimulation compared to saline treated animals. Further, clozapine treated animals had increased sensitivity compared to vehicle treated animals on this test day. \*\* $p < .01$ , comparing sham to surgery treated animals on Day 4, and comparing clozapine and vehicle treated animals on Day 32; \* $p < .05$ , comparing PCP treated animals to saline treated animals.

The analyses for weight showed no significant baseline differences between clozapine and vehicle treated animals ( $p > .05$ ). Clozapine rats did, however, gain significantly less weight than vehicle treated animals by Day 32 ( $p < .001$ ). No significant effects were found for surgery or condition (Fig. 3).

This experiment was the first to examine altered nociception using the PCP model of schizophrenia, and the first to investigate the affective aspect of pain in any model of schizophrenia. The major findings of this study were that (1) animals exposed to PCP experienced the expected decrease in sensitivity to mechanical stimuli, indicating altered processing of the sensory component of pain, and (2) PCP treated animals did not show altered responding during the place escape avoidance paradigm, indicating that the affective component of pain was unaltered.

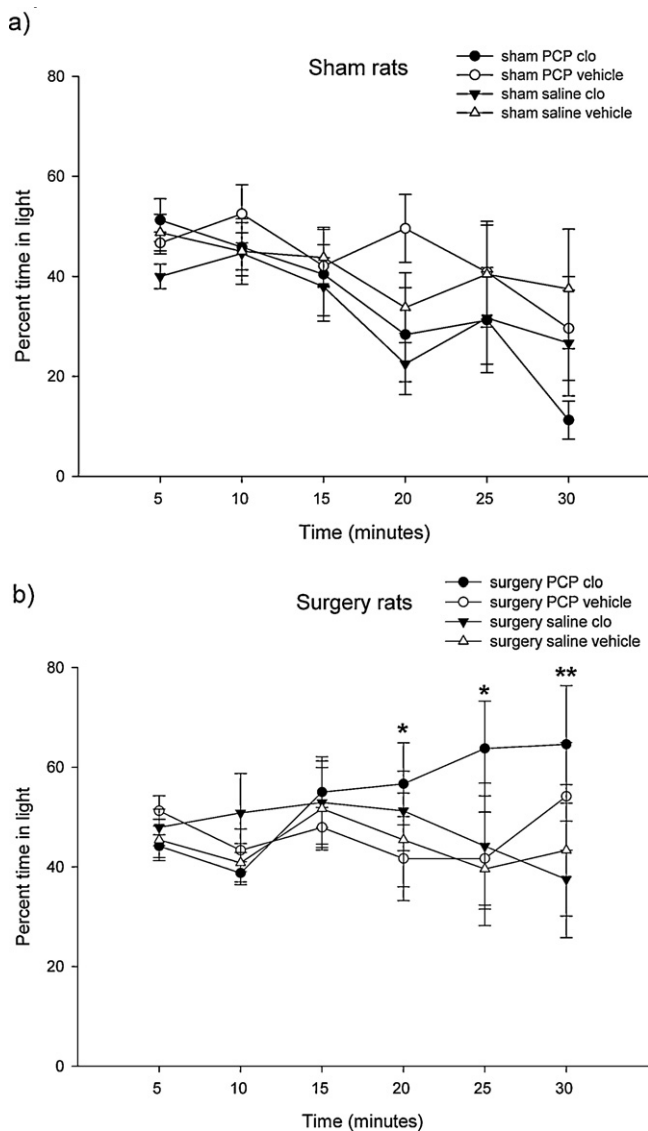
The discovery of decreased sensitivity to mechanical stimulation for animals treated with PCP is an exciting finding that supports the observation of decreased pain sensitivity in humans. For example, Merskey et al. [23] applied mechanical pressure, using an algometer, to the tibia of schizophrenic patients and found that "movement withdrawal" (i.e. no withdrawal, slight or moderate withdrawal, or complete withdrawal of the stimulated area) was hampered in this population. Potvin and Marchand [25] conducted a meta-analysis of twelve published articles investigating the phenomenon of pain insensitivity, taking into account the type of stimulation (i.e. thermal, electrical, or mechanical) and the exact measure used, the state of the patient (inpatient versus outpatient), and the number of subjects. Overall, their results supported the findings of decreased response to pain in those with schizophrenia. Therefore, the finding of the current study lends strength to the use of chronically administered PCP in investigating pain and schizophrenia, and opens the door for translational research on this topic.

Rats in the present study were examined for changes in mechanical sensitivity three times: at baseline, after surgery and before exposure to PCP, and at the conclusion of the treatment regimen.

This testing schedule allowed for examination of changes specific to the surgery (Day 4) as well as changes resulting from the PCP and was sufficient to detect PCP-induced decreases in mechanical sensitivity. Future research could investigate more time-sensitive changes in mechanical responding, such as testing every other day after starting PCP treatment, which may further contribute to an understanding of the PCP model and its effects on pain.

It should be noted that PCP is an NMDA receptor antagonist, and NMDA receptors are known to be involved in the processing and maintenance of painful stimuli. Acute blockage of NMDA receptors, such as with the use of PCP and other antagonists, hinders the development of hyperalgesia in response to painful stimuli [30]. Other studies have shown analgesia or reversal of hyperalgesia with the acute administration of NMDA receptor antagonists [8,24]. However, it is important to point out that NMDA receptors upregulate in response to chronic exposure to an antagonist [28], which could result in a hyperalgesic, not hypoalgesic, state. Although we did not observe this effect (i.e. sham/PCP/vehicle), we determined *a priori* that PCP be administered after a chronic pain condition had been established in an attempt to minimize this potential outcome. While future studies may need to investigate the consequence of PCP treatment prior to induction of pain, this is the first study to use this schedule of chronic PCP as a validated model of schizophrenia to show decreased pain sensitivity.

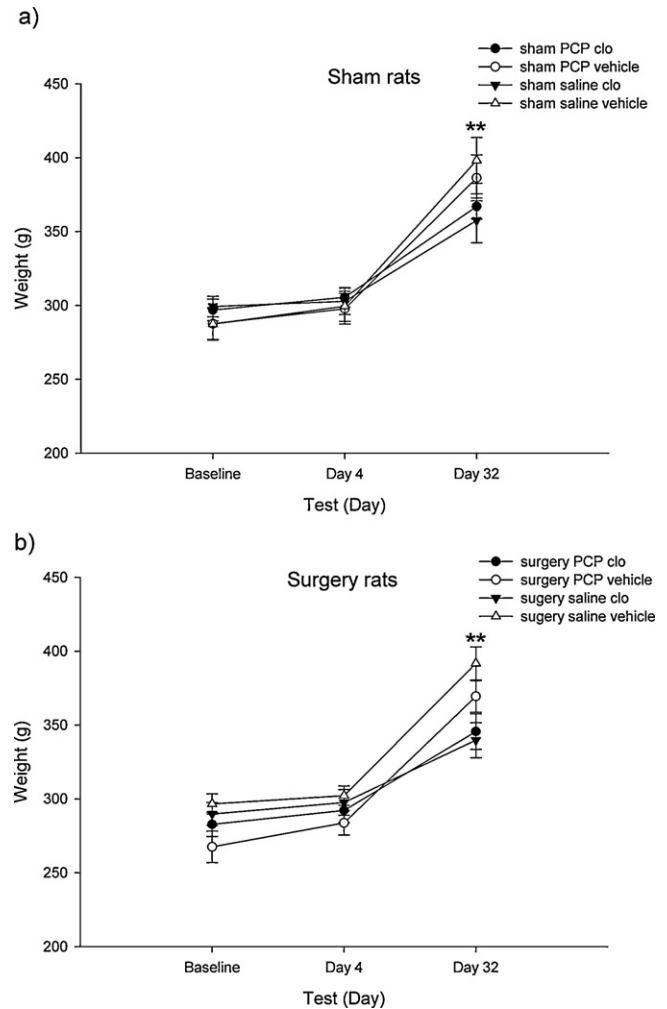
The results for the place escape avoidance paradigm suggest that PCP treatment did not alter the affective component of pain. Instead, it was found that animals in the pain condition spent more time in the light side of the chamber, regardless of drug treatment. A re-examination of the human literature reveals interesting corroboration for the findings of this study. The signal detection theory, described extensively by Clark [10], purports to measure sensory discrimination ( $d'$ ), which could be seen as a parallel to the MPWT measurement in this study, and affective pain processing (the response criterion), which is captured here with the place



**Fig. 2.** Mean ( $\pm$ SEM) percentage of time spent in the light side of the chamber during the 30 min place escape avoidance paradigm test for all animals ( $n=12$ ). Testing occurred on Day 32. Animals receiving L5 spinal nerve ligation (b) spent significantly more time in the light side of the chamber compared to control animals (a) at the 20, 25, and 30 min time points. \* $p < .05$ ; \*\* $p < .01$

escape avoidance paradigm. Using this theory to investigate pain in schizophrenia, Dworkin et al. [12] found that “patients with schizophrenia have poorer sensory discrimination of painful stimuli [compared to control subjects] but do not differ . . . with respect to their response criterion for reports of painfulness.” The results of this study support the findings of Dworkin and show decreased sensory responding and unaltered pain affect for the PCP group. Jochum et al. [19] suggest that this combination of increased thresholds for pain along with similar responses to a stimulus that is perceived as painful reflects an executive function problem, not necessarily a somatosensory issue.

At this point, more research needs to be conducted to determine if a somatosensory deficit can partially account for the changes in pain sensitivity in those with schizophrenia. Researchers using electroencephalograph (EEG) have found alterations in event-related potentials in the brains of patients with schizophrenia [13], but it would be beneficial to examine the changes in spinal processing as well. For obvious ethical reasons, invasive cellular electrophysiology has not been conducted on humans with



**Fig. 3.** Mean ( $\pm$ SEM) weight for sham treated (a) and surgery treated (b) animals ( $n=12$ ). Animals were weighed daily just prior to any manipulations. At baseline and Day 4, there were no significant differences between groups. However, clo treated animals displayed significantly less weight gain by the end of the study (Day 32). \*\* $p < .01$

schizophrenia. At this point, this method has also not been utilized in animals due to the lack of an adequate model of pain insensitivity in schizophrenia. Based on the findings of this study, it is now possible to begin to explore and juxtapose supraspinal processes, such as executive function, to spinally mediated changes that occur within the pain system for those with schizophrenia.

Surprisingly, none of the dependent variables revealed a significant PCP/clozapine interaction. Clozapine, an atypical antipsychotic that interacts with both dopaminergic and serotonergic receptors, was found to induce decreased weight gain and mechanical sensitivity compared to vehicle treated rats across the time course of the experiment. Antipsychotics often result in increased weight gain, not decreased weight gain as reported here [2]. It is possible that the chronic administration and relatively high dose of clozapine used in the present study produced toxicity. In humans, chronic treatment with clozapine has been associated with deleterious, and painful, side effects including recurrent pancreatitis [9], bowel obstruction, and constipation [27]. Clozapine treatment did not produce noticeably altered behavior aside from apparent minor sedation that lasted 15–30 min following injection. This effect was not quantified and did not likely mediate any reported outcomes due to testing occurring three days following the final dose of clozapine. Given that case studies have reported that treatment with

clozapine can provide pain relief [20], and at least one animal study has shown robust antinociception from a single dose of 30 mg/kg of clozapine [26], the finding of mechanical sensitivity was unexpected. As with the finding of changes in weight gain, it is possible that the chronicity of the treatment regimen produced unexpected effects. The 20 mg/kg dose and dosing regimen were chosen based on previous literature [11] reporting advantageous effects, including reversal of metabolic hypofunction in key brain areas, in the PCP model of schizophrenia; however, weight gain and other behavioral effects were not addressed. In animal studies, clozapine is generally not administered chronically, and as a result, the mechanisms of the hypersensitivity reported here have not been examined but provide an interesting avenue for future study.

In conclusion, the results of this study show decreased sensitivity to mechanical stimulation and unaltered affective pain responding in an animal model of schizophrenia. This is the first animal study to examine both the sensory and affective components of pain, and exploring these systems of pain is a needed step in understanding why patients fail to report painful and deleterious conditions. Greater insight into this condition may provide broader knowledge of schizophrenia etiology and disease course and treatment. This in turn will ultimately lead to a significant improvement in clinical outcomes for those diagnosed with schizophrenia.

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