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Emotional and cognitive impairments in the peripheral nerve chronic constriction injury model (CCI) of neuropathic pain: A systematic review

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ABSTRACT

Background and objective: Emotional and cognitive impairments are common comorbidities of chronic neuropathic pain that significantly impact the quality of life of patients. While the nociceptive components of the peripheral nerve chronic constriction injury (CCI) animal model have been extensively analyzed, data related to the development of mood and cognitive disorders, and especially its impact on female rats remains fragmented. We systematically reviewed the literature analyzing the methods used to induce and evaluate the development of emotional- and cognitive-like impairments and sex-specific differences in the CCI model.

Databases and data treatment: We searched PubMed, Google Scholar and Web of Science from inception to September 30th, 2019, and a total of 44 papers were considered eligible for inclusion. We included animal studies assessing nociception, locomotion, anxious-like, depressive-like and cognitive behaviours after the CCI induction.

Results: The overall quality of the studies was considered moderate to high. Overall, the induction of CCI leads to the development of emotional impairments, namely anxiety- and depressive-like behaviours, as well as cognitive impairments. With the majority of the studies using male subjects, the lack of evidence on female animals prevents the evaluation of sex-specific differences.

Conclusions: This review supports the development of an anxiodepressive-like phenotype, associated with cognitive impairments, in CCI-induced animals. These results support the use of this animal model for the study of the mechanisms underlying these comorbidities, as well as a screening tool for the development/repurposing of drugs that tackle both the neuropathy-induced nociceptive and emotional impairments, such as tricyclic antidepressants. Importantly, our review also highlights the need for studies performed in female rodents as these are almost non-existent.

1. Introduction

Chronic pain results from an abnormal function of the nervous system, in which pain persists beyond healing time [1]. This altered neuronal activity includes the sensitization of the peripheral and central nervous system [2], leading to a heightened perception of pain [3]. According to its aetiology, chronic pain can be divided into 7 categories [1]: (i) chronic primary pain, (ii) chronic cancer pain, (iii) chronic post-traumatic and post-surgical pain, (iv) chronic neuropathic pain, (v) chronic headache and orofacial pain, (vi) chronic visceral pain and (vii) chronic musculoskeletal pain – Table 1.

As mentioned in Table 1, neuropathic pain is defined as *pain caused by a lesion or disease of the somatosensory system* [4]. These injuries are commonly associated with diabetic neuropathy, viral infections (such as the *Herpes zoster* virus), major surgeries or traumas, spinal cord injury, and stroke [5]. Although the exact prevalence of chronic neuropathic pain is unknown, it is estimated it affects 7–10 % of the population [6], greatly reducing the quality of life of patients, as it impairs physical, mental, emotional and social functioning [7]. Importantly, many patients are refractory to current therapies involving classic analgesic (nonsteroidal anti-inflammatory drugs and opioids), anti-convulsants/gabapentinoids and antidepressants [8,9].

Pain is comprised of sensory, cognitive and foremost affective components [10]. Sleep disturbances and emotional disorders, such as

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Table 1
Classification and definition of the most common clinically relevant chronic pain disorders, according to the 11th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD).

Category	Description
Chronic primary pain	Pain in one or more anatomical regions, that is characterized by significant emotional distress or functional disability
Chronic cancer pain	Pain caused by the primary cancer itself or metastases, or its treatment.
Chronic post-traumatic and post-surgical pain	Pain that develops after a surgical procedure or a tissue injury and persists at least 3 months after surgery or tissue trauma.
Chronic neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system.
Chronic headache and orofacial pain	Headaches or orofacial pains that occur on at least 50 % of the days during at least 3 months.
Chronic visceral pain	Persistent or recurrent pain that originates from the internal organs of the head and neck region and the thoracic, abdominal, and pelvic cavities.
Chronic musculoskeletal pain	Persistent or recurrent pain that arises as part of a disease process directly affecting bone, joint, muscle, or related soft tissues.

anxiety and depression, are often associated with chronic pain [11]. For major depressive disorder, epidemiological studies show a prevalence of approximately 50 % in chronic pain patients [12,13]. Especially, in neuropathic patients, psychiatric comorbidities have an estimated prevalence of 30 % [14]. Indeed, a vicious circle is established whereby chronic pain triggers profound emotional changes, which in turn enhance pain perception [15].

In an attempt to mimic the many components of human neuropathic pain, several animal models of neuropathic pain were developed, being distinguishable by the location and method of injury. Thus, animal models of neuropathic pain can be divided into 5 gross categories [16,17]: (i) central pain models, (ii) peripheral nerve injury models, (iii) disease-induced and (iv) drug-induced models, and (v) inherited neuropathies. In rodents, the most common experimental approach is the traumatic peripheral nerve injury (full or partial) via ligation, transection, or compression, with the chronic constriction injury of the nervus ischiadicus (sciatic nerve) [18] (CCI), spared nerve injury (SNI) [19] and spinal nerve ligation (SNL) [20] models being mostly used – Table 2.

The CCI model mimics the symptoms of chronic nerve compression, such as nerve entrapment or compression syndromes [25,26], comprising both its inflammatory [27] and neuropathic components [28]. This model, established in 1988 by Bennet and Xie [18], results in hyperalgesia to thermal and mechanical stimuli with animals also displaying signs of spontaneous pain such as limping, limb guarding, excessive licking and avoidance of weight-bearing on the injured limb [18,28,29]. Autotomy has also been described [18], with gnawed claw tips, proposed to be triggered by abnormal afferent signalling generated in the ligation site [30], and can be influenced by the number of loose ligatures applied to the sciatic nerve [31]. It is a reliable and reproducible model, that leads to the formation of intraneural oedema, axotomizing some but not all of the sciatic nerve axons [32], and was also associated with increased spinal autophagy [33], which together contribute to the progression of nerve degeneration.

In comparison with other peripheral nerve injury models, it varies concerning the sciatic nerve inflammatory neuritis (SIN [34,35]) as it is not chemically induced; from the sciatic nerve cryoneurolysis [36,37] and laser- [38] and photochemically-induced sciatic nerve injury models [39,40] as in these the injury results from a noxious thermal stimulus without a compressive component. Within the mechanically-induced models, the trigeminal neuralgia [41,42] and brachial plexus avulsion [43,44] models imply compression or avulsion, respectively, of upper body nerves. Similarly, the partial injury of the nerve supplying the tail [45] and caudal trunk resection models [46,47] also imply avulsion of tail nerves. Within the hindlimb, the partial saphenous nerve injury is

Table 2
Animal models of neuropathic pain.

Category	Animal models
Central pain models	Thalamic syndrome
	Spinal cord injury: contusion, excitotoxic and photochemical
	Spinal hemisection
Peripheral nerve injury models	Neuroma model
	Chronic constriction injury of the sciatic nerve (CCI)
	Partial sciatic nerve ligation (pSNL)
	Spinal nerve ligation (SNL)
	Spinal nerve transection (SNT)
	Spared nerve injury (SNI)
	Brachial plexus avulsion
	Photochemically-induced sciatic nerve injury
	Polyethene cuff
	Partial injury of the nerve supplying the tail
	Partial saphenous nerve injury
	Tibial and sural transection (TST)
	Trigeminal neuralgia
	Sciatic nerve cryoneurolysis
	Caudal trunk resection
	Sciatic nerve inflammatory neuritis (SIN)
	Laser-induced sciatic nerve injury
Models of disease-induced neuropathic pain	Multiple sclerosis (EAE)[21,22] and TMEV
	Postherpetic peripheral neuropathic pain model
	HIV-associated sensory neuropathy
	Peripheral diabetic neuropathy (PDN)
	Cancer pain models
Models of drug-induced neuropathic pain	Vincristine-induced peripheral neuropathy model
	Paclitaxel-induced peripheral neuropathy model [23,24]
	Docetaxel-induced peripheral neuropathy
	Cisplatin-induced peripheral neuropathy
	Oxaliplatin-induced neuropathy
Inherited neuropathies	Spontaneous inherited neuropathy
	Engineered inherited neuropathies
Others	Chronic ethanol consumption/withdrawal-induced neuropathy
	Pyridoxine (vitamin B6)-induced neuropathy
	Orofacial pain model
	Acrylamide-induced neuropathy model

comparable to the pSNL model [48,49] but affecting sensibility only on the medial side of the hindpaw. When compared with other models of sciatic nerve injury, in CCI the lesion involves the common branch of the sciatic nerve while in other models the injury is applied partially to the same location (pSNL, polyethene cuff [50,51]), downstream to different combinations of sciatic nerve branches (SNI [19,52,53], Neuroma model [30,54], TST [55]) or upstream to spinal nerves (SNL [20,56,57]). Importantly, the compression through multiple ligatures induces inter- and intra-experimenter variability an effect not observed in other animal models, with the exception of the pSNL and the SNL animal models. In comparison with the latter, the CCI model displayed a smaller magnitude of mechanical allodynia responses, while enhancing spontaneous and ongoing pain [58].

In addition to the study of changes in nociception, animal models have also been used to study the anxiodepressive component of chronic pain [11,59,60]. Accordingly, in this literature search, we review the evidence from behavioural preclinical studies on the anxiodepressive and cognitive consequences of neuropathic pain in a peripheral nerve CCI model.

2. Methods

This systemic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [61]. The literature search was conducted using the following electronic databases: PubMed, Google Scholar and Web of Science. For each database, a combination of search criteria was used: ("Chronic

constriction Injury or CCI") AND ("anxiety or anxious" OR "depressive or depression" OR "cognition or cognitive") without any lower limit of time up to September 30th, 2019.

After removing duplicates, two researchers (DFR and FPR) independently screened the title and abstract of every citation found in the literature search. To qualify for inclusion both investigators had to reach an agreement. A third investigator was involved in the case of unsolved disagreement (DA). Original articles that evaluated nociceptive behaviour and emotional/cognitive behaviour after the induction of the chronic constriction model in the sciatic nerve (CCI) were included. There was no restriction on the disease severity and on the type of paradigms used to test emotional-like and cognitive impairments. Publications dealing with subjects other than chronic pain, lacking information on emotional/cognitive behaviour, non-original or written in languages other than English were excluded.

Two researchers conducted the data extraction individually (DFR and FPR), posteriorly merged and the discrepancies in data extraction were all resolved by consensus. The following data, when available, were extracted from the included studies: author, year of publication, species/strain of animals, age, sample size, gender, CCI-induction protocol, location and side of CCI, duration of the model, all tests used to evaluate nociception, locomotion and emotional-like and cognitive performance. The quality assessment of the included studies was estimated with the ARRIVE GUIDELINES for animal research: Reporting In Vivo Experiments [62].

3. Results

A total of 537 publication references were initially retrieved using this search strategy (Fig. 1). After the removal of 376 duplicates, 161 publications were screened based on titles and abstracts and 115 publications were identified as potentially eligible. After checking the full text for detailed information and data extraction, 50 publications were included in this review.

The potential range of our score of ARRIVE quality was 0–20 and the overall mean score for methodological quality of studies included was 15.6 ± 1.6. A score between 0–1 was attributed to each criterion, and the mean score calculated for each study. The proportion of studies that met each criterion and the global score are presented in Table 3. A global rating of strong was attributed to studies with a mean score higher than 15 (66 %), moderate between 12–15 (30 %) and week for those under 12 (4%).

3.1. Methodological approaches

To the extent of our knowledge, there is no current evidence of the CCI model being used on species other than rodents. However, it is important to note the majority of these studies use rats (64 %), while in

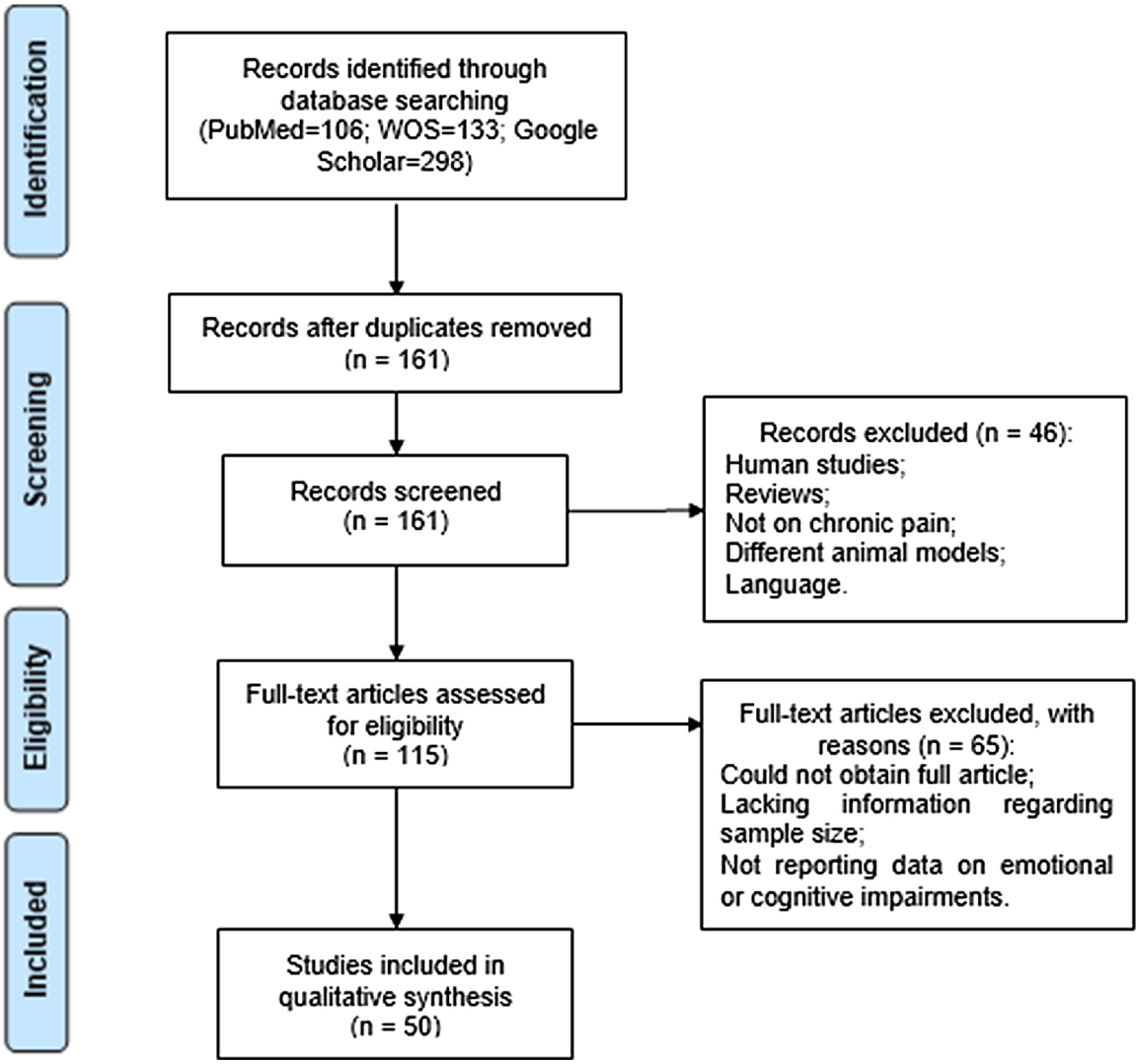

Fig. 1. Flowchart of the selection process.

Table 3
Summary of the methodological quality of included studies, assessed using the ARRIVE guidelines for the reporting of in vivo experiments. Summarized criteria: 1 – Title; 2- Abstract; 3 – Background; 4 - Objectives; 5- Ethical statement; 6 – Study design; 7 – Experimental procedures; 8 – Blinding; 9 - Experimental animals; 10 – Housing and husbandry; 11 – Sample size; 12 – Allocating animals to experimental groups; 13 – Experimental outcomes; 14 – Statistical methods; 15 – Baseline data; 16 – Numbers analyzed; 17 – Outcomes and estimation; 18 – Individual data points; 19 – Adverse events; 20 – Interpretation/scientific implications; 21 - Generalisability/translation; 22 – Funding.

Legend: Complete, Incomplete or non applicable, Absent.

Article/ Items	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Global rating
[95]																							Strong
[71]																							Strong
[140]																							Strong
[78]																							Moderate
[87]																							Strong
[79]																							Strong
[141]																							Strong
[142]																							Moderate
[143]																							Weak
[70]																							Strong
[144]																							Strong
[104]																							Moderate
[108]																							Strong
[111]																							Moderate
[86]																							Strong
[145]																							Moderate
[73]																							Strong
[146]																							Strong
[147]																							Moderate
[103]																							Strong
[148]																							Strong
[64]																							Strong
[149]																							Moderate
[74]																							Strong
[65]																							Strong
[106]																							Strong
[150]																							Strong
[97]																							Moderate
[84]																							Strong
[75]																							Strong
[66]																							Strong
[151]																							Strong
[93]																							Moderate
[152]																							Strong
[153]																							Moderate
[154]																							Strong
[98]																							Strong
[69]																							Strong
[155]																							Strong
[82]																							Strong
[156]																							Moderate
[94]																							Strong
[99]																							Strong
[67]																							Weak
[68]																							Strong
[157]																							Moderate
[100]																							Moderate
[158]																							Moderate
[76]																							Strong
[77]																							Strong

the remaining the mouse was chosen (36 %). Importantly, the great majority of these studies are performed on male subjects (98 %).

CCI induction was performed differently between studies. Regarding anaesthesia, the most commonly used was sodium pentobarbital (38 %), followed by isoflurane (32 %). Constriction of the sciatic nerve was also performed with different suture types, chromic (46 %) and non-chromic (48 %), and with different sides of injury – 52 % performing surgery on the right side and 38 % on the left.

Regarding experimental design, it is important to highlight these experiments are performed with different durations of chronic pain, ranging from 2 to 12 weeks. For model validation, nociceptive impairments, mechanical allodynia and thermal hyperalgesia were mostly assessed using the Von Frey (74 %) and Hargreaves (40 %) tests, respectively, and sensory impairments were reported from weeks post-CCI induction. Information regarding the time course of nociceptive impairments reported in the studies included in this review is represented in Fig. 2. Locomotor impairments were assessed in 58 % of the studies, with the open field test being the most commonly used (66 %) for this purpose.

Although there is a large number of studies that evaluate the emotional components of the CCI model (90 %), only a few take interest in associated cognitive impairments (10 %). Concerning emotional impairments, only 50 % of the studies evaluated anxiety-like behaviour by using primarily the elevated plus maze (48 %) and the open field (36 %)

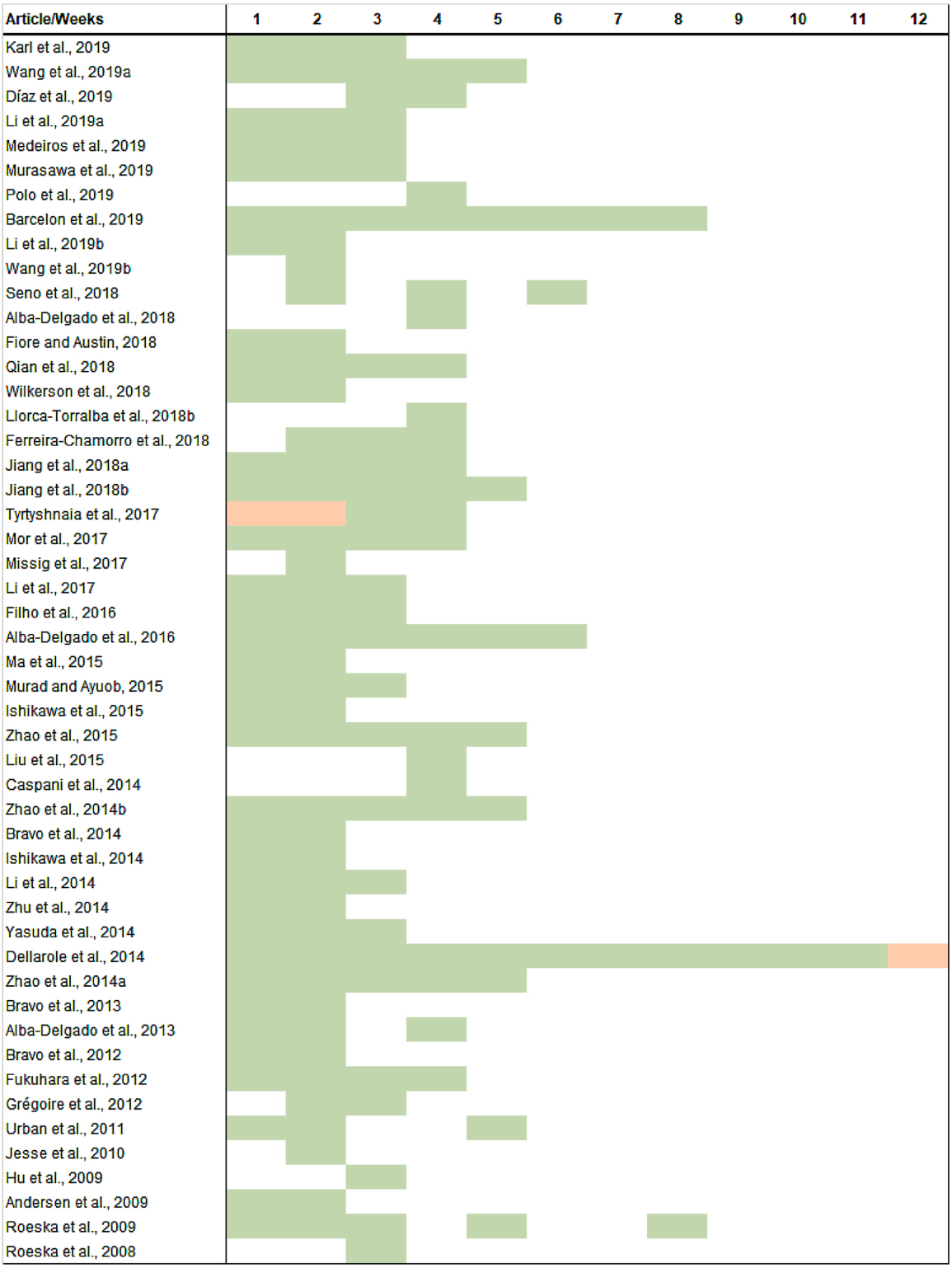

Fig. 2. Heatmap summary of the literature concerning the time course of nociceptive impairments (allodynia and/or hyperalgesia) reported in the chronic constriction injury model of neuropathic pain, regarding time post-CCI induction. (Green – Reporting of nociceptive impairments; Red – No alterations in nociception observed; White – Not reported).

tests. Depressive-like behaviour was assessed in 68 % of the studies using mostly the forced swimming test (85 %). Only 20 % of the studies evaluated cognition with the Y-maze being the most used paradigm (40 %).

3.2. *Anxiety-like behaviour*

Evaluation of anxiety-like behaviour (Table 4, Fig. 3) uses mostly exploratory-based tests, which play on the inner struggle of the animals between approaching or avoiding novel situations and/or stimuli [63]. The development of anxiety-like behaviour was mostly reported

Table 4
Summary of the literature concerning the development of anxiety-like behaviours in the chronic constriction injury model of neuropathic pain. (OVX - ovariectomized; M – male; F – female; L – left; R – right; ALB - anxiety-like behaviour; OF - open field test; EPM - elevated plus-maze; EZM - elevated zero-maze; LDB - light/dark box; MB - marble-burying test; PEAT - place escape/avoidance test; SI - Social interaction; N/D – unknown).

Paradigm	Species; strain	Gender	Side	Results	Ref.	Biochemical analysis
OF, EPM	Rat; Wistar	M	R	No alterations observed at week 2	[70]	c-FOS and stress hormones quantification
EPM	Rat; Wistar	M	R	ALB at post-surgery at week 3	[72]	
EPM	Rat; Wistar	M	L	ALB at post-surgery at weeks 3 and 4	[74]	Bradford protein quantification (BDNF)
EPM	Rat; Wistar	M	L	ALB at post-surgery at week 4	[66]	
EPM	Rat; Wistar	M	N/D	Anxiety-like behaviour both in HAB and LAB animals at week 5	[76]	
EPM	Rat; Wistar	M	L	ALB at week 3	[77]	
EPM	Rat; Sprague-Dawley	M	R	ALB at weeks 1 and 3	[78]	ELISA (IL-1β) and Western blot (Caspase 1 and PKR, Immunoprecipitation Caspase 1 and NLRP1)
EPM	Rat; Sprague-Dawley	M	L	ALB at week 5	[79]	
EZM, PEAP	Rat; Sprague-Dawley	M	N/D	ALB at weeks 4 and 6	[144]	Western blot (TH, NAT, pCREB, and α-tubulin)
PEAP, EZM	Rat; Sprague-Dawley	M	L	ALB at week 4; increased place escape/avoidance	[145]	
OF	Rat; Sprague-Dawley	M	N/D	ALB at week 2	[64]	Immunohistochemistry (PACAP, pERK, β-arrestin 1/2, c-Fos, vGlut1 and vGlut2)
OF, EZM	Rat; Sprague-Dawley	M	L	ALB at week 4	[65]	Immunohistochemistry (TH, NAT, pCREB, β-actin and α-tubulin)
EPM	Rat; Sprague-Dawley	M	R	ALB at weeks 1 and 3	[153]	Western blot (pNR1, NR1 and GAPDH)
EZM, MB, PEAP	Rat; Sprague-Dawley	M	L	No alterations observed in ALB; increased place escape/avoidance at week 2	[82]	Immunohistochemistry (TH)
EZM, PEAP	Rat; Sprague-Dawley	M	L	No alterations observed at week 1 and 2, ALB at week 4; increased place escape/avoidance at week 1	[156]	Immunoprecipitation and Immunoblotting (TH and NAT) and immunofluorescence (TH)
PEAP	Rat; Sprague-Dawley	M	L	Increased place escape/avoidance at weeks 1 and 2	[94]	Plasma corticosterone quantification, Histochemistry (thionin staining) and Western blot (p-ERK1/2 and t-ERK1/2)
OF, EPM	Rat; Sprague-Dawley	M	R	ALB only in OF at weeks 2 and 3	[67]	
OF, EPM, LDB	Mice; C57BL/6 J	M	N/D	No alterations observed at week 4	[95]	
OF	Mice; C57BL/6 J	M	R	No alterations observed at week 4	[104]	Western blot analysis (BDNF, TrkB, PSD-95 and tubulin)
MB	Mice; C57BL/6 J	M	L	ALB at week 1	[86]	
EPM	Mice; C57BL/6 J	M	N/D	ALB at week 4	[73]	Western blot (Nrf2, HO-1, NQO1, CD11b/c, JNK, ERK1/2, P38 and MOR)
LDB	Mouse; C57BL/6 J	M	R	ALB at weeks 2–5	[84]	HPLC (NA, serotonin, dopamine, 5-HIAA and DOPAC) and MOA activity
OF, EPM	Mouse; C57BL/6 J	OVX/F	R	ALB at week 4	[75]	Western blot (GPR30, GABAA-α2, PSD95, NR2A, NR2B and GluR1)
OF	Mouse; C57BL/6 J	M	R	No alterations observed from week 1–12	[69]	Corticosterone quantification and immunohistochemistry (Ki67, DCX, BrdU/NeuN)
OF, EZM, MB	Mice; C57BL/6 J + Balb/c	M	N/D	ALB at week 5 (only on C57BL/6 J, EZM test)	[68]	
MB	Mice; CD1	M	R	ALB at week 3	[87]	

between weeks 3 and 4 after CCI induction.

In the open field (OF) test, animals are placed in a square arena with an anxiogenic illuminated centre. Overall, CCI animals displayed a reduction in the time spent in the centre of the OF and the number of entries in the central area, an indicator of anxiety-like behaviour [64–68]. Some exceptions [68–71] saw no differences in time spent in the centre of the arena of the OF. Identical results were obtained in the elevated plus maze (EPM), consisting of two opposing open and brightly lit arms and two opposing closed arms, in a "plus sign" shape, elevated above floor level. A reduction in the number of entries in the open arms and in the time spent in the open arms, which was observed in the majority of the studies [67,72–79], hints the development of an anxious-like state. A few exceptions [67,70,71] found no differences between control and CCI animals. One modified version of the EPM is the elevated zero maze [80], which excludes the ambiguous central area in the traditional design [81]. Again, results were similar, with CCI animals spending less time in the open quadrants, with one exception [82] which showed no differences between CCI and SHAM animals. Only one article used the light/dark box test (LDB) [83], which uses a similar exploration/avoidance conflict as the OF, by allowing the animals to freely move between a dark and a bright chamber. A decrease in time spent in the lit compartment is an indicator of an anxiety state and, accordingly, CCI spent time in the bright compartment [84].

The marble-burying test (MB) [85] is based on the inherent burying behaviour of rodents on anxiogenic circumstances, and an increase in the number of marbles buried is then considered as an indicator of anxious and obsessive-compulsive behaviour. In the three studies that used this paradigm, different results were obtained: Wilkerson et al. [86] showed a decreased in the number of marbles buried by CCI animals, Medeiros et al. [87] showed an increase, whereas Bravo and colleagues [82] showed no differences.

The place escape/avoidance paradigm (PEAP) was used to evaluate aversion to painful experiences [88]: the animals are allowed to explore between a dark non-anxiogenic chamber, in which the injured paw was stimulated with a noxious stimulus and a mildly bright anxiogenic side in which there is no stimulation or of the injured paw. In all studies, CCI animals spent less time in the dark chamber, showing an aversion to painful stimuli.

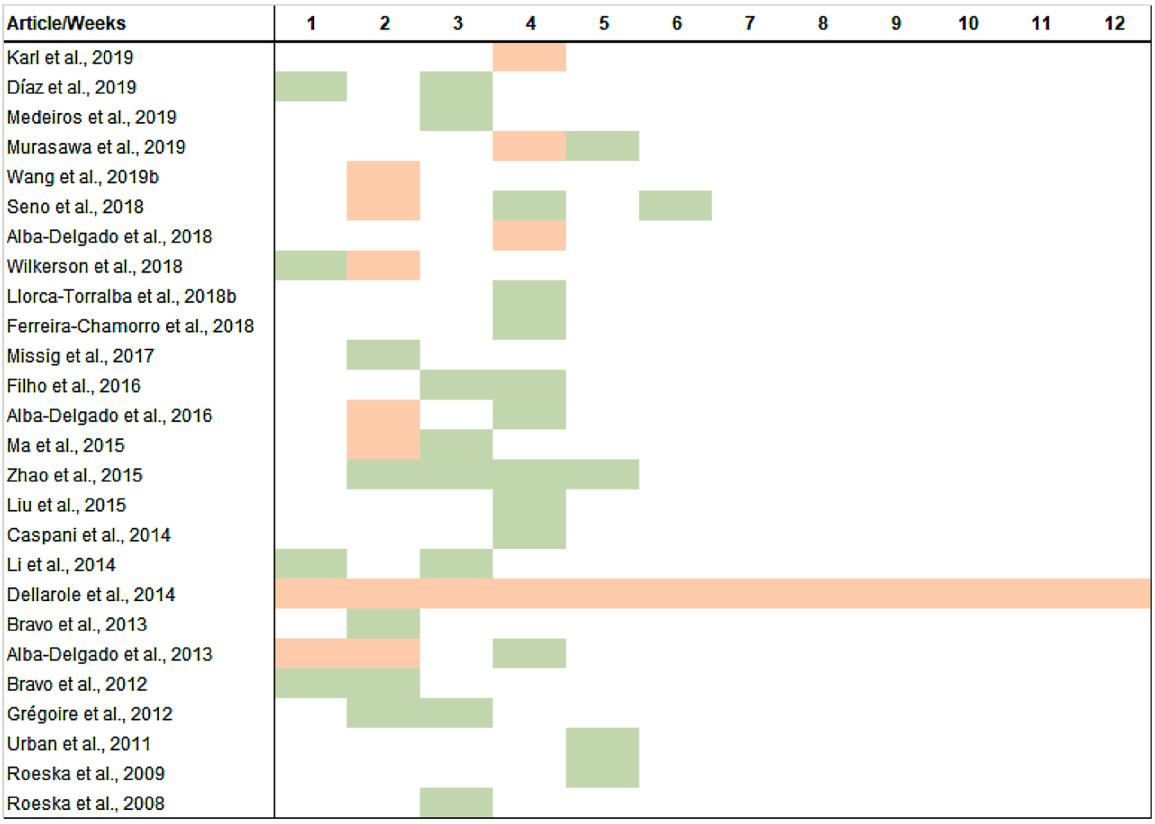

Fig. 3. Heatmap summary of the literature concerning the development of anxiety-like behaviour reported in the chronic constriction injury model of neuropathic pain, regarding time post-CCI induction. Green – Reporting of anxiety-like behaviour; Red – No alterations in anxiety-like behaviour observed; White – Not reported.

3.3. Depressive-like behaviour

For the study of depressive-like behaviours (Table 5, Fig. 4), the forced swimming (FST), tail suspension (TST), and sucrose preference (SPT) tests are the most frequently used. The development of depressive-like behaviour was mostly reported between weeks 3 and 6 after CCI induction.

The FST and TST (applied only in mice) evaluate the learned helplessness component of depression. In the FST [89], the animals are placed in cylinders filled with water, in a no-escape situation. Similarly, in the TST [90] mice are suspended by the tail and similar struggling/immobility behaviours are assessed. In both tests, an increase in immobility behaviour is an indicator of behavioural despair. CCI animals displayed an increased immobility time but no differences in the time spent swimming, thus indicating the increase in immobility occurs at the expense of the decrease in the time spent climbing. The distinction between active behaviours (swimming/climbing) is important, as it is known to be differentially due to serotonergic and noradrenergic mechanisms, respectively [91,92]. Three exceptions were found [79, 93–95], in which no differences were seen between SHAM and CCI animals in immobility, swimming and climbing time in the FST. Similarly, in the TST, an increase in immobility was also observed.

In the sucrose preference test (SPT), the animals are allowed to chose between a sweet (sucrose) and water bottle [96]. A decrease in the intake of sucrose indicates the development of anhedonic-like behaviour. This was observed on CCI animals [64,71,97–100], with one exception, where saccharin was chosen and no differences were found between sham and CCI animals on its preference [67].

In the novelty-suppressed feeding test (NFST), food-deprived animals are put in a chamber with a single pellet of food and the latency to approach it is recorded [101]. There is an underlying conflict between the drive to eat and the fear of a novel environment. Hesitation to eat in a novel environment is described as an intermix measure of anxiety and depression behavioural symptoms, observed in CCI animals [84,97].

3.4. Cognitive behaviour

In the CCI model, the results found in the literature regarding cognitive impairments are summarized in Table 6. Using a variety of behavioural paradigms, results show CCI animals display impaired cognition capabilities, namely regarding working, spatial and social recognition and fear memory.

In the Y-maze test [102], the animals are allowed to explore a three-arm maze, with one arm being different from the remaining two, and the number of entries on each arm being measured. CCI animals spent less time exploring the novel arm, an indicator of impaired working memory [87,103,104].

In the Morris Water Maze (MWM) [105], the animals are placed in a water pool and must find a hidden platform. CCI animals spent more time searching for the platform than naive animals [71,106], indicating impairments on spatial cognition. This was also assessed in the radial maze [107], consisting of a platform with several radially extending arms. Spatial cognition was evaluated by the ability to visit each arm only once, which was shown to be impaired on CCI animals [108]. Regarding social recognition memory, this parameter is evaluated through the duration of the exploration of a novel animal [83]. When re-exposed to this animal, not reducing the time spent exploring is an indicator of recognition memory impairments. CCI animals showed impairments by continuing spending time interacting with the novel animal when this interaction time decreases in sham animals [67].

The Novel Object Recognition test (NOR) [109] evaluates various components of learning and memory in rodents, during which the animal is allowed to explore two different objects and, in the testing day, is introduced to a novel object. No differences were found between SHAM

Table 5
Summary of the literature concerning the development of depression-like behaviours in the chronic constriction injury model of neuropathic pain. (M – male; F – female; L – left; R – right; DLB - Depressive-like behaviour; FST - forced swimming test; TST - tail suspension test; SPT - sucrose preference test; NSFT - novelty suppressed feeding test).

Paradigm	Species; strain	Gender	Side	Results	Ref.	Biochemical Analysis
FST	Rat; Wistar	M	R	DLB at week 2	[70]	c-FOS and stress hormone quantification
FST, NFST	Rat; Wistar	M	L	DLB at weeks 2 and 4	[146]	Immunohistochemistry (ki67, BrdU and NeuN)
FST, SPT	Rat; Wistar	M	R	DLB at week 4	[148]	
FST	Rat; Wistar	M	L	DLB at week 4	[65]	
FST	Rat; Wistar	M	L	DLB at week 3	[99]	
SPT	Rat; Wistar	M	R	DLB from week 1 to week 2	[157]	
FST	Rat; Sprague-Dawley	M	L	No alterations at weeks 6 and 8	[78]	
FST	Rat; Sprague-Dawley	M	R	DLB at weeks 1 and 3	[77]	ELISA (IL-1β) and Western blot (Caspase 1 and PKR, Immunoprecipitation Caspase 1 and NLRP1)
FST	Rat; Sprague-Dawley	M	R	DLB at week 2	[142]	Western Blot (IL-1β, IL-18, IL-6, IL-1RA, IL-18BP, IL-10 and GAPDH)
FST	Rat; Sprague-Dawley	M	N/D	DLB at week 6	[143]	Western blot (TH, NAT, pCREB, and α-tubulin)
FST	Rat; Sprague-Dawley	M	L	DLB at weeks 1, 2 and 3	[149]	Immunohistochemistry (GFAP)
FST	Rat; Sprague-Dawley	M	L	DLB at week 2	[96]	ELISA (5-HT and BDNF), RT-PCR (BDNF) and Immunohistochemistry (pERK1/2 and pCREB)
FST	Rat; Sprague-Dawley	M	L	No alterations observed at week 2	[92]	Immunohistochemistry (TH)
FST	Rat; Sprague-Dawley	M	L	DLB at week 2	[151]	Immunohistochemistry (pERK and c-FOS)
FST	Rat; Sprague-Dawley	M	R	DLB at weeks 1 and 3	[152]	Western blot (pNR1, NR1 and GAPDH)
FST	Rat; Sprague-Dawley	M	R	DLB at week 3	[153]	
FST	Rat; Sprague-Dawley	M	L	DLB at week 3	[97]	Immunohistochemistry (pERK1/2 and pCREB)
FST	Rat; Sprague-Dawley	M	L	No alterations observed at week 1 and 2, DLB at week 4	[155]	Immunoprecipitation and Immunoblotting (TH and NAT) and immunofluorescence (TH)
Anhedonia (with cereals), FST	Rat; Sprague-Dawley	M	L	No alterations observed at weeks 1−2.	[93]	Plasma corticosterone quantification, Histochemistry (thionin staining) and Western blot (p-ERK1/2 and t-ERK1/2)
FST	Rat; Sprague-Dawley	M	L	DLB at week 2	[98]	
SPT	Rat; Sprague-Dawley	M	R	No alterations observed at week 2	[66]	
FST	Mice; C57BL/6 J	M	N/D	No alterations observed at week 3	[94]	
FST, SPT	Mice; C57BL/6 J	M	R	DLB at week 6	[70]	Immunohistochemistry (BrdU and Ki67)
TST, FST	Mice; C57BL/6 J	M	R	DLB at week 4	[139]	Western blot (CD11b/c, PI3K, p-Akt, NF-κB and MAPK)
TST	Mouse; C57BL/6 J	M	R	DLB at week 4	[140]	Western blot (Nrf2, HO-1, NQO1, PI3K, Akt, NOS2, DOR, and ERK1/2)
TST, FST	Mouse; C57BL/6 J	M	R	DLB at week 8	[141]	Immunohistochemistry (GFP) and RT-PCR (CD11b, TMEM119, P2RX7, P2RY12, TNF-α, iNOS and IL-6)
TST	Mice; C57BL/6 J	M	N/D	DLB at week 4	[72]	Western blot (Nrf2, HO-1, NQO1, CD11b/c, JNK, ERK1/2, P38 and MOR)
FST, NFST	Mouse; C57BL/6 J	M	R	DLB from week 2–5	[83]	HPLC (NA, serotonin, dopamine, 5-HIAA and DOPAC) and MOA activity
FST	Mouse; C57BL/6 J	M	R	DLB from week 2–5	[150]	HPLC (NA, serotonin, dopamine, 5-HIAA and DOPAC) and MOA activity
SPT	Mouse; C57BL/6 J	M	R	DLB from week 4–10	[68]	Corticosterone quantification and immunohistochemistry (Ki67, DCX, BrdU/NeuN)
FST, TST	Mouse; ICR	M	R	DLB from week 1 to week 5	[146]	HPLC (5-HT, 5-HIAA, TRY and KYN), RT-PCR (KYN/TRY) and Western blot (IDO and β-actin)
FST, TST	Mouse; ICR	M	R	DLB from week 2, 4 and 6	[154]	HPLC (NA, serotonin, dopamine, 5-HIAA and DOPAC) and MOA activity
FST	Mouse; Swiss	M	L	DLB at week 2	[156]	
TST, FST	Mice; CD1	M	R	DLB at weeks 2 and 3	[86]	

and CCI animals' cognitive performance [95].

Fear memory was also tested through the passive avoidance test [110], where the animals explore two chambers, dark and bright, connected by a passage and receive an electric discharge in the dark chamber. CCI animals showed reduced fear memory [111], with reduced latency to enter the dark chamber.

4. Discussion and conclusions

Taking together, the studies herein summarized show the development of anxiety- and depressive-like behaviours, as well as cognitive-like impairments in the CCI model of neuropathic pain. Despite the general inference, results vary between studies (even between those using the same behavioural tests) concerning the post-CCI time at which emotional and cognitive impairments are observed and concerning test outcomes for the same variable on the same animals. This variability is

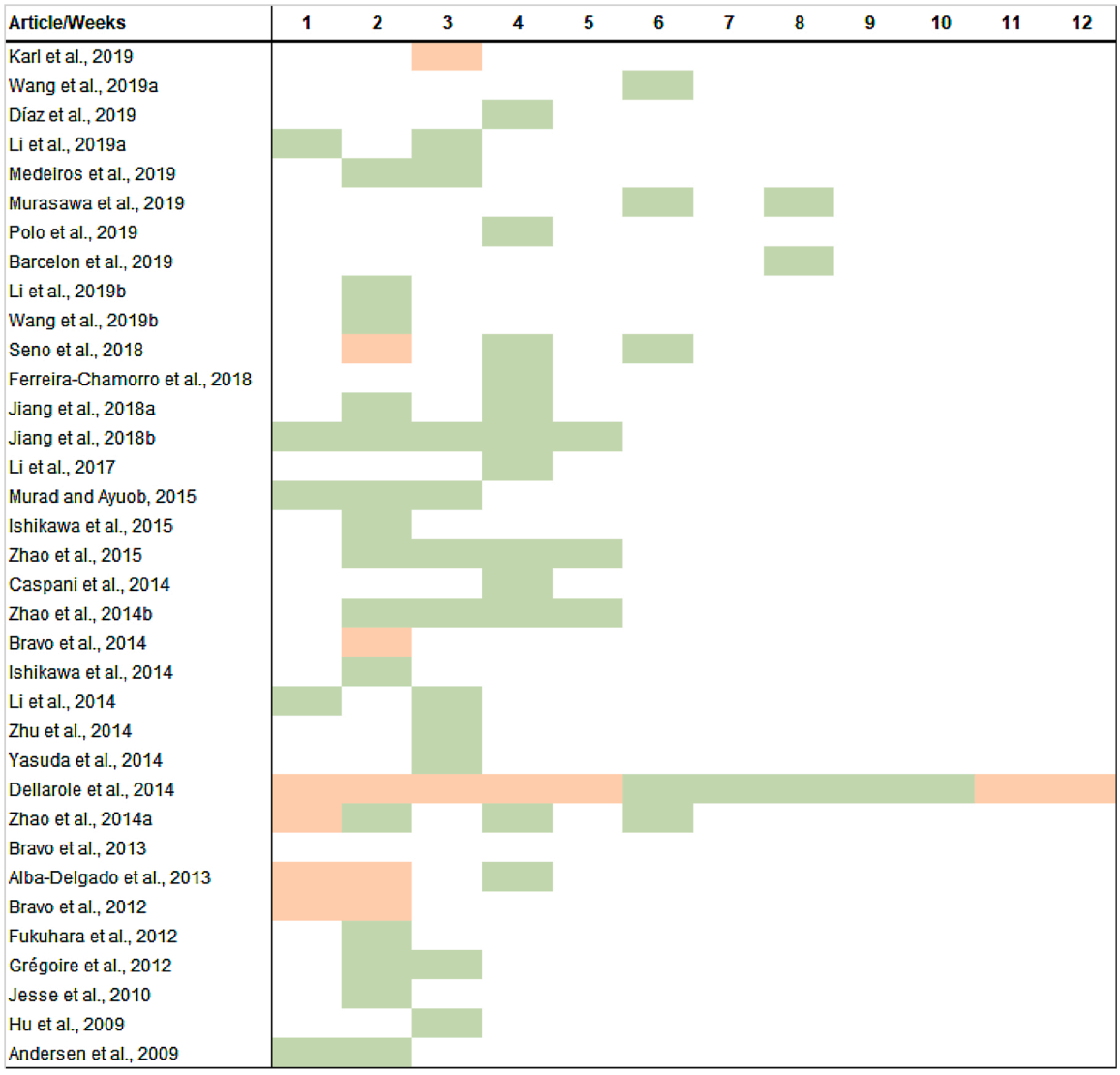

Fig. 4. Heatmap summary of the literature concerning the development of depressive-like behaviour in the chronic constriction injury model of neuropathic pain regarding time post-CCI induction. Green – Reporting of depressive-like behaviours; Red – No alterations in depressive-like behaviour observed; White – Not reported.

Table 6
Summary of the literature concerning the development of cognitive impairments in the chronic constriction injury model of neuropathic pain. (M – male; F – female; L – left; R – right; MWM – Morris Water Maze, NOR – Novel Object Recognition).

Paradigm	Species; strain	Gender	Side	Results	Ref.	Biochemical Analysis
Radial maze	Rat; Sprague-Dawley	M	R	Impaired spatial memory at week 2	[107]	Immunofluorescence (GFAP, IBA-1, IL-1b, MCP-1 and FosB/DFosB)
Passive avoidance test	Rat; Sprague-Dawley	M	R	Impaired fear memory from week 1 to week 4	[110]	Western blot (β-actin, NR2A, NR2B, CaMKII-α and CaMKII-β)
Outcome devaluation	Rat; Sprague-Dawley	M	R	No alterations in goal-directed behaviour at week 4	[147]	
MWM	Rat; Sprague-Dawley	M	R	Impaired spatial cognition on day 4 and 5	[105]	Immunohistochemistry (substance P) and RT-PCR (GluR, PKC, IL-6, NF-jβ, and β-actin)
Y-maze, Social recognition test	Rat; Sprague-Dawley	M	R	No deficits in the Y-maze; impaired social recognition memory at week 3	[66]	
NOR, MWM	Mice; C57BL/6 J	M	N/D	No alterations in learning behaviour and memory	[94]	
MWM	Mice; C57BL/6 J	M	R	Impaired spatial memory at week 6	[70]	Immunohistochemistry (BrdU and Ki67)
Y-maze	Mouse; C57BL/6 J	M	R	Impaired working memory at week 4	[103]	Western blot analysis (BDNF, TrkB, PSD-95 and tubulin)
Y-maze	Mouse; C57BL/6 J	M	R	Impaired working memory at week 2 and week 4	[102]	Immunohistochemistry (IBA-1, CD86, PCNA and DCX)
Y-maze	Mice; CD1	M	R	Impaired working memory at week 3	[86]	

mostly attributable to the use of different methodological approaches, namely the animal's species and strains, the behavioural paradigms and experimental designs used, turning the comparison between studies difficult.

4.1. Species, strains, sex and age

Not only different species (rats and mice) but also different strains are used in these works. The choice of species used is a confounding issue on chronic pain preclinical studies, as mice seem to not be affected by chronic pain conditions [112] and are genetically, physiologically and behaviorally distinct from rats [113]. These species are differentially affected by their environment, handling, and testing [113][112]. Consequently, stress can impact not only emotional and cognitive assessments but also nociceptive measurements, as stress has an inhibitory effect on nociceptive sensitivity, an effect known as stress-induced analgesia [114].

Importantly, nociceptive [115], emotional as well as cognitive [116–118] impairments were shown to vary greatly between strains and the use of different strains can be a source of variability. In the rat, outbred strains of rats showed higher thermal hyperalgesic responses to ligation of the sciatic nerve than inbred strains [115]. A study by Roeska and colleagues [76] also showed an effect of the genetic background (namely trait anxiety) on mechanical allodynia. While low-anxiety rats recovered 21 days post-CCI, high-anxiety animals maintained nociception until day 57. Also, strain differences have been described, in both rats and mice, regarding contextual and spatial learning [116], social behaviours [117] and in object recognition memory [118].

Sex should also be taken into consideration, as previous basic and clinical studies showed that pain- and emotional-related behaviours differ between males and females [116,119–121]. Only one study used female animals, even though research guidelines have highlighted the need to perform studies using females [122]. Also, epidemiological studies show the prevalence of chronic pain [122], anxiety disorders, and depression [123,124] is higher in women than men. In preclinical research, females showed increased anxiety-like behaviour than males animals in Sprague-Dawley [125] and Wistar Han rats [116], as well as in C57BL/6 J and BALB/cJ mice [117]. Also, a study of Keeley et al. [116] showed not only rat strain but sex differences concerning anxiety-like behaviours and cognition, with Long Evans rats outperforming Wistar Han in learning and memory tasks in a sex-specific manner.

Lastly, while epidemiological studies have shown an increased prevalence of chronic pain conditions with age [126], preclinical studies use mostly young adult animals. Ageing is associated with numerous anatomical and functional changes of the somatosensory system, from increased inflammation and Wallerian degeneration to a decrease in the density of both myelinated and unmyelinated fibres [127,128]. The choice of using young animals is thus difficult to understand, especially when, in SNI animals, an age-dependent effect was already observed on affective and cognitive behaviour by Leite-Almeida and colleagues. In fact, in this work ageing in Wistar Han rats was associated with increased anxiety-like behaviour and decreased cognitive performance [129]. Interestingly, this same work also shows middle-aged animals, but not young or old rats, display depressive-like behaviours in the FST four weeks post-induction.

4.2. CCI induction and experimental design

While in nerve injury models, it has been suggested the evaluation of altered mechanisms for more than a few days or weeks [130], the studies herein are performed with different duration of chronic pain. Consequently, results may depend on the time-dependent development of comorbid mood disorders as it has been shown that, in the cuff model of neuropathic pain, the development of anxiety- preceded that of depressive-like behaviours [129]. In fact, in this review anxiety-like behaviour was mostly described 2–3 weeks after CCI induction, while depressive-like behaviours were observed predominantly after week 4.

Importantly, the suture used for nerve ligation was shown to have an impact on the outcome of the CCI model [27,131,132], being a possible variability-causing factor. The originally-described chromic catgut ligature contributes to the inflammatory component of this model [27] but is used in only half (51 %) of the studies herein summarized. Also, the type of suture used is not always mentioned in the original articles [76,82,84,93,133]. The major limitation of the CCI model is the tension of the ligatures, as there is a great inter- and intra-individual experimenter variability. Similarly, the number of ligatures can influence the results as the nerve self-strangulates between the ligatures, which induces further damage [18].

A study by Leite-Almeida and colleagues [134] showed a differential effect of the side of injury in the emotional and cognitive consequences of neuropathy using the spared nerve injury model. Accordingly, they showed that left- and right-sided injuries differentially affected anxiety-like and cognitive behaviours, implicating lateralization of these impairments. To be best of our knowledge no laterality study was performed using the CCI model but authors seem to be inducing CCI indiscriminately in the left and right sciatic nerves which might also contribute to increased variability between reports.

4.3. Behavioural paradigms

Even though the studies in this review use widely known behavioural tests, these are performed differently between groups – manual or automated, different test durations, equipment used and the environments in which these are performed. Likewise, anxiety and depression are seldom evaluated simultaneously.

The validity of behavioural results greatly depends on the locomotor ability of the animals, but most studies do not show how CCI affected this parameter. Moreover, some studies that do, evaluate locomotion using the distance travelled on the OF tests or free exploratory ambulation in chambers. However, while animals might not show differences in locomotor ability in behavioural tests that do not require effort, such as the SP, the OF, the EPM or variations, that is not the case of the FST. Thus, when reporting FST results, researchers should always evaluate CCI locomotor ability using rotarod.

4.4. CCI model: benefits and pitfalls

Although not the subject of our systematic review, we believe it is important to acknowledge this model's shortcomings as well as its advantages. Overall, this model is frequently used for behavioural studies, as it is considered to mimic human peripheral nerve injuries including tumour compression, heavy metal poisoning, hypoxia, metabolic abnormalities and post-traumatic peripheral painful neuropathy states in humans [32].

One of the major benefits of the CCI model is that it comprises both inflammatory and neuropathic components [32]. Regarding the lesion, its induction leads to a diffused lesion of efferent fibres that compromise sciatic-dependent muscle innervation [135]. Additionally, intraneural oedema and demyelination at the ligation site or distally are also often reported [32,135]. Demyelination was reported to affect mostly large myelinated axons (Aα and Aβ), with less impact on small myelinated (Aδ) or unmyelinated axons [32,136,137]. Importantly, since CCI induction leads only to partial denervation, behavioural responses to peripheral stimuli are preserved [32], which is of great advantage in the use of this model, and CCI animals display spontaneous pain, thermal (hot and cold) and mechanical hyperalgesia lasting between 15–30 days which decrease over time [32,135].

Some authors consider the CCI model is better suited for studies focused on spontaneous and stimulus-evoked pain, rather than chronic conditions, as its, similarly to other neuropathic pain models, correlation with human symptoms is limited [138,139]. Per example, CCI

animals display thermal hyperalgesia, a symptom not observed in the clinics [32], or may develop autotomy, a rare condition in humans. Additionally, there is a discrepancy between the observed animal "pain like" behaviours and the painful sequelae of human nerve injury [139], namely tingling paresthesia and numbness. Finally, while this model is considered reliable and easily reproducible, both are greatly dependent on the ligature tension which varies with the experimenter experience and fatigue [32].

4.5. Concluding remarks

The studies herein reviewed support the development of an anxiodepressive phenotype in animals with CCI-induced neuropathy, along with cognitive alterations, thus validating the use of this rodent model to study the molecular and neuronal mechanisms underlying neuropathic pain and its anxiodepressive and cognitive consequences. Nonetheless, in this review, we have emphasized some variability-inducing factors that highlight the need for conformity between research groups concerning the experimental design, to enable a successful interpretation and comparison of results. Likewise, the use of female animals as experimental subjects is imperative since these neuropathic-induced comorbidities are sex-specifically expressed in humans, with a special impact in women, but data in female animal models remains scarce.

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CRediT authorship contribution statement

Diana Fonseca-Rodrigues: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft. **Diana Amorim:** Supervision, Data curation, Writing - review & editing. **Armando Almeida:** Writing - review & editing, Supervision, Funding acquisition. **Filipa Pinto-Ribeiro:** Conceptualization, Methodology, Writing - original draft, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflicts of interest.

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