Submitted to the European Journal of Pain

Section Editor: Prof. Maria Giamberardino

Sustained attention deficits in rats with chronic inflammatory pain

Miguel Pais-Vieira [1,3], Deolinda Lima [2,3] and Vasco Galhardo [1,3*]

1. Instituto de Histologia e Embriologia, Faculdade de Medicina, Universidade do Porto, Porto, Portugal
2. Laboratório de Biologia Molecular e Celular, Faculdade de Medicina, Universidade do Porto, Porto, Portugal
3. IBMC – Instituto de Biologia Molecular e Celular, Universidade do Porto, Portugal

Number of text pages: 22

Number of figures: 3

Number of words: 6071

Running header: attention impairments in chronic pain rats

Acknowledgements:

Supported by: Bial Foundation (grant 84/04), FCT (POCI/SAU-NEU/63034/2004)

Keywords: Cognitive deficits, monoarthritis, Complete Freund's Adjuvant, Five Choice Serial Reaction Time Task, accuracy, impulsivity

**Corresponding author:*

Vasco Galhardo, PhD

IBMC – Instituto de Biologia Molecular e Celular

Rua do Campo Alegre, 823

4150-180 Porto

PORTUGAL

Tel: +351 22 6074900

Fax: +351 22 6099157

e-mail: galhardo @ med.up.pt

ABSTRACT

Attention deficits is a common clinical manifestation in chronic pain patients. The cause for this impairment is not clear, with explanations ranging from behavioral attentional distraction caused by sudden painful sensations to permanent affects of brain regions which are simultaneously related to attention processing. However, few studies addressed similar issues in animal models. In this study we compared sustained attention in the 5 Choice Serial Reaction Time Task in rats before and after chronic pain. Persistent pain was induced by intra-articular injection of Complete Freund's Adjuvant and the development of monoarthritis was accessed by sensitivity to von Frey filaments. Results showed that after the induction of persistent pain, animals presented more errors in accuracy and omissions in two different versions of this task. When the same animals were studied with two different doses of carprofen (5 and 10 mg/kg) a recovery in the number of omissions was observed, but not in accuracy. Our results suggest that chronic pain affects specific components of attention.

INTRODUCTION

Chronic pain has been associated with attention (Iezzi et al., 1999); (Jamison et al., 1988); (Wade and Hart, 2002); (Dick et al., 2002)), decision-making (Apkarian et al., 2004a) and memory impairments in humans (Grace et al., 1999); (Brown et al., 2002); (Dufton, 1989); (Crombez et al., 2000); (Harris et al., 2003); (McCracken and Eccleston, 2003);(Dehghani et al., 2003); (Grisart and Van Der, 2001); (Kewman et al., 1991). Although anatomical, neurochemical, and psychological (e.g.stress, anxiety and depression) causes have been proposed to be on the basis of these deficits (Apkarian et al., 2004b); (Grachev et al., 2000); (Iezzi et al., 1999); (Brown et al., 2002); (McCracken and Iverson, 2001); (Grace et al., 1999) it is not clear how chronic pain generates these impairments.

Extensive research has been done describing the effects of attention in chronic pain in rats (Finn et al., 2004); (Ford et al., 2008), but surprisingly attention deficits in animal models of chronic pain have almost not been studied. Only a single study has analyzed the effect of a chronic visceral inflammatory state in a non-sustained attention task (Millecamps et al., 2004) and a second work has analyzed the effect of acute pain in sustained attention (Boyette-Davis et al., 2008). In the first work authors report that chronic pain animals spent less time exploring new objects in an arena, but that this deficit could be reversed with analgesic drugs. In the second work the authors report no impairment in accuracy (i.e. the number of correct responses to a light stimulus), although an increased number of omissions was present. It is not clear from these works if animal models of chronic pain present a general deficit in attention or if specific systems that allow the complex set of behaviors necessary for adequate attention processing are differentially affected.

The neural basis of attention processing in rats has been widely studied in the last years with the use of the 5 Choice Serial Reaction Time Task (5CSRTT). The 5CSRTT was modeled after a human task of sustained attention (ROSVOLD and DELGADO, 1956) and specific deficits have been related to specific lesions and/or neurochemical modulation (see (Robbins, 2002); (Chudasama and Robbins, 2004) for reviews). It has been proposed that two distinct prefrontal systems are active during this task: a dorsal system regarding the executive control (responsible for vigilance and discriminative attention, dependent on the dorsal pre-genual Anterior Cingulate Cortex – Cg1) and a ventral system regarding the inhibitory control (responsible for inhibition of inappropriate or repetitive responses, constituted by the Orbitofrontal cortex and the Infra-Limbic Cortex) (Robbins, 2002); (Passetti et al., 2002); (Chudasama et al., 2004). Interestingly, previous works in humans and rats have shown relevant changes for these same regions (or the human equivalent) in pain processing (Finn et al., 2004); (Ford et al., 2008); Pais-Vieira et al., 2009a; (Apkarian et al., 2004b); (Brooks and Tracey, 2005). A specific role has been attributed to the monoaminergic system in rats (Finn et al., 2004); (Ford et al., 2008); Pais-Vieira et al., 2009a) in the presence of chronic pain and it has also been shown that monoaminergic modulation can induce several deficits in the 5CSRTT (Passetti et al., 2003); (Pezze et al., 2007).

Here, we specifically hypothesized that animals with chronic pain would present deficits in a sustained attention task, namely a reduction in the ability to discriminate and respond to a brief light stimulus. We also hypothesized that if the deficits in accuracy were due to ongoing pain, the reduction of mechanical allodynia through the administration of an anti-inflammatory drug would restore control levels of accuracy. This hypothesis is supported by both previous works that have found pain-dependent attention deficits in rats with chronic or acute pain (Millecamps et al., 2004), (Boyette-Davis et al., 2008). In order to evaluate the presence of these deficits, rats were studied before and after injection with Complete Freund's Adjuvant in the 5CSRTT.

To test the effects of chronic pain and analgesia in sustained attention three experiments were performed in this work. In the first experiment a small group Sprague Dawley rats were tested in the standard 5CSRTT with a light stimulus of 0.5 seconds before and after chronic pain. In the second experiment, Lister-Hooded rats were tested in the 5CSRTT with a light stimulus of 1.5 seconds. In the third experiment; the same group of animals was tested after the injection of 5 and 10 mg of carprofen.

MATERIALS AND METHODS

All the work was done in accordance to EU ethics committee on animal research as well as IASP guidelines for work in wake animals. Lister Hooded (n=8) and Sprague Dawley (n=6) rats with weights between 200-250g at the beginning of the experiments were used (Charles River, Barcelona). During the experimental period, animals received water *ad libitum*, but were food deprived to 85% of baseline body weight by limiting their access to food to a single daily meal. All the experiments were conducted in accordance with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Chronic inflammatory pain model

Chronic inflammatory pain was induced by injection in the tibio-tarsal joint under anesthesia with 50µg of *Mycobacterium butiricum* (Complete Freund's Adjuvant - CFA). Anesthesia was induced with an i.m. injection of xylazine and ketamine (10 and 60 mg/kg mixture, respectively, to create a model of persistent monoarthritic inflammatory pain (as described by (Butler et al., 1992).

Sensory threshold

Sensory threshold as measured by von Frey filaments was studied as previously described (Chaplan et al., 1994). Briefly, the von Frey filaments (Somedic, Sweden) were a series of filaments with different diameters applied perpendicular to the plantar surface until slight buckling was caused, and maintained for 6-8 seconds. Each filament was applied 10 times with an interval of 5 seconds between stimuli. A positive response was considered if the paw was sharply withdrawn or flinching occurred. Sensory threshold was considered has a minimum of 5 positive responses. Force values are presented in grams.

Apparatus

To study the effect of chronic pain in attention processes, animals were tested in a five choice serial reaction time task built in our laboratory. The task consisted in a 25 width × 25 length × 30 height chamber enclosed in a sound attenuating box with fan ventilator that provided both low level background noise as well as air circulation. Four white LEDs provided house light in one of the walls of the chamber. The rear curved wall had five 2.5cm holes. A video camera connected to a computer, using the Open Control software adapted to the five Choice Serial Reaction Time Task, was placed in the top of the chamber detected the entrance of the rat in each aperture. Illumination of each aperture was provided by a white LED located bellow each aperture. Food pellets (20 mg chocolate flavor sucrose pellets, Research Diets Inc., New Brunswick, NJ, USA) were delivered in a magazine tray connected to a feeder (Coulbourn Instruments, Allentown, PA, USA) in the wall opposite to the wall that contained the apertures. The magazine tray was bisected by a photo beam (Coulbourn Instruments, Allentown, PA, USA) to detect animal entrance.

Sustained attention testing

The procedures used to train the animals were similar to those previously reported by (Carli et al., 1983). Animals were first habituated to the chamber and to the pellets for three consecutive days.

Two additional sessions were performed with pellets dispensed at every 20 seconds for 20 minutes. After these initial sessions animals were trained six days per week with one daily session of 30 minutes or 100 trials whichever came first. Each session started with a free food pellet delivered in magazine tray and with the house light on. After the animal poked the nose in the magazine tray an inter-trial interval of 5 seconds started, after which one of the lights in the front panel was lit for 0.5 seconds in the first experiment and for 1.5 seconds in the second and in the third experiments. If a response was made within 5 seconds in the same nose aperture then a correct response was recorded and a food pellet was delivered in the magazine tray. The latency between the light presentation and the correct response was measured. If an additional response was made before collecting the food pellet, a perseverative response was recorded and the house lights would be turned off for 5 seconds. If a response was made in a different aperture from the one with the light an incorrect response was recorded and a timeout of

5 seconds with the house lights off started. If no response was made during the period of light presentation or in the following 5 seconds a timeout of 5 seconds also started. A feeder response initiated a new trial, when a timeout was not occurring. The same number of light presentations occurred in each aperture.

In the beginning, animals were trained with light presentations of 30 seconds with a time hold of 60 seconds. These intervals were subsequently reduced until reaching a light presentation of 0.5 or 1.5 seconds and a time hold of 5 seconds. Adequate performance criterion was considered when animals presented >60% of accuracy for three consecutive sessions and <20% omissions (Puumala et al., 1997); (Semenova et al., 2007). A total number of twenty sessions were analyzed for each animal in the first experiment: ten previous to CFA injection and ten after the CFA injection. CFA was injected after session number ten and the animal was not further tested in that day, so the first session of 5CSRTT with the animal in pain was performed about 24 hours after the injection of CFA.

Measures of task performance

Accuracy was computed as the percentage of correct responses/(correct + incorrect responses). Correct responses were considered as nose pokes in the aperture were a light was presented within a 5 seconds period. Incorrect responses were considered as nose pokes in an aperture different from the one were a light stimulus was presented, during the 5 seconds period. Premature responses were considered as responses during the 5 seconds period between the beginning of a new trial and the presentation of a light stimulus. Omissions were considered as the absence of a response in an aperture during the light stimulus period. Perseverative responses were considered as responses in the nose pokes after a correct response was made. Response latency was considered as the time between the presentation of the stimulus and a response either correct or incorrect. Premature responses latency was considered as the time between the beginning of a new trial and a premature response.

All the data from the 5 CSRT was collected using Open Control, open source software for behavioural analysis (Aguiar et al., 2007).

Drug testing

In the experiment 2 the mean value of control and monoarthritic conditions was compared with the value of each drug dose. In experiment 3 values were compared across sessions before and after CFA injection. All the animals were injected with two doses of carprofen. Animals were tested with drugs in day 13 of chronic pain (with 5 mg/kg) and in the day 15 (with 10 mg/kg), animals were also trained in the days 12 and 14. Animals were injected subcutaneously in the left hind limb and were tested approximately 45 minutes after the injection. Values of mechanical sensitivity were compared before and after the injection of carprofen.

Statistical Analysis

All data were initially explored with 'boxplots' to seek for outliers or skewed data and if necessary data were adequately transformed with arcsine, logarithmic or square root transformations.

In experiment 1 data for each variable was studied with Repeated Measures ANOVA with Session as the within subjects factor) was used to compare performances in the 5 CSRT during sessions after the induction of chronic pain. We also performed a Repeated Measures ANOVA separately for control and monoarthritic conditions to study the evolution across sessions before and after chronic pain. Dunn's Multiple Comparison Test was used for *post hoc* comparisons. In experiment 2, data of each drug dose was compared with Repeated Measures ANOVA with the mean values of all sessions for each rat in Control and CFA conditions. In experiment 3, data for each variable was studied with Repeated Measures ANOVA with Session as the within subjects factor. Values of sensory threshold were compared with the Wilcoxon or Friedman's test, followed by Dunn's Multiple Comparison test.

RESULTS

Sensory threshold

CFA injection induced lower values of sensory threshold in all the animals in comparison to Control condition and the administration of two different doses of carprofen showed a significant improvement in sensory threshold measured with von Frey filaments (Friedman statistic = 16.53; $P = 0.0001$; Dunn's multiple comparison test showed significant differences between control and monoarthritic condition, q=15.50; $P < 0.01$; between control and 5 mg/kg of carprofen q=9.50; $P < 0.05$; but not between control and 10mg/kg of carprofen q=1.00; $P > 0.05$).

Five Choice Serial Reaction Time Task

Animals that were not able to reach the minimum performance criterion were excluded from the experiment (n=1 in the first experiment and n=2 in the second and third experiments). In any case animals presented 100% omissions.

Results experiment 1 – Control and monoarthritic conditions in Sprague Dawley rats with a 0.5 stimuli in the 5CSRTT

The results of the first experiment suggested that a clear impairment in the task after the induction of chronic pain. As Sprague Dawley rats injected with CFA presented both an extremely reduced number of trials per session and accuracy levels of performance close to chance (20% correct responses) these results were not further analyzed, suggesting that the animals were one of the following: not motivated, severely impaired or unable to perform the task (e.g. lack of attention). The second and third experiments were performed with Lister Hooded rats and the stimulus latency was increased to 1.5 seconds.

Results experiment 2 – Control and monoarthritic conditions in Lister Hooded rats with a 1.5 seconds stimuli in the 5CSRTT

The percentage of accuracy showed a significant difference across all sessions ($F_{19,95}$ = 10.89; $P < 0.0001$), but not when separately studying the control condition ($F_{9,45}$ = 1.623; $P = 0.1375$) or monoarthritic condition ($F_{9,45}$ = 0.4337; $P = 0.9097$), revealing that there was no evolution in each condition when analyzed separately. The number of perseverative responses showed a significant difference across all sessions ($F_{19,95}$ = 3.014; $P = 0.0002$), but not when separately studying the control condition ($F_{9,45}$ = 1.518; $P = 0.1708$) or the monoarthritic condition ($F_{9,45}$ = 1.034; $P = 0.4248$), revealing that there was no evolution in each condition when analyzed separately. The percentage of premature responses showed a significant difference across all sessions ($F_{19,95}$ = 2.839; $P = 0.0004$), but not when separately studying the control condition ($F_{9,45}$= 1.772; $P = 0.1006$) or the monoarthritic condition ($F_{9,45}$= 1.427; $P = 0.2054$), revealing that there was no evolution in each condition when analyzed separately. The percentage of omissions showed a significant difference across the total number of sessions ($F_{19,95}$= 5.989; $P < 0.0001$), but not when separately studying the control condition ($F_{9,45}$= 1,859; $P = 0.08$) or the monoarthritic condition $F_{9,45}$= 1.839; $P = 0.0871$, revealing that there was no evolution in each condition when analyzed separately. The total number of trials initiated was similar across all sessions ($F_{19,95}$ = 0.9472; $P = 0.5285$), as well as in control condition ($F_{9,45}$= 1.021 ; $P = 0.4381$) and in monoarthritic condition ($F_{9,45}$= 3.014; $P = 0.7901$), revealing that there was no evolution in any condition.

Results experiment 3 – Carprofen testing

As there was no significant difference across different days for accuracy, perseverative responses, omissions or premature responses, the mean values for the ten sessions of control and monoarthritic conditions were calculated and used to compare with the values of each session for the two different drug doses.

After the induction of chronic pain the rats presented decreased values of accuracy and this was not recovered with the administration of two different doses of carprofen ($F_{3,15}$ = 5.989; $P = 0.0068$). Dunnett's Multiple Comparisons test shows significant differences between Control and all other conditions tested (Control *vs* CFA, q = 3.458, P < 0.01; Control *vs* 5 mg/kg, q = 3.251, P<0.05; Control *vs* 10 mg/kg, q = 3,631, P<0.01). The reduction in accuracy was accompanied by an increase in the number of omissions in responses ($F_{3,15}$ = 3.644; *P*=0.0373). Dunnett's Multiple Comparison test doesn't show significant differences between Control and all other conditions tested (Control *vs* CFA, q = 2.495, P > 0.05; Control *vs* 5 mg/kg, q = 0.5018, P>0.05; Control *vs* 10 mg/kg, q = 1.309, P>0.05). The number of premature responses was not different across different conditions ($F_{3,15}$ = 1.754; *P* = 0.1991). Results also show that the latency to make a nose poke was not different between the four conditions ($F_{3,15}$=1.255, *P*=0.3253). As a floor effect was observed in the von Frey filaments we did not compare individual values of sensory threshold with each animal's performance. Comparison between Control, CFA and the two doses of carprofen in the number of trials performed shows a significant difference between groups ($F_{3,15}$=4.017, p=0.0278). Dunnett's Multiple Comparison Test shows a significant difference in the number of trials performed beween Control vs 5mg/kg of carprofen (q=3.008, P < 0.05) and 10 mg/kg of carprofen (q=2.883 , P<0.05), but not between Control and monoarthirtic animals (q=1.404, *P*>0.05). After the induction of chronic pain rats presented decreased values in the number of perseverative responses and this result was not altered with the administration of two different doses of carprofen ($F_{3,15}$ = 5.932; *P* = 0.0071). Dunnett's Multiple Comparison test showed significant differences between Control and all other conditions tested (Control *vs* CFA, q = 2.869, P < 0.05; Control *vs* 5 mg/kg, q = 3.452, P<0.01; Control *vs* 10 mg/kg, q = 3,767, P<0.01).

DISCUSSION

The present study evaluated the behaviour of an animal model of chronic pain in a sustained attention task and results showed that the development of monoarthritis was accompanied by attention impairments. These deficits developed after the induction of chronic inflammatory pain and were not due to motor incapacity of the animal to perform the task. Specifically, monoarthritic rats presented an increased number of incorrect responses to a short light stimulus, an increased number of trials with no response (omissions), and a decreased number of perseverative responses and total number of trials performed. The administration of an anti-inflammatory non-steroidal drug reduced the number of trials with no response and increased the threshold of mechanical sensitivity, but did not change the accuracy, the number of trials initiated or the number of perseverative responses in the task.

Our initial hypothesis was that animals in chronic pain would develop sustained attention deficits and was confirmed. After the induction of inflammatory pain rats presented a reduction in the accuracy to detect a brief visual stimulus and adequately respond to it in both experiments (Robbins, 2002). Our second hypothesis was that the reduction of mechanical allodynia would restore levels of accuracy to control levels and was rejected. Despite the presence of a clear decrease in referred cutaneous hypersensitivity after administration of carprofen, the levels of accuracy were not improved with either dose. Nevertheless, carprofen improved monoarthritic rat's errors of omission. Errors by omission can be considered as gross deficits in attention (Robbins, 2002), and thus, it can be argued that carprofen partially improved monoarthritic animal's performance.

Despite the presence of inflammation and the use of a relatively high dose of carprofen (Roughan and Flecknell, 2001), animals were able to perform the task in all conditions in the second and third experiments. The results of the second and third experiments show that the test, the animal model of chronic pain and the drug tested were adequate to study the effects of chronic pain in sustained attention. It is, however, important to refer that in our task animals presented a slightly reduced number of trials per session in comparison to other works (both control and experimental conditions) (Puumala et al., 1997); (Semenova et al., 2007). We attribute this difference most likely to the fact that we used tracking software to detect the animal's nose in each poke instead of photo beams (see materials and methods for details). Tracking in these conditions required the presence of a small amount of light in the front wall which could possibly lead to increased difficulty in our task. Although we haven't measured the latency to collect the reward after a correct response, there were no differences in the latency to respond between any of the different conditions tested. Despite these two variables are different, they suggest that animals were able to perform the task in all conditions tested. It is, however, possible that animals presented differences in the latency to collect the reward and this would most likely be related to emotional factors and the incentive value attributed to reward (Robbins, 2002). As the values of sensory threshold were similar across days and in most cases reached the minimum value of the test, a floor effect was observed, and thus it was not possible to comparable individual values of sensory threshold with performance in the test. As previous results from our and other groups have shown stable values of sensory threshold in this model of chronic pain (Schadrack et al., 1998;Neto et al., 1999) it is unlikely that the decreased accuracy performance might be due to a minor day variation in the threshold for pain. Results observed are most likely not related to secondary effects of the drug, deficits in visual processing, due to rats being exhausted or satiated, since we have tested this animal model in several behavioural tasks dependent on vision (water maze and radial arm maze, Pais-Vieira et al., 2009b) and with prolonged training, rewarding and the same drug doses (rodent gambling task, Pais-Vieira et al., 2009a).

Attention as been functionally described has having two main components: the executive and the inhibitory (Passetti et al., 2002), (Chudasama and Robbins, 2004). The executive component of attention processes information related to the vigilance/detection of new events (i.e. beginning of a new trial in the 5CSRTT) and the ability to distinguish between close stimulus (i.e. discriminate between different lights in the 5CSRTT), and is known to be mediated by the dorsal system (constituted by Cg1) (Passetti et al., 2002). The inhibitory component is responsible for the ability to start and stop responding at adequate intervals (i.e. premature and perseverative responses in the 5CSRTT), and is mediated by the ventral system (PrL-IL and OFC), (Passetti et al., 2002); (Chudasama and Robbins, 2004);(Robbins, 2002). These regions are further connected and modulated by the monoaminergic and cholinergic systems (see Daley et al., 2004 for a review). Comparison of rat's performances under the four different conditions studied reveals deficits in both components. Deficits in the vigilance component (increase in omissions and decrease in accuracy) and in the inhibitory component (premature and perseverative responses), were only partially reversed with carprofen. A similar pain-dependent omissions deficit was also reported in a previous work with rats in an acute model of pain in the 5CSRTT (Boyette-Davis et al., 2008). In that study animals presented an increase in the number of errors by omission, but no differences in the accuracy to detect the light stimulus before or after the injection of formalin. The authors also reported that this vigilance decrement was reversed with analgesic treatment (variables such as premature and perseverative responding were not reported). The same pattern of increased omissions that was reversed with analgesia was observed in both studies, but the differences found in the effects of pain in accuracy are difficult to interpret since these authors used a 5 seconds light stimulus which is considerably longer than the one used in our work. Our results suggest that general vigilance deficits and decreased premature responding can be reversed with temporary analgesia, while deficits related to accuracy, perseverative responses and the number of trials are most likely related to the chronic pain process and either may not be restored or only if repeated treatment or different drugs are used. It is possible that the decreased number of premature responses and the increased number of omissions were due to motor impairment and were recovered with carprofen administration, but if this was to be the case we would have expected also to see a decrease in the number of trials performed by each group, which remained similar before and after CFA injection. Also, the number of perseverative responses remained decreased after carprofen injection.

The deficits that were not reversed with analgesia suggest that areas fundamental to attention processing were specifically affected with the development of the chronic pain process. We have previously reported that monoarthritic rats present OFC lesion-like behaviours, as well as monoaminergic changes in several areas, namely reductions of dopamine in the OFC and in the hippocampus (Pais-Vieira et al., 2009a; Pais-Vieira et al., 2009b). The effect of lesions in each of these regions in the 5CSRTT has been previously reported and results show that lesions of the OFC are associated with an increase in premature responses, if inter-trial time intervals are unpredictable and long (Passetti et al., 2002;Chudasama and Muir, 2001). As we have not tested the effects of long and unpredictable inter-trial intervals and no specific role for dopamine has been described for this region in this task, it is not clear if deficits observed are related to OFC changes. Although no work has specifically studied the effect of dopamine antagonists in the hippocampus in this task, rats with hippocampal lesions have been shown to have no significant effect in any measure of performance in a self-paced serial reaction time task (Burk and Mair, 2001), suggesting that the decrease in hippocampal dopamine is most likely also not be the cause for the deficits observed. Altogether, our results do not clearly allow inferring if monoaminergic changes in hippocampus or OFC are related to the deficits found in our work. According to previous studies on the effects of lesions of the ACC (Passetti et al., 2002) and the known engagement of this region in the chronic pain process (see Brooks and Tracey, 2005 for a review), it is possible that the deficits found here were related to this region. Future works may address this issue.

Several studies with human subjects with chronic pain report attention deficits (Dufton, 1989;Crombez et al., 2000); (Dehghani et al., 2003); (Grisart and Van Der, 2001);(Harris et al., 2003); (McCracken and Eccleston, 2003) with several works showing a possible role for medication in cognitive deficits in chronic pain patients (see (Chapman et al., 2002) for a review). Our results have implications for human studies of cognitive deficits in chronic pain, since we clearly show that chronic pain can induce specific attention deficits that are not directly related to secondary effects of medication and that were not reversed with it. These results further enhance the necessity of studies in animal models where such variables can be controlled.

Conclusion

The present work shows that chronic pain can induce sustained attention deficits that are only partially reversed with analgesia. Specifically, we showed that in conditions of chronic pain there is a general vigilance decrement that is reversible with adequate analgesia, but that specific accuracy deficits were not.

Reference List

Aguiar P, Mendonca L, Galhardo V (2007) OpenControl: A free opensource software for video tracking and automated control of behavioral mazes. J Neurosci Methods 166:66-72.

Apkarian AV, Sosa Y, Krauss BR, Thomas PS, Fredrickson BE, Levy R, Harden RN, Chialvo DR (2004a) Chronic pain patients are impaired on an emotional decision-making task. Pain 108:129-136.

Apkarian AV, Sosa Y, Sonty S, Levy RM, Harden RN, Parrish TB, Gitelman DR (2004b) Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. J Neurosci 24:10410-10415.

Boyette-Davis JA, Thompson CD, Fuchs PN (2008) Alterations in attentional mechanisms in response to acute inflammatory pain and morphine administration. Neuroscience 151:558-563.

Brooks J, Tracey I (2005) From nociception to pain perception: imaging the spinal and supraspinal pathways. J Anat 207:19-33.

Brown SC, Glass JM, Park DC (2002) The relationship of pain and depression to cognitive function in rheumatoid arthritis patients. Pain 96:279-284.

Burk JA, Mair RG (2001) Effects of intralaminar thalamic lesions on sensory attention and motor intention in the rat: a comparison with lesions involving frontal cortex and hippocampus. Behav Brain Res 123:49-63.

Butler SH, Godefroy F, Besson JM, Weil-Fugazza J (1992) A limited arthritic model for chronic pain studies in the rat. Pain 48:73-81.

Carli M, Robbins TW, Evenden JL, Everitt BJ (1983) Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats; implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. Behav Brain Res 9:361-380.

Chaplan SR, Bach FW, Pogrel JW, Chung JM, Yaksh TL (1994) Quantitative assessment of tactile allodynia in the rat paw. J Neurosci Methods 53:55-63.

Chapman CR, Donaldson GW, Nakamura Y, Jacobson RC, Bradshaw DH, Gavrin J (2002) A psychophysiological causal model of pain report validity. J Pain 3:143-155.

Chudasama Y, Dalley JW, Nathwani F, Bouger P, Robbins TW (2004) Cholinergic modulation of visual attention and working memory: dissociable effects of basal forebrain 192-IgG-saporin lesions and intraprefrontal infusions of scopolamine. Learn Mem 11:78-86.

Chudasama Y, Muir JL (2001) Visual attention in the rat: a role for the prelimbic cortex and thalamic nuclei? Behav Neurosci 115:417-428.

Chudasama Y, Robbins TW (2004) Psychopharmacological approaches to modulating attention in the five-choice serial reaction time task: implications for schizophrenia. Psychopharmacology (Berl) 174:86-98.

Crombez G, Hermans D, Adriaensen H (2000) The emotional stroop task and chronic pain: what is threatening for chronic pain sufferers? Eur J Pain 4:37-44.

Dehghani M, Sharpe L, Nicholas MK (2003) Selective attention to pain-related information in chronic musculoskeletal pain patients. Pain 105:37-46.

Dick B, Eccleston C, Crombez G (2002) Attentional functioning in fibromyalgia, rheumatoid arthritis, and musculoskeletal pain patients. Arthritis Rheum 47:639-644.

Dufton BD (1989) Cognitive failure and chronic pain. Int J Psychiatry Med 19:291-297.

Finn DP, Beckett SR, Roe CH, Madjd A, Fone KC, Kendall DA, Marsden CA, Chapman V (2004) Effects of coadministration of cannabinoids and morphine on nociceptive behaviour, brain monoamines and HPA axis activity in a rat model of persistent pain. Eur J Neurosci 19:678-686.

Ford GK, Moriarty O, McGuire BE, Finn DP (2008) Investigating the effects of distracting stimuli on nociceptive behaviour and associated alterations in brain monoamines in rats. Eur J Pain 12:970-979.

Grace GM, Nielson WR, Hopkins M, Berg MA (1999) Concentration and memory deficits in patients with fibromyalgia syndrome. J Clin Exp Neuropsychol 21:477-487.

Grachev ID, Fredrickson BE, Apkarian AV (2000) Abnormal brain chemistry in chronic back pain: an in vivo proton magnetic resonance spectroscopy study. Pain 89:7-18.

Grisart JM, Van Der LM (2001) Conscious and automatic uses of memory in chronic pain patients. Pain 94:305-313.

Harris S, Morley S, Barton SB (2003) Role loss and emotional adjustment in chronic pain. Pain 105:363-370.

Iezzi T, Archibald Y, Barnett P, Klinck A, Duckworth M (1999) Neurocognitive performance and emotional status in chronic pain patients. J Behav Med 22:205-216.

Jamison RN, Sbrocco T, Parris WC (1988) The influence of problems with concentration and memory on emotional distress and daily activities in chronic pain patients. Int J Psychiatry Med 18:183-191.

Kewman DG, Vaishampayan N, Zald D, Han B (1991) Cognitive impairment in musculoskeletal pain patients. Int J Psychiatry Med 21:253-262.

McCracken LM, Eccleston C (2003) Coping or acceptance: what to do about chronic pain? Pain 105:197-204.

McCracken LM, Iverson GL (2001) Predicting complaints of impaired cognitive functioning in patients with chronic pain. J Pain Symptom Manage 21:392-396.

Millecamps M, Etienne M, Jourdan D, Eschalier A, Ardid D (2004) Decrease in non-selective, non-sustained attention induced by a chronic visceral inflammatory state as a new pain evaluation in rats. Pain 109:214-224.

Neto FL, Schadrack J, Ableitner A, Castro-Lopes JM, Bartenstein P, Zieglgänsberger W, Tólle TR (1999) Supraspinal metabolic activity changes in the rat during adjuvant monoarthritis. Neuroscience 94:607-621.

Passetti F, Chudasama Y, Robbins TW (2002) The frontal cortex of the rat and visual attentional performance: dissociable functions of distinct medial prefrontal subregions. Cereb Cortex 12:1254-1268.

Passetti F, Dalley JW, Robbins TW (2003) Double dissociation of serotonergic and dopaminergic mechanisms on attentional performance using a rodent five-choice reaction time task. Psychopharmacology (Berl) 165:136-145.

Pezze MA, Dalley JW, Robbins TW (2007) Differential roles of dopamine D1 and D2 receptors in the nucleus accumbens in attentional performance on the five-choice serial reaction time task. Neuropsychopharmacology 32:273-283.

Puumala T, Riekkinen P, Sr., Sirvio J (1997) Modulation of vigilance and behavioral activation by alpha-1 adrenoceptors in the rat. Pharmacol Biochem Behav 56:705-712.

Robbins TW (2002) The 5-choice serial reaction time task: behavioural pharmacology and functional neurochemistry. Psychopharmacology (Berl) 163:362-380.

Rosvold HE, Delgado JM (1956) The effect on delayed-alternation test performance of stimulating or destroying electrically structures within the frontal lobes of the monkey's brain. J Comp Physiol Psychol 49:365-372.

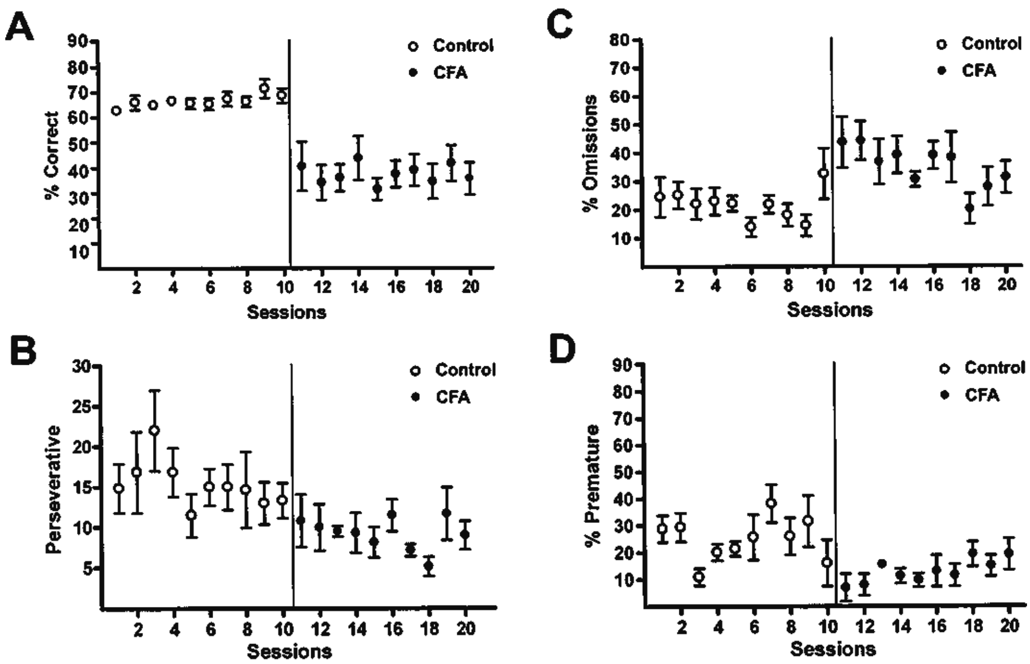
Roughan JV, Flecknell PA (2001) Behavioural effects of laparotomy and analgesic effects of ketoprofen and carprofen in rats. Pain 90:65-74.

Schadrack J, Castro-Lopes JM, Avelino A, Zieglgänsberger W, Tolle TR (1998) Modulated expression of c-fos in the spinal cord following noxious thermal stimulation of monoarthritic rats. J Neurosci Res 53:203-213.

Semenova S, Stolerman IP, Markou A (2007) Chronic nicotine administration improves attention while nicotine withdrawal induces performance deficits in the 5-choice serial reaction time task in rats. Pharmacol Biochem Behav 87:360-368.

Wade JB, Hart RP (2002) Attention and the stages of pain processing. Pain Med 3:30-38.

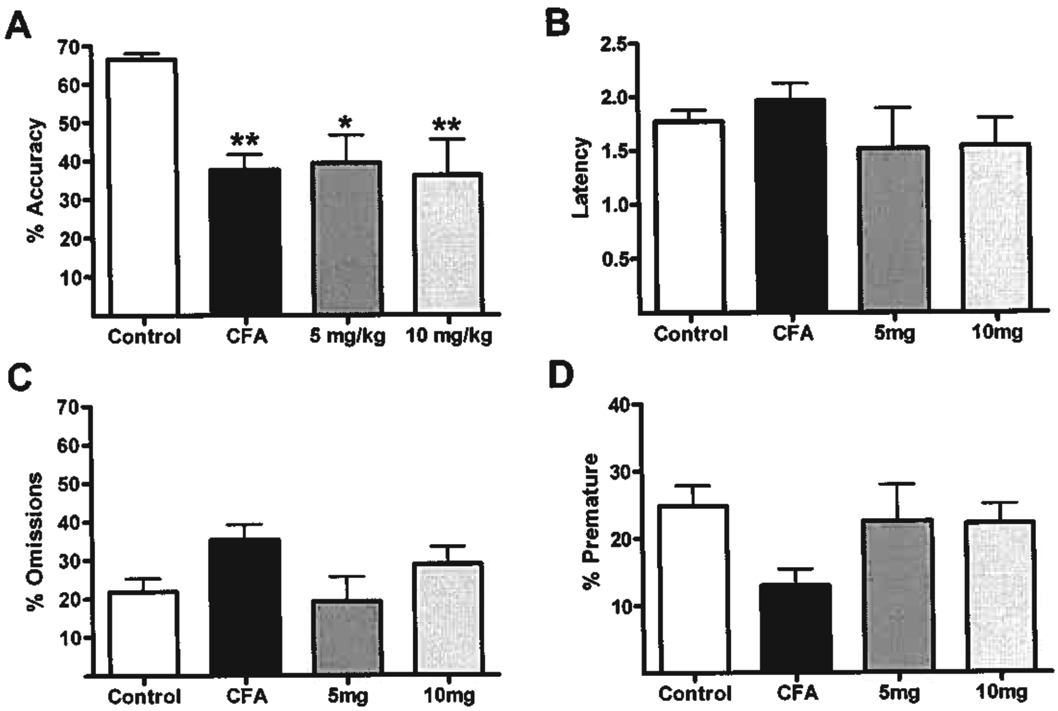
Figure 1 – Performance in the 5CSRTT before and after the injection of CFA in Lister Hooded rats.



Legend

Figure 1 – Performance of Lister Hooded rats under control (Control) and monoarthritic (CFA) conditions in the 5CSRTT with a 1.5 second stimulus. A) Percent Accuracy, B) Percent Omissions, C) Number of Perseverative Responses, D) Percent Premature Responses.

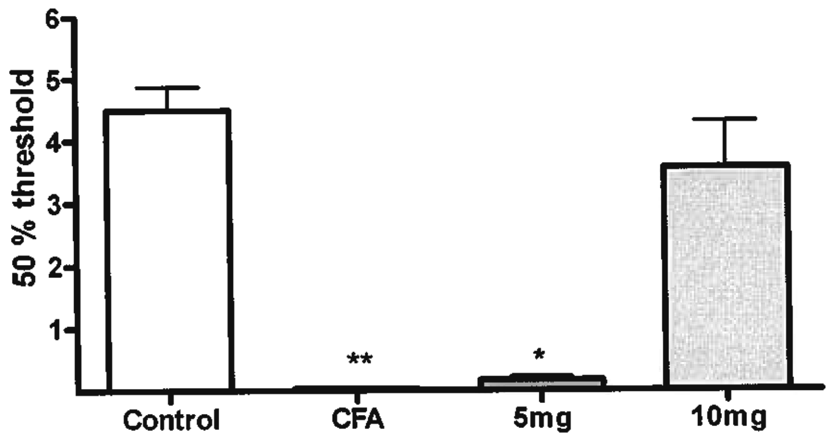
Figure 2 – Performance in the 5CSRTT after the injection of CFA with carprofen.



Legend

Figure 2 – Performance of Lister Hooded rats under control (Control), monoarthritic (CFA) and two different doses of carprofen in the 5CSRTT with a 1.5 second stimulus. A) Percent Accuracy, B) Latency to respond, C) Percent Omissions and D) Percent Premature Responses. In graph C the overall ANOVA is significant despite individual comparisons do not show a difference between Control and any other condition tested. Symbols * and ** represent Dunn's Multiple Comparison's test significant results for 0.05 and 0.01 respectively.

Figure 3 – Comparison of mechanical sensory threshold between Control, Monoarthritic and Carprofen conditions.



Legend

Figure 3 – After the injection of CFA rats developed mechanical allodynia that was only restored with the 10mg/kg dose of carprofen. Symbols * and ** represent Dunn's Multiple Comparison's test significant results for 0.05 and 0.01 respectively.