Differential effects of left/right neuropathy on rats' anxiety and cognitive behavior

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

ABSTRACT

Chronic pain is frequently accompanied by a deterioration of emotional behavior and cognitive function. A small number of studies in humans concluded that pain-associated negative affect is more pronounced when pain is localized in the left side of the body. It has been suggested that such side bias results from cortical function lateralization. It is not known, however, if other pain-associated behavioral changes are differentially affected by left- and right-sided pain. To test this hypothesis, the performance of rats with a unilateral spared nerve injury neuropathy installed in the left (SNI-L) or in the right (SNI-R) side was compared in anxiety (elevated-plus maze) and cognitive (spatial working and reference memory, attentional set-shifting task, and delay-to-signal impulsivity task) behavioral paradigms. Results show that SNI-L animals presented an increased anxiety-like profile while maintaining preserved cognitive function. On the contrary, SNI-R animals presented cognitive deficits in all tasks except in the reference memory, but displayed a normal anxiety-like profile. Our results show that left- and right-sided neuropathic pain differentially affects emotional behavior, which is in accordance with previous observations in human subjects, both in experimentally induced pain and in chronic pain conditions. Additionally, our results demonstrate that the cognitive function deterioration associated with unilateral neuropathic chronic pain conditions is also differentially affected.

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1. Introduction

Emotional disturbances and cognitive impairments are a common feature of prolonged pain conditions [61]. These pain-induced behavioral alterations are associated with structural and functional changes in several brain regions [53]. However, the prefrontal cortex (PFC) emerges as one of the most affected brain centers because it has been consistently shown to present morphological and functional alterations in patients with chronic pain syndromes [1,25,53]. This region is involved in the modulation of emotional behavior [87] and in a wide range of cognitive functions [59], including working memory, attention, impulsivity, and the construction of flexible adaptive behaviors [59], collectively named executive functions, therefore appearing as a good candidate to mediate the abovementioned effects.

The PFC is the only cortical area that receives direct projections from the spinal cord [46], which might explain its selective vulnerability to the effects of prolonged pain. In fact, it has been shown that the thalamus, which also receives spinal cord projections, is similarly affected upon prolonged pain [1], supporting this view. If the plasticity observed in cortical and subcortical areas in chronic pain conditions relates totally or partially with a disturbance of the ascending pathways, we can postulate that lateralized pain would have a differential behavioral impact according to its left/right origin. In fact, the PFC itself has been shown to be functionally lateralized [15]. Additionally, a small number of human studies demonstrated an increased negative effect of left-sided pain [24,66,77,79], but none has studied a lateralized effect on cognitive performance.

To test this hypothesis, we assessed the behavior of young Wistar-Han rats after 1 month of either left- or right-sided neuropathic pain (spared nerve injury (SNI) model [20]) on a battery of tests for sensory, emotional, and cognitive functions.

2. Methods

2.1. Animals and surgery

Two-month-old male Wistar-Han rats (Charles River Laboratories, Barcelona, Spain) were used in all experiments (Table 1).

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Animals were kept in a room with controlled temperature (22°C ± 1°C), 12-hour light/dark cycle (lights on at 8 am), and housed in groups of 2 to 3 animals in plastic cages with food and water available ad libitum. All procedures with animals were approved by the respective local organizations, and the experiments were performed according to the guidelines of the European Communities Council Directive 2010/63/EU.

The SNI model of peripheral neuropathy [20] was used in all experiments. Animals were deeply anesthetized with mixture of 1.5:1.0 of ketamine (Imalgene, 100 mg/mL – Merial, Lyon, France)/ medetomidine (Dormitor, 1 mg/mL – Orion Pharma, Espoo, Finland) at a dose of 1 mL/kg. The unilateral ligation and distal axotomy of the tibial and common peroneal nerves on the left (SNI-L) or right (SNI-R) hindpaws was performed as described in detail elsewhere [20]. Briefly, the skin of the lateral surface of the thigh was incised and a longitudinal section was made directly through the biceps femoris muscle exposing the sciatic nerve and its 3 terminal branches. After ligation and removal of 2 to 4 mm of the distal nerve stumps of the tibial and common peroneal nerves (the sural nerve was left intact), muscle and skin were closed in 2 layers. Sham-operated animals underwent identical surgical procedures (half of the group in the left and the remaining in the right paw) except that tibial and common peroneal nerves were left intact. After the surgery, animals were allowed to recover before the actual testing that was performed, 1 month after the operation. Details on the organization of the behavioral paradigms are given on Table 1.

Animals participating in the conditioned place preference (CPP) experiment had, additionally, an intrathecal catheter for drug delivery to the spinal cord. The catheter (Intramedic PE-10, Becton Dickinson, Sparks, MD) was placed at the spinal cord lumbar level under pentobarbital anesthesia (50 mg/kg intraperitoneally) 1 week before actual testing, as described in detail elsewhere [86]. After recovery from anesthesia, the correct placing of the catheter was verified by injecting lidocaine (4%, 7 to 10 μL followed by 10 μL of saline for flushing) with a 50-μL Hamilton syringe (Hamilton Company, Bonaduz, Switzerland). Only those rats that had no motor impairment before lidocaine injection but had a bilateral paralysis of hind limbs after intrathecal administration of lidocaine were studied further.

All behavioral experiments were performed during the light period of the daily cycle. Acclimatization to the testing room was allowed for approximately 1 hour. To avoid possible bias, in particular related to the testing period, animals belonging to different groups were tested alternately.

2.2. Pain assessment

2.2.1. Von Frey monofilaments

Development of neuropathic hypersensitivity was verified in all animals. In the group undergoing CPP, this was done in the beginning before the installation of the intrathecal catheter and was used to compare the lesion lateralization, hypersensitivity was assessed 1 week after the end of emotional/cognitive behavioral assessment to verify the successful development and maintenance of the neuropathy. Animals were habituated to the experimental conditions 1 to 2 hours daily for 2 to 3 days. For assessment of tactile allodynia, the hind limb withdrawal threshold was determined by stimulating the sural nerve areas in the hind paw of the nerve-injured or sham-operated limb with monofilaments. The calibrated series of monofilaments used in this study produced forces ranging from 0.008 to 60 g (North Coast Medical Inc., Morgan Hill, CA). The monofilaments were applied to the lateral foot pad with increasing force until the rat withdrew its hind limb. The lowest force producing a withdrawal response was considered the threshold. The threshold for each hind paw of each rat was based on 3 separate measurements, and the median of these values was considered to represent the threshold. Limb withdrawal threshold was assessed in a separate session 1 month after nerve injury or sham operation.

2.2.2. CPP

For analysis of ongoing pain 1 month after the nerve injury or sham operation, rats received spinal clonidine hydrochloride (α-2 adrenoceptor agonist, Sigma–Aldrich, St. Louis, MO) as previously described for a single conditioning trial protocol [40]. Animals were tested in automated CPP apparatuses (Place Preference System, San Diego Instruments Inc., San Diego, CA) that recorded their movement/location in each chamber using a computer-controlled 4 × 16 array of photobeams. All rats were habituated to the apparatus with 3 daily sessions, during which they had access to all 3 chambers (days 1 and 2: 30 min/session, day 3: 15 min/session). Rats that spent more than 720 seconds in one of the conditioning chambers on day 3 were eliminated from the study. The following day (day 4), all rats received a morning injection of saline and were immediately placed in one of the pairing chambers for 30 minutes. Four hours later, all rats received clonidine and were immediately placed in the opposite chamber for 30 minutes. Clonidine was administered intrathecally at the dose of 10 μg/10 μL and was flushed with 10 μL of saline. Clonidine and saline control injections were monitored by movement of an air bubble between the drug/saline control and the saline used for flushing. At 20 hours after drug pairing (day 5), animals were placed drug-free in the CPP boxes with access to all chambers. The amount of time spent in each of the 2 chambers (saline- and drug-paired) was automatically registered and used to quantify the analgesia conditioning effect.

2.3. Anxiety-like behavior

The elevated plus-maze (EPM) was performed in a plus-shaped maze made on black polypropylene plastic, with 2 opposed open arms (50.8 × 10.2 cm) and 2 opposed closed arms with the same dimensions but surrounded by walls (40.6 cm height, Med Associates Inc., St. Albans, VT). The whole structure was elevated 72.4 cm from the floor and was surrounded by 4 black walls perpendicular and at equal distances from each arm of the maze. Animals were placed at the centre of the maze and allowed to explore for 5 minutes. At the end of each trial, all areas were cleaned with 10% alcohol and carefully dried. The number of arm entries and the time spent in each arm was registered. The percentage of the time spent in the open arms is inversely related with anxiety-like behavior. The number of closed-arm entries was used as an index of locomotor activity.

2.4. Paradigms of cognitive behavior

2.4.1. Working and reference memory tasks

Working memory (WM) and spatial reference memory (Morris water maze, MWM) tests were performed in a circular tank (diam-

Table 1
Organization and distribution of the experimental groups.

Group	N	Von Frey/CPP	EPM	MWM/WM	ASST	Impulse control
1	18	X	–	–	–	–
2	23	–	X	–	X	–
3	24	–	X	–	–	X
4	27	–	–	X	X	–
5	25	–	–	X	–	–

To avoid repetition interferences, a maximum of 2 behavioral assays were carried out in each group of animals. Except for group 1, all animals were tested for allodynia using von Frey monofilaments at the end of the behavioral proceedings to minimize the distress associated with the pain test. Group 1 was used exclusively to assess laterality-related differences in evoked and ongoing pain (see text). ASST = attentional set-shifting test; CPP = conditioned place preference; EPM = elevated-plus maze; MWM = spatial reference Morris water maze; WM = spatial reference working memory.

eter 170 cm) with black walls located in the center of a room with white walls where black geometric figures had been placed as spatial references. A video camera positioned in the ceiling captured the image to a video tracking system (Viewpoint, Champagne au Mont d'Or, France). A black, circular (diameter 12 cm) platform was placed within one of the quadrants virtually assigned in the computer. During the tests, the water temperature was kept in the range of 22°C to 24°C and the level was such that it slightly covered the platform (therefore, invisible to the rats). In the beginning of each trial the animal was placed in the respective quadrant (Table 2) facing the maze walls. The trial was interrupted if the platform was found or if 120 seconds had elapsed (thereafter the animal was guided to the target). The animal was then allowed to spend 30 seconds on the platform before starting a new trial. In the WM paradigm, the daily trial-to-trial progression of the swim distance was averaged for the different platform locations, whereas in the MWM, day-to-day progression (learning) was averaged across the 4 daily trials for the same platform location.

2.4.2. Attentional set-shifting task

In the attentional set-shifting task (ASST) [7], animals are required to find rewards hidden in 1 of 2 bowls, according to a series of rules involving 2 different stimuli sets, textures and odors, that are simultaneously presented. On each rule, only stimuli in 1 category are relevant for finding the reward (see Table 3 for a general description of the rules and Supplemental Table 1 for more detailed information). Because rules change throughout the task (4 rules with odor as the relevant stimulus set, 4 rules with texture as the relevant stimulus set), the animal is prompted to shift its attention from one set to the other, hence the name of the test. The ASST apparatus is a rectangular arena (40 × 70 cm), made of black acrylic, with 20-cm-high walls, and near one of its extremities, 2 bowls (7 cm diameter/4 cm depth) side by side, buried with their upper limit at floor level and filled with digging media (sawdust); an immovable wall separated the areas containing each bowl to prevent an animal from quickly moving from one to the other. Textures were attached to the floor of the arena, at the entrance of the area containing each bowl, whereas odors were presented by rubbing the edge of the bowls with cotton embedded in concentrated aromatic oils; to preventing fading, odor was renewed every 10 trials or whenever there was a rule change.

Six days before the beginning and throughout the experimental period, food availability was restricted to the last hour of the day cycle, with the weight of the animals being maintained between 85% and 90% of free feeding values. During this period, 2 pieces of Cheerios (Nestle, Portugal) per animal were given to the animals in their cages. In addition, in the last 3 days before the experiment, animals were placed in the apparatus and accustomed to dig in

Table 2
Sequence and organization of the spatial reference WM and MWM tests.

Day	Platform location	Protocol	Starting quadrant			
			T1	T2	T3	T4
1	W	WM	N	S	**W**	E
2	N	WM	W	**N**	S	E
3	E	WM	**E**	S	N	W
4	S	WM/MWM	E	W	N	**S**
5	S	MWM	N	**S**	E	O
6	S	MWM	**S**	N	O	E
7	S	MWM	O	E	**S**	N

Platform location on each day and the starting quadrant for each trial are given. Note that when the animal initiates the trial in the quadrant where the platform is located (bold), there is an increased chance of finding the platform by accident. To avoid this possible bias, these trials were distributed evenly in the 4 days. MWM = spatial reference Morris water maze; WM = spatial reference working memory.

Table 3
Attentional set-shifting task (ASST) sequence.

Step	Dimensions		Combinations	
	Odor	Texture	Correct	Incorrect
SD_{odo}	Relevant	–	$O_1/–$	$O_2/–$
SD_{tex}	–	Relevant	$–/T_1$	$–/T_2$
CD	Relevant	Irrelevant	$O_3/T_{3 \ (or \ 4)}$	$O_4/T_{4 \ (or \ 3)}$
Rev_1	Relevant	Irrelevant	$O_4/T_{3 \ (or \ 4)}$	$O_3/T_{4 \ (or \ 3)}$
IDS_1	Relevant	Irrelevant	$O_5/T_{5 \ (or \ 6)}$	$O_6/T_{6 \ (or \ 5)}$
Rev_2	Relevant	Irrelevant	$O_6/T_{5 \ (or \ 6)}$	$O_5/T_{6 \ (or \ 5)}$
EDS	Irrelevant	Relevant	$O_{7 \ (or \ 8)}/T_7$	$O_{8 \ (or \ 7)}/T_8$
Rev_3	Irrelevant	Relevant	$O_{7 \ (or \ 8)}/T_8$	$O_{8 \ (or \ 7)}/T_7$
IDS_2	Irrelevant	Relevant	$O_{9 \ (or \ 10)}/T_9$	$O_{10 \ (or \ 9)}/T_{10}$
Rev_4	Irrelevant	Relevant	$O_{9 \ (or \ 10)}/T_{10}$	$O_{10 \ (or \ 9)}/T_9$

Simple (SD_{odo} and SD_{tex}) and compound (CD, Rev_{1-4}, IDS_{1-2}, and EDS) presentations were performed in 2 different and sequential days. In the first, only 1 perceptual dimension (odor or texture) was present at each time, whereas in the second, both dimensions, whether or not relevant to located the reward, were present. The organization of the presentations on each trial is detailed in Supplemental Table 1. ASST = attentional set-shifting task; CD = compound discrimination; EDS = extra-dimensional shift; IDS = intradimensional shift; O = odor; Rev = reversal; SD = simple discrimination; T = texture.

both bowls by burying progressively deeper Cheerios in the digging media. In the first experimental day animals were presented only with odors (first rule) or textures (second rule), whereas on the second day both sets of stimuli were always present in a total of 8 rules (see Table 3 for a general description); presentation of different rules was separated by a 10-minute interval, during which animals returned to their home cages. Each trial was initiated by lifting a removable barrier, allowing the animal to exit the waiting area (located in the side opposite to the bowls), and terminated when the animal dug vigorously in the media in one of the bowls. A performance criterion of 6 consecutive correct trials was adopted for each rule throughout the test, with the number of trials necessary to reach such criteria used as the main performance measure. Of note, the combination odor/texture and its association with the left/right bowl varied in each trial according to a pre-established order (see detailed information in Supplemental Table 1).

2.4.3. Inhibitory control to variable delay

This task was performed in the classical 5-choice serial reaction time task apparatus [4], consisting of a nearly squared arena with 20-cm-high walls, one being curved and having 5 apertures at the animal head level with nose-poke detectors and a light. In the opposite wall, a single aperture with similar dimensions is connected to a food dispenser. In this test, only the middle aperture out of the 5 nose-poke apertures was available (the remaining 4 were closed). The day before the first session, food was removed from animals' cages, and from then on its availability was restricted to the last hour of the light cycle. Animals were trained to nose-poke the open aperture to receive a sugar pellet (dustless precision pellets, Bio-Serv, Frenchtown, NJ). Each trial in the training sessions started with the house-light on, signaling an ongoing trial. After a 3-second delay interval, the light-signaling aperture lit up. A nose poke before the signal (impulsive response) interrupted the trial and initiated a "punishment" period of 5 seconds (house-light off). On the other hand, a nose poke after the signal triggered a pellet delivery. Each training session spanned 30 minutes or 100 trials. After 9 training sessions all animals were able to accomplish 100 trials, and except for 2 (1 sham and one SNI-L), had <30% of impulsive responses. In the 10th session, animals were tested in a sequence of 25 trials at a 3-second delay, followed by 70 trials at a 7- or 10-second delay attributed randomly by the computer and returning finally to a 3-second delay for 25 additional trials. In this session, premature responses were not

punished. The total number of premature responses per total amount of delay time was used to compare groups' performances.

2.5. Statistics

The data are presented as mean ± SEM and analyzed using 1- or 2-way analysis of variance, with repeated measures when appropriate, followed by a Tukey post-hoc test for multiple comparisons (comparison of 3 or more groups), or t test (comparison of 2 groups). $P < .05$ was considered to represent a significant difference.

3. Results

3.1. Pain measurements

Using established paradigms to assess acute evoked (von Frey monofilaments) and ongoing nonprovoked pain (analgesia-derived conditioned place-preference) [40], we firstly showed that 1 month after the installation of the SNI model, SNI-L and SNI-R neuropathies have similar algogenic properties. Both right and left sham-operated animals were used as control subjects, but their performances were clustered together because there were no differences between them. Nerve-injured animals presented an expected decrease of the monofilament-induced limb withdrawal threshold ($F_{2,13} = 25.98$, $P < .0001$), which was of similar magnitude irrespective of lesion side (Fig. 1A).
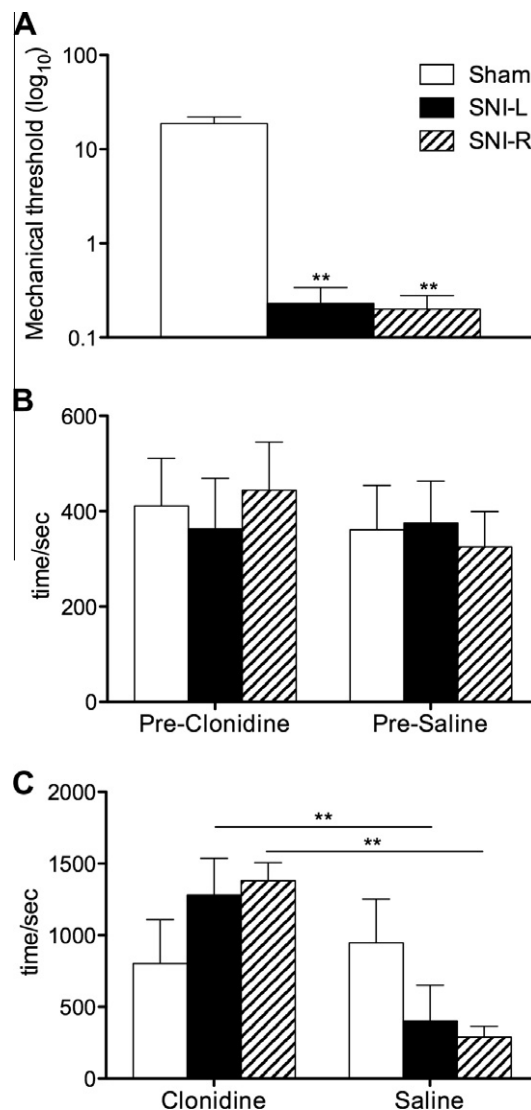
In the CPP, before clonidine-derived conditioning, animals failed to show a preference for any of the chambers ($F_{1,26} = 0.45$, $P = .51$, Fig. 1B), independent of the experimental group ($F_{2,26} = 0.24$, $P = .79$). However, a single intrathecal injection of clonidine at the dose of 10 µg produced a significant place-preference for the clonidine-paired chamber ($F_{1,26} = 9.03$, $P = .0058$, Fig. 1C) and the clonidine-induced place-preference varied with the experimental group ($F_{2,26} = 3.54$, $P = .044$). Post hoc testing indicates that the clonidine-induced place-preference was observed only in SNI animals but not in sham-operated ones (Fig. 1C). Moreover, the clonidine-induced place-preference was of equal magnitude in the SNI-L and SNI-R groups.

3.2. Anxiety-like behavior

Because increased anxiety is frequently reported in both humans with prolonged pain conditions and animal models of chronic pain, we assessed anxiety-like behavior, in a different cohort of animals, in the EPM. We observed an effect of the neuropathy side in the percent of time spent in the EPM openarms ($F_{2,37} = 3.888$, $P = .03$, Fig. 2A). SNI-L animals spent significantly less time when compared with both SNI-R and sham-lesioned animals ($P = .05$ in both comparisons). The number of closed arms entries, an index of locomotor activity, was similar in all groups ($F_{2,37} = 1.640$, $P = .21$, Fig. 2B), indicating that the differences observed in openarms were specifically related with SNI-L anxiogenic properties and not with a locomotor impairment caused by the lesion.

3.3. Cognitive performance

Repeated-measures analysis of the trial-to-trial efficiency gain in the water maze revealed a statistically significant impact of the lesion ($F_{2,48} = 4.987$, $P = .01$), with SNI-R performing significantly worse than both sham ($P = .01$) and SNI-L ($P = .04$) in the WM test (Fig. 3A). On the contrary, the daily efficiency gain on the spatial reference memory task, MWM, is not affected by the experimental condition ($F_{2,48} = 1.628$, $P = .21$, Fig. 3B).


Fig. 1. Measures of evoked (Von Frey) and ongoing (conditioned place preference) pain in the SNI model of neuropathic pain. Nerve injury produced a significant decrease in the monofilament-induced limb withdrawal threshold, whereas the side of nerve injury had no significant effect on the withdrawal threshold (A). Contralateral to the SNI, the threshold did not differ from that of sham-operated control (not show). During the preconditioning period of the conditioned place preference, animals failed to show preference for any of the chambers independent of the experimental group (B); clonidine treatment, however, produced a significant place preference for the clonidine-paired chamber in SNI animals independent of the injury side (C). Note that total testing times were different in (B) (15 minutes) and (C) (30 minutes), because of which the scales of their Y axes are different. **$P < .01$. Data presented as mean ± SEM. SNI = spared nerve injury; SNI-L = left spared nerve injury; SNI-R right spared nerve injury.

Similarly, the side of the SNI lesion had a significant effect on the ASST reversal (Rev) steps 1 to 4 (Rev 1 - $F_{2,45} = 14.522$, $P < .001$, Rev 2 - $F_{2,45} = 11.347$, $P < .001$, Rev 3 - $F_{2,45} = 46.343$, $P < .001$, Rev 4 - $F_{2,45} = 24.661$, $P < .001$, Fig. 4). In these cases, SNI-R animals required a significantly higher number of trials to reach the criteria than sham and SNI-L animals ($P < .001$ in all comparisons) to accomplish the task. No differences were found between groups in the other task steps, particularly in the extradimensional shift ($F_{2,45} = 2.949$, $P = .063$, Fig. 4).

Finally, in the delay-to-signal task, no differences were found between groups concerning the absolute number of impulsive responses at 3, 7, and 10 seconds delay (Fig. 5A). However, the variation ($\triangle$) to baseline differed significantly at 10 seconds delay
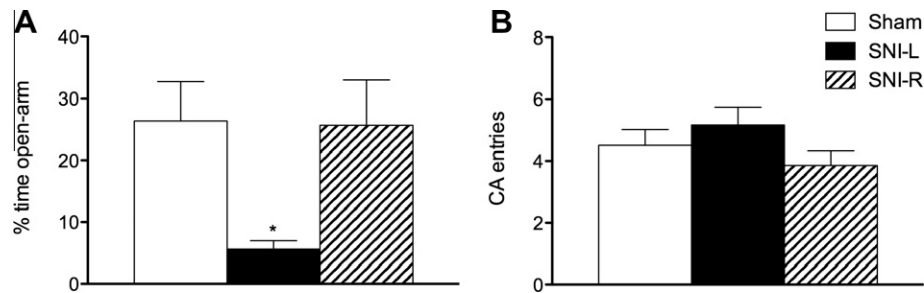
Fig. 2. Anxiety-like behavior in the EPM. Left- but not right-sided spared nerve injury animals presented a decreased percentage of time spent in the EPM openarms, indicating anxiety-like behavior (A). This result cannot be attributed to differences in the locomotor behavior because neither left-sided nor right-sided spared nerve injury influenced the number of EPM closed armentries (B). $^*P < .05$. Data presented as mean ± SEM. EPM = elevated-plus maze. CA = xxx; SNI-L = left spared nerve injury; SNI-R right spared nerve injury.
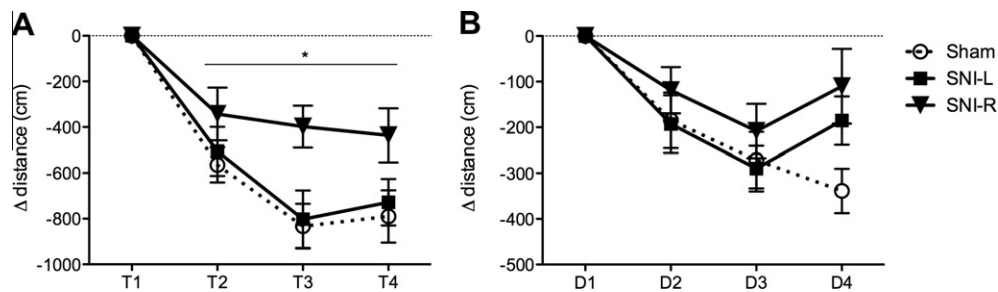
Fig. 3. Working memory and spatial reference memory. In the working memory paradigm (A), the side of the SNI had an impact on animals' performance with the SNI-R group performing significantly worse than both sham and SNI-L groups. In the spatial reference memory group (B), however, SNI had no effect on the ability to learn the platform location. $^*P < .05$. Data presented as mean ± SEM. D_{1-4} = day 1 to 4; SNI = spared nerve injury; SNI-L = left spared nerve injury; SNI-R right spared nerve injury; T_{1-4} = trial 1 to 4.

($F_{2,21}$ = 7.884, P = .003, Fig. 5B), namely SNI-R presented close to 6 times more impulsive responses, twice the value presented by sham (P = .01) and SNI-L (P = .007) animals.
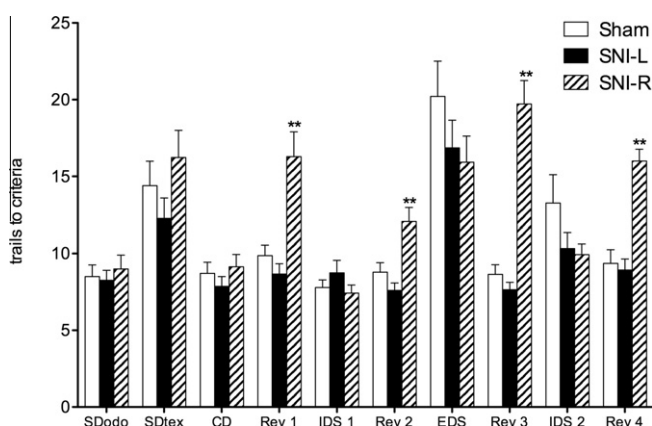
4. Discussion

Aside from sensory abnormalities (e.g., hyperalgesia and allodynia) that are considered to be hallmarks of neuropathies [45,61], rodent models of neuropathic pain proved to be robust enough to manifest a whole range of emotional and cognitive

Fig. 4. Attentional set-shifting task. SNI-R animals required a significantly higher number of trials to criteria than sham and SNI-L animals to accomplish the reversal (Rev_{1-4}) steps of the attentional set-shifting task. No differences were found between groups in the other task steps, simple discrimination (odor, SD_{odo} and texture, SD_{tex}), compound discrimination (CD), intradimensional shift (IDS 1-2), and extradimensional shift (EDS). $^{**}P < .001$. Data presented as mean ± SEM. SNI-L = left spared nerve injury; SNI-R right spared nerve injury.
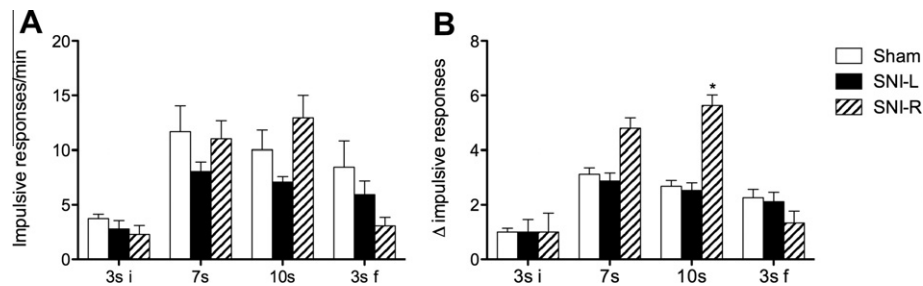
disturbances that have also been observed in the human disease. In the present study we confirmed that indeed SNI animals manifest a deterioration of emotional behavior and poorer cognitive performances, and additionally, that such effects depended on the side of peripheral nerve injury. Left-sided lesions were detrimental to emotional behavior, whereas right-sided lesions affected cognitive performance, particularly in PFC-dependent tasks.

A small number of studies in human volunteers addressed in the past a putative differential impact of left-/right-sided pain on emotional arousal [24,66,77,79]. It was demonstrated that left-sided pain was more distressful and emotionally disruptive than similar right-sided painful conditions. Our finding that left-sided but not right-sided SNI lesioned rats displayed a hyperanxious phenotype is therefore in line with these observations. Other animal studies, using left-sided [33,34,43,71,72,88–91] or right-sided [5,28,41,52,62,63,94] pain diverge, however, in their results concerning pain-related anxiogenic effect. A number of factors can reasonably explain the disparate findings, including differences in the pain model, experimental organization (some investigators report pain tests immediately before anxiety assessment), and pain duration. In what concerns the latter, it has been demonstrated that anxiety-like manifestations emerge only about 4 weeks after pain onset [88,94], which is in accordance with the temporal frame of our analyses. Importantly, none of these studies compared the impact of left- and right-sided pain under the same experimental conditions.

The detrimental effect of prolonged pain on cognitive function was also addressed in the past by a small number of studies using experimental models of chronic pain [12,36,41,45,47,57,64,65,68] (see also Moriarty et al. for review [61]). Again, none of these studies compared the differential effect of left- and right-sided pain on cognitive performance. We assessed animals' performance in several PFC-dependent executive functions, including WM (assessed in the water maze), behavioral flexibility (assessed in an ASST),

Fig. 5. Impulsive responses at variable delay-to-signal. The absolute number of impulsive responses at 3 [initial (i) and final block (f)], 7, and 10 seconds delay-to-signal (A) and the variation (△) to baseline (3s i) (B) are presented. The SNI-R group presents a significantly increased △ when the delay-to-signal is increased to 10 seconds. *P < .05. Data presented as mean ± SEM. SNI-L = left spared nerve injury; SNI-R right spared nerve injury.

and impulse control [18,21,58,69,76], because it has been consistently demonstrated that PFC presents robust morphological and functional alterations in prolonged pain conditions both in humans [1,19,25,26,29,39,44,49,53,60,70,81,84] and rats [56,83]. Results from our cognitive multimodal analyses confirmed that PFC-dependent domains are affected in chronic pain conditions, particularly when lesions are right-sided (SNI-R). These are generally in agreement with previously reported observations, although some inconsistencies have been detected, probably due to differences inherent to the cognitive paradigms used. The work of Ren et al. is amenable for comparison because they used the same neuropathy model (installed on the left side, SNI-L), for a similar amount of time (cognitive tests at 11 to 20 and 31 to 40 postsurgery days) [68]. In their study, and contrary to our observations, SNI-L presented deficits in a WM task performed in an 8-arm radial mazetest. This discrepancy is most probably due to the different nature of the water maze and 8-arm paradigms. In both cases, animals can adopt strategies unrelated to WM (e.g., stereotyped search), reinforcing the importance of a multimodal behavioral approach [23]. In a different study, Hu et al. tested rats with a left-sided neuropathy (spinal nerve lesion model, SNL-L) of 30 days' duration in the MWM [36]. The learning curves of SNL-L and control animals had a similar slope, suggesting that pain has no effect on long-term spatial reference memory, which is in agreement with our results [36]. Concerning impulsive behavior, our results are in agreement with those obtained by Pais-Vieira et al., who evaluated the performance of rats with a left-sided monoarthritis in a 5-choice serial reaction time task paradigm [64].

The behavioral domains affected in SNI animals support the idea that PFC-dependent functions are particularly susceptible in chronic pain conditions. The fact that the behavioral performance of the SNI-R in the ASST task was specifically impaired in the reversal but not in the extradimensional shift steps further suggests that PFC malfunction is restricted to the medial/orbital PFC (mPFC/OFC) while sparing dorsomedialprelimbic and cingulate PFC [7,8,22]. Experimental evidence is still needed to confirm this hypothesis. However, data obtained by others may be considered in this context. Firstly, the mPFC/OFC are the only cortical areas where direct projections from the contralateral spinal cord dorsal horn terminate (reviewed by Lima [46]). Secondly, manipulations of ventral mPFC/OFC subareas have been shown to influence behavioral outcomes in anxiety paradigms and the levels of anxiety-related biomarkers such as corticosteroids. Importantly, this effect is lateralized, depending exclusively on the right PFC, expectably the area affected in SNI-L (reviewed by Sullivan and Gratton [87]). Finally, Luerding et al. found in fibromyalgia patients an impairment on nonverbal working memory that was positively correlated with the grey matter volume of the left middle frontal gyrus [49]. It should, however, be acknowledged that the distinctive features of the left/right mPFC contribution to cognitive construction are still a matter of debate [15], and factors such as age

must be considered. For instance, older subjects frequently present bilateral PFC activity in tasks that are associated with unilateral PFC activation in young subjects [6,75]. This phenomenon probably underlies the cognitive deficits observed in mid-aged SNI-L animals shown by our group in a previous study [45].

It has long been a matter of dispute whether some pain-related phenomena occur with a lateralization bias. Among them are pain frequency [13,30,31,51,55], threshold [2,3,9,16,27,32,37,48,50,54, 66,67,73,74,77–79,82,85,92,93], changes in central processing and/or plasticity [10,11,14,17,35,38,42,80], and emotional charge [24,66,77,79]. Our data support the proposal that left- and right-sided neuropathic pain differentially impact on emotional behavior. Additionally, our data demonstrate that the side-dependent effect extends to cognitive domains. Measurements of both evoked and ongoing pain-related behaviors presented no differences between SNI-L and SNI-R, and therefore do not differ between the SNI groups. Altogether, the body of evidence presented strongly supports our initial hypothesis that peripheral nerve injury results in functional impairments that depend on the cortical termination sites of the ascending pathways mediating the injury discharge. Morphofunctional studies centered in the PFC must be carried out in the future to clarify this possibility.

Conflict of interest statement

None of the authors report a conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pain.2012.07.007.

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