How to study anxiety and depression in rodent models of chronic pain?

Mélanie Kremer, Léa Becker, Michel Barrot, Ipek Yalcin

DR. MÉLANIE KREMER (Orcid ID : 0000-0003-2814-5706)

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How to study anxiety and depression in rodent models of chronic pain?

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Mélanie Kremer[1], Léa J. Becker[1], Michel Barrot[1]*, Ipek Yalcin[1]*

[1]Centre National de la Recherche Scientifique, Université de Strasbourg, Institut des Neurosciences Cellulaires et Intégratives, Strasbourg, France.

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Corresponding authors: **Ipek Yalcin**, PhD, PharmaD
INCI CNRS UPR3212
8 allée du Général Rouvillois
67000 Strasbourg, France
E-mail: yalcin@unistra.fr

Michel Barrot, PhD
INCI CNRS UPR3212
8 allée du Général Rouvillois
67000 Strasbourg, France

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E-mail: mbarrot@inci-cnrs.unistra.fr

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Author's Contributions

M.K. and L.B. did the bibliographic research; M.K. wrote parts 1, 2, 3 and 5; L.B. wrote parts 4 and 5; M.K. realized all the figures and L.B. has completed Figures 2 and 5; I.Y. and M.B. have supervised and revised the article.

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Abbreviations

ACC: Anterior Cingulate Cortex; BT: Burrowing Test; CCI: Chronic Constriction Injury: CeA: Central Nucleus of the Amygdala; CFA: Complete Freund's Adjuvant; CION: Infraorbital Nerve Constriction; DM3T: Dimethyl-3-transferase; EPM: Elevated Plus Maze; EZM: Elevated Zero Maze; FST: Forced Swim Test; HB: Hole-Board test; HDAC: Histone Deacetylase; HIV: Human Immunodeficiency Virus; IASP: International Association for the Study of Pain; ICS: Intermittent Cold Stress; IDO1: Indoleamine 2,3-dioxygenase 1; IL: Interleukin; LC: Locus Coeruleus; LDB: Light/Dark Box test; MAPK: Mitogen-Activated Protein Kinases; MB: Marble Burying test; MDD: Major Depressive Disorder; NAc: Nucleus Accumbens; NSF: Novelty Suppressed Feeding; OF: Open Field; PAG: Periaqueductal Gray; PFC: Prefrontal Cortex; PSNL: Partial Sciatic Nerve Ligation; RCS: Repeated Cold Stress; SCI: Spinal Cord Injury; SI: Social Interaction test; SNI: Sciatic Nerve Injury; SNL: Spinal Nerve Ligation; SPT: Sucrose Preference Test; ST: Splash Test; TIC: Trigeminal Inflammatory Compression; TNF: Tumor Necrosis Factor; TNT: Tibial Nerve Transection; TST: Tail Suspension Test

Abstract

Mood disorders such as depression and anxiety are frequently observed in patients suffering from chronic pain. Over time, different tests and models have been developed in rodents to study the anxiodepressive-like consequences of chronic pain. This review describes these pre-clinical tools (models and tests) used for studying behavioural aspects of the comorbid relationship between chronic pain and anxiety and/or major depressive disorder (MDD). Three major types of chronic pain strongly associated with anxiodepressive-like comorbidity as well as their animal models are presented: neuropathic pain, inflammatory pain and fibromyalgia. After a description of chronic pain animal models and of the tests that allows determining nociceptive responses, this review presents and discusses the various behavioural tests that have been used to assess anxiety and depressive-like behaviours in these models of chronic pain. Finally, this review highlights the progress that remains to be made to homogenize the results in the field of pain-induced mood disorders and summarizes the recent advances achieved through these tests and models.

1. Introduction

Pain is a multidimensional and subjective experience which is considered as a debilitating disease when it becomes chronic. Chronic pain does indeed affect various aspects of the patient's quality of life, including mood, sleep and cognitive processes (Maletic & Raison, 2009; Haanpaa *et al.*, 2011; Radat *et al.*, 2013). In chronic pain patients, mood disorders such as major depressive disorders and anxiety are frequently observed (Bair *et al.*, 2003; Gustorff *et al.*, 2008; Maletic & Raison, 2009; Radat *et al.*, 2013).

Major depressive disorders are highly disabling psychiatric disorder which affects around 16% of the population at some point over their lifespan (Bromet *et al.*, 2011) and is among the main contributors to the disease burden worldwide (Kessler *et al.*, 2003; Olesen *et al.*, 2012). Due to its multifactorial nature and heterogeneous symptomatology, the precise aetiology of this debilitating disorder remains poorly understood (Menard *et al.*, 2016). However, besides chronic stress and psychosocial trauma (Liu & Alloy, 2010), chronic pain can also be cited among the first determinants of mood disorders (McWilliams *et al.*, 2004; Breivik *et al.*, 2006; Attal *et al.*, 2011), as shown by the mean prevalence rate around 50% for major depressive disorder reported in these patients (Bair *et al.*, 2003). Besides, anxiety is also among mood disorders frequently diagnosed in chronic pain patients. Indeed, this psychopathology, defined by excessive fear and worry, affects up to 60% of chronic pain patients. This prevalence is however highly dependent on the considered type of pain, with the lowest rate (between 1 and 27%) for neuropathic pain and the highest (between 18 and 60%) for fibromyalgia (Hooten, 2016).

Different models have been developed in rodents to study the various types of clinically observed chronic pain conditions (Mogil, 2009; Jaggi *et al.*, 2011; Muley *et al.*, 2016; Sluka & Clauw, 2016; Fischer *et al.*, 2017; Kumar *et al.*, 2018), as well as their anxiodepressive consequences (Liu & Chen, 2014; Leite-Almeida *et al.*, 2015). While several groups successfully achieved to model this comorbidity in animals (Narita *et al.*, 2006a; Narita *et al.*, 2006b; Suzuki *et al.*, 2007; Goncalves *et al.*, 2008; Matsuzawa-Yanagida *et al.*, 2008), many initial studies and some of the recent ones failed to show any association between chronic neuropathic or inflammatory pain and anxiety- and depression-related behaviours (Kontinen *et al.*, 1999; Hasnie *et al.*, 2007b; Urban *et al.*, 2011; Pitzer *et al.*, 2019). However, some of the negative studies (but not all) were done at early pain stages, *i.e.* during the first week or the first 3 weeks following inflammatory and neuropathy induction, respectively. While it may not be the only aspect that allows explaining the presence or not of anxiodepressive-like consequences in rodent models of

chronic pain, the time factor appears as critical (Yalcin *et al.*, 2011; Yalcin & Barrot, 2014; Humo *et al.*, 2019). Others factors, such as the species, the strains of animals, the chosen models of chronic pain, and the time of the day-night cycle when the animals are tested, could also be involved.

In this review, based on the literature up to December 2019, we summarized the pre-clinical tools (models and tests) used over the past two decades and pertaining to behavioural aspects of the comorbid relationship between chronic pain and anxiety and/or major depressive disorder (MDD). After a brief description of the types of chronic pain and of their animal models, as well as the tests that allow determining nociceptive responses, we will present and discuss the various behavioural tests that have been used to assess anxiety and depressive-like behaviours in these models of chronic pain.

2. Animal models of pain that have been used in research on anxiety and/or depression

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Acting as an alarm signal, acute pain triggers reactions to preserve the integrity of the organism (Scholz & Woolf, 2002; Morrison *et al.*, 2013). When pain persists beyond several months, it is considered as chronic. Contrary to acute pain, chronic pain is regarded as an illness *per se*, and mood disorders are among its comorbidities (Attal *et al.*, 2011; Haanpaa *et al.*, 2011). According to the epidemiological studies the prevalence rate of major depressive disorder in patients with chronic pain (Bair *et al.*, 2003; Maletic & Raison, 2009) varies from around 30% for patients suffering from neuropathic pain (Gustorff *et al.*, 2008; Radat *et al.*, 2013), to around 80% in fibromyalgia patients (Fietta *et al.*, 2007). Up to recently, the mechanism(s) underlying this comorbidity remained unclear (Yalcin & Barrot, 2014; Doan *et al.*, 2015; Fasick *et al.*, 2015; Zis *et al.*, 2017). However, main advances have been achieved in the past decade, thanks to the development of animal models that allow studying anxiodepressive consequences of chronic pain (Yalcin & Barrot, 2014; Leite-Almeida *et al.*, 2015). We will focus here three major types of chronic pain strongly associated with anxiodepressive-like comorbidity: **neuropathic pain**, **inflammatory pain** and **fibromyalgia**.

2.1. Neuropathic pain and its animal models

By definition, neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system (Treede *et al.*, 2008). It is a syndrome usually chronic, with various

possible aetiologies. For most patients it has a peripheral origin, arising as a consequence of peripheral nerve injury (nerve section or compression), or as a consequence of a metabolic disease such as diabetes. Nerve injuries and diabetic peripheral neuropathy account for almost two-thirds of the patients. However, neuropathic pain can also result from infectious diseases, as in post-herpetic neuralgia, from exposure to neurotoxic compounds, such as those used for cancer chemotherapy, or be of central origin, as observed after spinal cord injury or local post-stroke ischemia (Attal *et al.*, 2008; Colloca *et al.*, 2017; Zilliox, 2017; Scholz *et al.*, 2019).

A large number of animal models of neuropathic pain has been developed (Sorkin & Yaksh, 2009; Colleoni & Sacerdote, 2010; Jaggi *et al.*, 2011; Kumar *et al.*, 2018), but their exhaustive presentation is beyond the scope of this review. Here, we will simply focus on the few models in which most of the comorbidity studies on anxiodepressive aspects were performed. Almost 90% of the published studies used trauma models based on chronic nerve compression (see **Figure 1**). This nerve compression has been achieved either by ligation, as for the partial sciatic nerve ligation (PSNL) which is a tight ligation of one-third to half of the sciatic nerve (Seltzer *et al.*, 1990), the spinal nerve ligation (SNL) which is a tight ligation of L5 and L6 spinal nerves (Kim & Chung, 1992) or of L5 spinal nerve only (LaBuda & Little, 2005), the chronic constriction injury (CCI) consisting in four loose ligatures applied around the sciatic nerve (Bennett & Xie, 1988), or by the implantation of a polyethylene cuff around the main branch of the sciatic nerve (Mosconi & Kruger, 1996). Another frequently used trauma model is the spared nerve injury (SNI), which relies on the axotomy of two of the three branches of the sciatic nerve (Decosterd & Woolf, 2000). The tibial nerve transection (TNT) is a variant of this model in which the axotomy concerns the tibial nerve only (Andrews *et al.*, 2012). The anxiodepressive comorbidity has also been studied using trigeminal neuralgia models, such as the infraorbital nerve constriction (CION) which corresponds to CCI of the infraorbital nerve (Vos *et al.*, 1994), or in animals with trigeminal inflammatory compression (TIC) induced by a chromic gut suture alongside the infraorbital nerve (Ma *et al.*, 2012).

Beside nerve lesion, diseases affecting the somatosensory system constitute another main aetiology of neuropathic pain (Jolivalt *et al.*, 2016). In this regard, anxiodepressive-like comorbidities have also been studied in a streptozotocin model, which is a common model of diabetic polyneuropathy (Lenzen, 2008), and in models of human immunodeficiency virus (HIV) 1 protein gp120 (Wallace *et al.*, 2007b) or zoster varicella virus (Hasnie *et al.*, 2007a) as infection models. Exposure to neurotoxic drugs, such as the HIV antiretroviral stavudine (Joseph *et al.*,

2004) or the chemotherapy drugs oxaliplatin (Cavaletti *et al.*, 2001) or paclitaxel (Cavaletti *et al.*, 1995), have also been used to study the comorbidity between neuropathic pain and anxiety/depressive-like behaviours.

Concerning central neuropathies, studies of anxiety/depressive-like behaviours have been done using a model of spinal cord injury (SCI) induced by dropping a weight over the exposed spinal cord (Behrmann *et al.*, 1992), or by using a photochemical reaction to form a thrombosis and occlusion in small vessels supplying the spinal cord (Verdu *et al.*, 2003).

2.2. Inflammatory pain and its animal models

When inflammation becomes chronic, it loses its role as natural physiological response to tissue injury or infection, and it becomes a maladaptive and physiopathological condition. The chemical mediators that are responsible for tissue inflammation affect nociceptive nerve endings to lower neuronal excitation thresholds and sensitize afferent firing rate, leading to the development of allodynia and hyperalgesia, respectively (Kidd & Urban, 2001; Lipnik-Stangelj, 2013). One of the main organ systems that is particularly susceptible to the development of inflammatory pain is joints.

Arthritis, which literally means joint inflammation, refers to a group of rheumatic diseases and other conditions that can cause pain, stiffness and swelling in the joints. It includes forms ranging from those related to wear and tear of cartilage (such as osteoarthritis (Kuyinu *et al.*, 2016)), to those associated with inflammation resulting from an overactive immune system (such as rheumatoid arthritis) (Di Paola & Cuzzocrea, 2008). Recent surveys report that rheumatoid arthritis is one of the most common chronic inflammatory pain conditions in developed countries, affecting approximately 15 million people worldwide (Fiest *et al.*, 2017). Rheumatoid arthritis is a chronic debilitating autoimmune disorder characterized by synovitis that leads to cartilage and bone erosion by invading fibrovascular tissue (Scott *et al.*, 2010). The pathogenesis of rheumatoid arthritis is complex and involves genetic predispositions as well as environmental factors (Imboden, 2009). Psychiatric disorders are highly associated with rheumatoid arthritis (Nerurkar *et al.*, 2019). Depression is diagnosed in up to 66% and anxiety in up to 70% of individuals with rheumatoid arthritis (Fiest *et al.*, 2017).

Animal models have contributed to improve our understanding of the pathophysiological mechanisms responsible for the generation of chronic inflammatory pain and its associated comorbidities (Kuyinu *et al.*, 2016; Muley *et al.*, 2016; Fischer *et al.*, 2017). The most widely used model for studying the comorbidity between inflammatory pain and anxiodepressive-like disorders

has been the complete Freund's adjuvant (CFA)-induced inflammation of the paw (Fehrenbacher *et al.*, 2012). This model is based on a unilateral intraplantar injection of CFA, which can produce a long-lasting (> 3 weeks) decrease in mechanical and thermal thresholds compared to the contralateral non-inflamed paw (Cook & Moore, 2006). Carrageenan can also be injected into the paw to model arthritis, but this model is more acute than chronic because the associated mechanical and thermal hypersensitivity usually lasts no longer than 72 hours (Mert *et al.*, 2014). Monoarthritis models have also been used, by injecting an inflammatory agent such as CFA, uric acid or a kaolin-carrageenan mix directly into the tibiotarsal (Butler *et al.*, 1992), knee (Lopez-Munoz & Salazar, 1993; Radhakrishnan *et al.*, 2003) or temporomandibular (Harper *et al.*, 2001) joint. Obesity is also a main risk factor for the development of arthritis (Georgiev & Angelov, 2019), and a model of arthritis based on dietary obesity (Silberberg & Silberberg, 1950) has also been used to test anxiodepressive-like aspects (Griffin *et al.*, 2010).

2.3. Fibromyalgia and its animal models

Fibromyalgia is a condition characterized by chronic widespread musculoskeletal pain, which includes widespread tenderness to pressure stimuli and morning stiffness (Clauw, 2014; Hauser *et al.*, 2015; Sluka & Clauw, 2016). The pathogenesis of fibromyalgia is complex and controversial, but some recent advances in the field showed the possible involvement of lipid mediators (Hsu *et al.*, 2019), autoimmunity, neuroinflammation and small fiber neuropathy (Ryabkova *et al.*, 2019). There is however no evidence of any single event causing this condition; instead, it is considered to be triggered or aggravated by multiple physical and/or emotional stressors, such as infections, or emotional and physical trauma (Schmidt-Wilcke & Clauw, 2011; Sluka & Clauw, 2016). Fibromyalgia is more common in women than in men, and its worldwide prevalence is 2 to 3% (Cabo-Meseguer *et al.*, 2017). Fibromyalgia is also associated with a number of other symptoms, including pronounced fatigue, sleep disturbances and psychological disturbances (depression and/or anxiety) (Hauser *et al.*, 2015). Overall depression and anxiety are among the most common comorbidities of fibromyalgia, with prevalence rates ranging from 20-80% and 13-64% respectively (Maletic & Raison, 2009).

Some studies tried to address the anxiodepressive consequences in animal models of fibromyalgia. However, as there is no well-defined aetiology of fibromyalgia, the validity of animal models remains imperfect and simply based on symptoms and on the response to treatment (mostly antidepressant drugs). The most frequently used fibromyalgia model addressing depression-like behaviours is based on biogenic amine depletion by systemic reserpine

administration (Nagakura *et al.*, 2009). However, the chronic widespread musculoskeletal pain model induced by repeated intramuscular acid injections in rodents has been suggested to have better face validity to human's conditions, but few studies have dealt with the anxiodepressive consequences in this model yet (Liu *et al.*, 2014). Anxiodepressive consequences have also been described in stress-induced fibromyalgia models, such as the cold stress models, *i.e* intermittent (ICS) (Nishiyori & Ueda, 2008) or repeated cold stress (RCS) (Nasu *et al.*, 2019), the unpredictable sound stress model (Khasar *et al.*, 2008), or the subchronic swim stress inducing chronic widespread-like pain (Nazeri *et al.*, 2018). Although existing models mimic some symptoms of fibromyalgia, it is still critical to develop new models which can reflect the different aspects of this syndrome.

3. Nociceptive tests frequently used to evaluate chronic pain

An important notion in the field of pain is the distinction between pain and nociception. If nociception corresponds to "neural process of encoding noxious stimuli" (*i.e.* stimuli presenting a risk for the integrity of the body) (Basbaum, 2000), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (**Box 1**) (Loeser & Melzack, 1999; Basbaum *et al.*, 2009; Baliki & Apkarian, 2015; Apkarian & Reckziegel, 2019). These two facets of the same phenomenon distinguish the sensation (nociception) from its interpretation (pain). In patients, pain is evaluated verbally, which is not possible in rodents. Thus, rodent "pain tests" are actually nociceptive tests, based on reflex responses, and the preclinical measurement of pain itself is still a challenge for this field of research (Barrot, 2012; Deuis *et al.*, 2017). For a long time, fundamental research on pain and its preclinical treatments has been based on nociceptive tests performed on naive animals, *i.e.* not painful (Le Bars *et al.*, 2001). But in the past decades, the combination of nociceptive tests and pain models has improved the relevance of studies in the field of pain research (Mogil, 2009).

The main nociceptive tests used in animal studies addressing the comorbidity between pain and anxiodepressive-like disorders are based on thermal or mechanical stimuli (Barrot, 2012; Leite-Almeida *et al.*, 2015). Some of them, like the tail-flick test, the hot- or cold-plate tests and the radiant heat paw-withdrawal test, rely on the latency for avoidance behaviour: a withdrawal reflex of the paw or the tail (Barrot, 2012; Deuis *et al.*, 2017). Here, the stimulus may be considered as fixed. The tail withdrawal test, the first developed (D'Amour & Smith, 1941), is based on the latency of the withdrawal reflex after applying a heat beam at the end of the tail or

after having immersed it in a bath at fixed temperature. Although the observed response results from a spinal reflex, it remains under the influence of supraspinal controls as well as mechanisms of thermoregulation (Barrot, 2012). This test, sensitive to opiates, has been used extensively for analgesic research. Nevertheless, this test is much less used in models of chronic pain such as inflammatory pain or trauma models of neuropathic pain since these models rather focus on one of the paws of the animal. The hot-plate (Woolfe & MacDonald, 1944; O'Callaghan & Holtzman, 1975) is another classic test developed in the 1940s, most often with a plate temperature set at 52 or 55°C for rodents. These temperatures, which are 10 to 15°C higher than the nociceptor response thresholds, are necessary for the increase in skin temperature to activate the nociceptors and thus to observe a supraspinal response within less than 10 seconds. The measurement is most often the latency of withdrawal and licking of the paw, but in the mouse the jump of the animal is sometimes taken into consideration (Deuis *et al.*, 2017). In the late 1980s, Hargreaves *et al.* have described a test to differentiate the nociceptive response of the two hind paws in rodents: the Hargreaves test or Plantar® test (Hargreaves *et al.*, 1988; Muley *et al.*, 2016). The animal is placed on a glass floor and the point source of heat is brought under the paw to be tested, the system automatically detects the withdrawal of the paw. This test is useful in unilateral pain models, like most models of inflammatory and neuropathic pain. Similarly, the cold nociceptive response can be tested using a cold-plate test (Bennett & Xie, 1988; Choi *et al.*, 1994), but this measure can be more difficult to establish as the response latency is sometimes unreliable, and the number of responses over a given period of time is generally preferred (Deuis *et al.*, 2017).

Finally, some of the thermal nociceptive tests are based on the observation and quantification of nociceptive behaviours, as is the case with the acetone test. To assess cold allodynia, a drop of acetone can be applied on the hind paws (Choi *et al.*, 1994). Its evaporation produces a cold stimulus, which is usually not detected as nociceptive by naive animals but results in cold allodynia in pain models (Barrot, 2012; Deuis *et al.*, 2017).

Other nociceptive tests, such as the von Frey filaments or the Randall-Selitto analgesimeter, can rely on the mechanical stimulus threshold necessary to elicit an avoidance behaviour (Barrot, 2012; Muley *et al.*, 2016; Deuis *et al.*, 2017). In this case, the stimulus is variable with increasing value. An advantage of these tests is to measure allodynia, *i.e.* the response to a normally non-nociceptive stimulus, or hyperalgesia, an exaggerated response to a nociceptive stimulus. While all mechanical tests are feasible in rats, the von Frey test mostly remains preferred in mice. These filaments of various diameters are generally applied to the plantar surface, until they bend exerting

a calibrated pressure. The threshold filament inducing a response gives the value of the mechanical sensitivity threshold. This value is nevertheless influenced by the speed and the duration of application of the filaments, and the standardization of the procedure is therefore particularly important (Barrot, 2012). In recent years, automated versions of this test have been developed (Deuis *et al.*, 2017). Manual or motorized, based on pressure gauges, they have the advantage of offering a continuous scale and no longer logarithmic values. With the Randall-Selitto analgesimeter (Randall & Selitto, 1957; Kayser *et al.*, 1990), the plantar surface of the rat's paw is placed on a fixed element and a mobile element exerts an increasing pressure on the other face. According to the protocols, the parameter measured will be either the threshold expressed in grams of appearance of a withdrawal reflex or that of a vocalization. This test gives highly stable and reproducible values, but requires a strong behavioural expertise (Barrot, 2012; Deuis *et al.*, 2017). Indeed, the rat is restrained in a vertical non-natural position to maintain its paw on the apparatus. A similar system has been developed to assess mechanonociception in models of arthritis where calibrated forceps are oriented along the joint line and an increasing compression force is applied (Ji *et al.*, 2007; Amorim *et al.*, 2014).

The various tests that we described above have been used to validate the presence of nociceptive hypersensitivity in animal models of pain used to study the anxiodepressive comorbidity. Most of these studies were based on measuring the evoked nociceptive response instead of spontaneous or ongoing pain since the latter cannot be easily measured in rodents. In the past decade, however, an effort from some research groups has focused on the search for objective and quantitative measures of pain, or at least for indirect parameters that may reflect the ongoing pain in the animal (Mogil, 2009; Deuis *et al.*, 2017). One of the strategies to obtain such parameters has been based on the evaluation of the affective dimension of the pain experience, which comprises its unpleasantness and salient fear negative-stimuli-related escape and avoidance behaviours (Price, 2000; Fuchs & McNabb, 2012; Navratilova *et al.*, 2013). One of the most frequently used methods to evaluate such avoidance consists in giving the choice to the animal between environments associated or not with the painful experience. This can for example be done in response to mechanical stimulation (LaBuda & Fuchs, 2000; Llorca-Torralba *et al.*, 2018), by using plates with temperature gradient or allowing the choice between two surfaces with different temperatures (Moqrich *et al.*, 2005). Another indirect measure of ongoing pain has been done by using a modified version of the conditioned place preference test, which is based on an animal's preference for a context paired with a pain-relieving treatment (King *et al.*, 2009; Barthas *et al.*,

2015; Sellmeijer *et al.*, 2018), such as intrathecal or systemic administration of non-rewarding analgesic drug (Sufka, 1994; Navratilova *et al.*, 2013).

Another strategy is to consider the emotional component of pain through facial or vocal expression. The "grimace scale" of pain can actually be recognized and evaluated in rats (Sotocinal *et al.*, 2011) and mice (Langford *et al.*, 2010) exposed to acute or short-term pain. Unfortunately, as observed in chronic pain patients, this facial signature may not necessarily be present in chronic pain models (Langford *et al.*, 2010). The evaluation of pain through ultrasonic vocalizations has also been explored by some teams (Calvino *et al.*, 1996; Han *et al.*, 2005; Kurejova *et al.*, 2010), but the reliability of this parameter still remains low, limited to certain pain models and not necessarily relevant in a context of chronic pain (Jourdan *et al.*, 2002; Wallace *et al.*, 2005).

4. Evaluating anxiety-like and depression-like behaviours in animal models of chronic pain

4.1. Anxiety-like behaviours

4.1.1. Elevated plus maze

One of the most widely used test to assess anxiety-like behaviours in rodents is the elevated plus maze (EPM). It has been pharmacologically validated in rats (Pellow *et al.*, 1985) and in mice (Lister, 1987) using chlordiazepoxide, diazepam, phenobarbitone and yohimbine. The EPM apparatus consists in a cross composed of two open and two closed arms, joined by a common central platform (Narita *et al.*, 2006a). This apparatus is set 40 to 80 cm above the floor and the closed arms are enclosed by 15 to 40 cm walls depending on the considered species (Narita *et al.*, 2006a; Hasnie *et al.*, 2007b; Goncalves *et al.*, 2008; Roeska *et al.*, 2008). Animals are placed in the middle of the apparatus and let free to explore the maze. The number of entries as well as time spent in both closed and open arms is assessed over 5 to 15 minutes depending on the protocols (Narita *et al.*, 2006a; Ji *et al.*, 2018). Arm entry and exit are often considered when all four paws are into or out of a given arm. This paradigm induces a conflict between the innate exploratory behavior of the rodent and the fear generated by the open and heighten environment. Thus, a decrease in the amount of time spent in open arms is thought to reflect anxiety-like behaviour. To strengthen the aversion created by the open arms, it is possible to create a contrast in light setting between open and close arms. Thus, light intensity in closed arms may sometimes be below 10 lux while it can go up to 100 lux for the open arms. However, since very few studies indicate the light

intensity used in their paradigm it is difficult to conclude about the optimal light setting. Besides, analysis of the number of arm entries can be used as an indicator of the animal locomotion, a decrease in the number of arm entries suggesting a deficit in locomotion. This internal control is then very useful to make sure that the effect seen in the EPM arises from anxiety-like behaviour and not from motor impairment (Benbouzid *et al.*, 2008).

Concerning pain induced-anxiety, the majority of published studies using the EPM test succeeded in highlighting the presence of anxiety-like behaviours in both mouse and rat pain models (**Figure 2**). Indeed, a decreased time spent in the open arms of the EPM has been observed after 5 to 14 post-induction days in fibromyalgia models (Green *et al.*, 2011; Liu *et al.*, 2014; Wu *et al.*, 2017; Nazeri *et al.*, 2018) (see also **Table 3**) and within a few hours to one day (Fernandez-Guasti *et al.*, 2005; Ji *et al.*, 2007; do Nascimento & Leite-Panissi, 2014) in inflammatory models (**Table 2**). The anxiety-like behaviours observed in the EPM for rodents with inflammatory pain have also been shown to last up to 3-4 weeks post-pain induction (Narita *et al.*, 2006a; Narita *et al.*, 2006b; Parent *et al.*, 2012; Amorim *et al.*, 2014; Borges *et al.*, 2014; Wang *et al.*, 2015b). In traumatic neuropathic pain models, a decrease in the time spent in the open arms has mainly been observed after 3 to 4 weeks post-surgery (**Table 1**, **Figure 3**) (Narita *et al.*, 2006a; Narita *et al.*, 2006b; Benbouzid *et al.*, 2008; Matsuzawa-Yanagida *et al.*, 2008; Roeska *et al.*, 2009; Leite-Almeida *et al.*, 2012; Caspani *et al.*, 2014; Jiang *et al.*, 2014; Li *et al.*, 2014; Sawada *et al.*, 2014; Ji *et al.*, 2017; Wang *et al.*, 2017; Ferreira-Chamorro *et al.*, 2018; Chen *et al.*, 2019). This phenotype is usually still present at 8 weeks post-surgery (Suzuki *et al.*, 2007; Lyons *et al.*, 2015; Descalzi *et al.*, 2017; Sang *et al.*, 2018) or even at 19-24 post-operative weeks in the SNI model (Seminowicz *et al.*, 2009), but it can also start to recover at this time point in PSNL (Gonzalez-Sepulveda *et al.*, 2016). Some studies, however, failed to show the presence of anxiety-like behaviours, in some cases due to the time point chosen for the test. Indeed, anxiety-like behaviours related to peripheral neuropathic pain in this test tend to mostly develop around 3-4 weeks following induction of the chronic pain, so testing too early may sometimes explain the lack of anxiety-like behaviours in some studies (Kontinen *et al.*, 1999; Hasnie *et al.*, 2007b; Roeska *et al.*, 2008; Gregoire *et al.*, 2012; Pitzer *et al.*, 2019). Conversely, anxiety-related behaviours generally disappear after a certain delay, thus testing this component of chronic pain at a very late time points can be misleading (Goncalves *et al.*, 2008; Pitzer *et al.*, 2019). Moreover, it has been shown that the side of the nerve lesion might also impact the affective consequences of chronic pain. For instance, Leite-Almeida et al. showed that when SNI is performed on the left nerve, male Wistar-

Han rats displayed more pronounced anxiety-like profile than when SNI was performed on the right nerve (Leite-Almeida *et al.*, 2012). Finally, the repetition of the EPM procedure on the same animals can also effect the interpretation of results (Hubbard *et al.*, 2015). Indeed, the EPM has been depicted as sensitive to one-trial tolerance phenomenon, namely a decrease of time spent in open arms with the repetition of the test and independent of experimental groups (Tucker & McCabe, 2017).

4.1.2. Elevated zero maze

To avoid the one trial tolerance phenomenon, the elevated-zero maze (EZM) was developed and validated for anxiety assessment using diazepam and chlordiazepoxide treatments (Shepherd *et al.*, 1994). It consists of an elevated (40-70 cm above from floor) annular platform (5-10 cm wide; 46-120 cm diameter) with two opposite closed quadrants and two open quadrants (Urban *et al.*, 2011; Alba-Delgado *et al.*, 2016). Animals are placed in one of the enclosed quadrants and let free to explore the apparatus. As for the EPM, the number of entries and time spent in open quadrants are usually recorded during 5 minutes (Alba-Delgado *et al.*, 2016; Llorca-Torralba *et al.*, 2018; Martinez-Navarro *et al.*, 2019). Other parameters can also be considered like head dips or "stretch attend" postures if a finest assessment of anxiety-related behaviours is searched for (Alba-Delgado *et al.*, 2016; Alba-Delgado *et al.*, 2018). As for the EPM, the EZM produces a conflict between exploratory behaviour and fear induced by a bright (the light intensity is set between 40 and 100 lux) and open environment (Kulkarni *et al.*, 2007). Thereby, a decrease in the time spent in open quadrants suggests the development of anxiety-like behaviours.

Using this test, studies showed that neuropathic pain conditions, either caused by traumatic event (Alba-Delgado *et al.*, 2013; Dimitrov *et al.*, 2014; Alba-Delgado *et al.*, 2016; Alba-Delgado *et al.*, 2018; Llorca-Torralba *et al.*, 2018) or by streptozotocin-induced diabetes (Alba-Delgado *et al.*, 2016), can decrease the time spent in open quadrants at 4 to 6 weeks post-surgery, indicating the development of chronic pain-induced anxiety-like behaviours (**Table 1**, **Figure 3**). Interestingly, Martinez-Navarro and collaborators selected Swiss albino male mice based on their high or low anxiety trait at the beginning of the experiment, and demonstrated that animals expressing higher anxiety-like behaviours prior neuropathic pain induction developed anxiety-like behaviours at earlier time points (2 weeks) (Martinez-Navarro *et al.*, 2019). In CFA-induced inflammatory pain, anxiety-like behaviours were observed using the EZM one day after induction (Refsgaard *et al.*, 2016), while these behaviours were observed at week 41 in an osteoarthritis

model (Griffin *et al.*, 2010) (**Table 2**). However, Urban and collaborators couldn't observe anxiety-like behaviours using the EZM in the SNI, CCI and CFA models (Urban *et al.*, 2011). For the CFA model, the late time point used in this study, 33 days post-induction (against 1 to 10 days for other studies), could explain the lack of effect in EZM. Indeed, conversely to Urban and collaborators, other studies assessing anxiety-like behaviours (with either the EPM or the EZM) in CFA-induced inflammation never tested it after 4 post-induction weeks (Chen *et al.*, 2013; do Nascimento & Leite-Panissi, 2014; Refsgaard *et al.*, 2016). Regarding the results obtained in the SNI and CCI models, the authors suggest that the absence of effect could arise from the protocol used in their study (Urban *et al.*, 2011).

4.1.3. Open field

Anxiety-related behaviours can also be assessed with the open field test (OF). The OF consists in a square arena (40x40x30 cm: mice, 100x100x60 cm: rats), lighted with dim to bright light (4-580 lux) (Wallace *et al.*, 2007b; Zhu *et al.*, 2017). Animals are placed in the centre of the OF (Hasnie *et al.*, 2007a) or facing one wall of the arena (Zhu *et al.*, 2017) and let free to explore the test. The time spent as well as the number of entries in the centre of the arena (area located 10 cm (mice) or 40 cm (rats) to the walls) are measured during 5 to 15 minutes. Again, this paradigm creates a conflict between the innate exploratory behaviour and the fear generated by an open and bright area. Administration of anxiolytic drugs such as diazepam or chlordiazepoxide was shown to elicit an increase in time spent and entries in the center area (Choleris *et al.*, 2001).

When conducted in an inflammatory pain model, a decrease in time spent in the centre of the OF is observed from one to 28 post-induction days (Kim *et al.*, 2012; Parent *et al.*, 2012; Chen *et al.*, 2013; Amorim *et al.*, 2014; Gregoire *et al.*, 2014; Guo *et al.*, 2016; Sun *et al.*, 2016; Tian *et al.*, 2017; Yue *et al.*, 2018) (**Table 2**). Liu and collaborators tested anxiety-like behaviours in the acid-induced hyperalgesia model of fibromyalgia and observed an effect 13 days after induction (Liu *et al.*, 2014) (**Table 3**). Regarding models of neuropathic pain, OF results are quite heterogeneous (**Table 1**, **Figure 2**). Indeed, over 39 published studies, 25 showed decreased time spent in the centre of the OF at time points mainly between 2 and 8 weeks after pain induction; while the other 14 studies failed to find any effect in this test (**Figure 3**). A main explanation for these discrepancies could again arise from the time point used to assess anxiety-related behaviours. Indeed, some studies (Kontinen *et al.*, 1999; Norman *et al.*, 2010; Kodama *et al.*, 2011) only tested animals at early or very late stage of chronic pain (Goncalves *et al.*, 2008)

although it is known that the temporality of the development of affective consequences of chronic pain is a critical parameter (Yalcin *et al.*, 2011). The choice of the neuropathic model has also an impact on results obtained in OF. For instance, in spinal cord injury models either no differences or cohort-dependent effect was observed (Galan-Arriero *et al.*, 2014; Maldonado-Bouchard *et al.*, 2016; Boadas-Vaello *et al.*, 2018). Also, in the PSNL model (**Figure 1**), near 50% of the studies didn't report change in OF (Hasnie *et al.*, 2007a; Hasnie *et al.*, 2007b; Kodama *et al.*, 2011). The reason why huge variability is frequently observed with this test can also be due to the protocol parameters, such as light setting (from 4 to more than 100 lux), test duration (4 to 60 min), area size, definition of the central zone etc. Indeed, over the 18 studies for which light parameters are provided in methods, 10 out of the 14 studies conducted with a light intensity set at 60 lux or less succeeded in demonstrating pain-induced anxiety-like behaviours (Hasnie *et al.*, 2007a; Suzuki *et al.*, 2007; Wallace *et al.*, 2007a; Wallace *et al.*, 2007b; Wallace *et al.*, 2007c; Avila-Martin *et al.*, 2015; Galan-Arriero *et al.*, 2015; Missig *et al.*, 2017; Zhang *et al.*, 2017; Gong *et al.*, 2018), while the 4 studies using an intensity equal or higher than 100 lux failed (Kontinen *et al.*, 1999; Kodama *et al.*, 2011; Urban *et al.*, 2011; Chen *et al.*, 2018). These data suggest that too high light intensity might induce anxiety strong enough in controls to mask the difference between experimental groups, and that milder light setting should perhaps be preferred for better discrimination between groups. Finally, it has been shown that even when the test conditions are strictly controlled, a strong variability between different laboratories can still be present (Robinson *et al.*, 2018). Regarding these results, it seems that the OF should not be the only test used to assess anxiety in pain condition, and indeed several groups rather employ a battery of behavioural tests to depict rodent emotional state (Suzuki *et al.*, 2007; Leite-Almeida *et al.*, 2009; Wang *et al.*, 2015b; Descalzi *et al.*, 2017) and often use the OF as a marker of locomotor activity rather than an anxiety test (Goncalves *et al.*, 2008; Lyons *et al.*, 2015; Wu *et al.*, 2016; Pan *et al.*, 2018).

4.1.4. Light/dark box test

Another test aiming at assessing anxiety-like behaviour is the light/dark box test (LDB) developed by Crawley and Goodwin who also showed the sensitivity of this test to benzodiazepines (Crawley & Goodwin, 1980). Several other groups reproduced the results obtained by Crawley and Goodwin with various benzodiazepines, as well as with drugs acting on the serotonergic neurotransmission system (for an extensive review see (Bourin & Hascoet, 2003)). The LDB is formed by two communicating chambers, one dimly lit with black walls and one brightly lit (100-

500 lux) with white (Narita *et al.*, 2006a) or transparent (Gambeta *et al.*, 2018) walls. Animals are placed in the dark compartment and let free to explore the apparatus for 5-10 minutes. Entries and time spent in the light box are recorded, and latency to enter in the light box and rearing can also be considered among parameters (Lyons *et al.*, 2015). Since the bright compartment represents an aversive environment for rodents, a decrease in the time spent/or number of entries in this zone is defined as an anxiety-like behaviour.

As for the previously described tests, when LDB is performed in neuropathic pain models anxiety-like behaviours can be observed 4 (Narita *et al.*, 2006a; Narita *et al.*, 2006b; Matsuzawa-Yanagida *et al.*, 2008; Yalcin *et al.*, 2011; Chen *et al.*, 2013; Sieberg *et al.*, 2018; Guimaraes *et al.*, 2019) to 8 weeks post-surgery (Suzuki *et al.*, 2007; Yalcin *et al.*, 2011; Lyons *et al.*, 2015; Barthas *et al.*, 2017; Lyons *et al.*, 2018; Sellmeijer *et al.*, 2018), except for the SCI model in which no decrease in time spent in light box was detected (Boadas-Vaello *et al.*, 2018) (**Table 1**, **Figure 2 & 3**). Three studies also demonstrated a decrease in the time spent in the light box already detectable at 2 weeks after neuropathic pain induction (Mutso *et al.*, 2012; Gambeta *et al.*, 2018; Chen *et al.*, 2019). Again difficulties to show anxiety-like behaviours can generally be explained by the testing time point being too early (Kontinen *et al.*, 1999; Pitzer *et al.*, 2019) or too late (Pitzer *et al.*, 2019). When done in inflammatory condition, anxiety-like behaviour was observed in the LDB from 1 day to 28 days after induction (Narita *et al.*, 2006a; Narita *et al.*, 2006b; Parent *et al.*, 2012; do Nascimento & Leite-Panissi, 2014; Omorogbe *et al.*, 2018) (**Table 2**).

4.1.5. Social interaction

The social interaction test (SI) was first developed to enable a measure of anxiety based on ethological behaviours and to replace tests including electric shock or food deprivation used so far (File & Seth, 2003). This test was shown to be sensitive to anxiogenic (yohimbine, benzodiazepine receptor antagonists, picrotoxin) and anxiolytic drugs (lorazepam, diazepam, buspirone), as well as to stress-related hormones like the corticotropin-releasing factor and the adrenocorticotropic hormone (File & Seth, 2003). Originally, animals were isolated for several days prior to testing, but recent studies only used an isolation of 5 to 120 minutes (Gregoire *et al.*, 2012; Hisaoka-Nakashima *et al.*, 2019). After this isolation period, a juvenile congener is introduced in the cage and the amount of time spent in interaction (sniffing, following, grooming, licking) is recorded during 5 min (Hisaoka-Nakashima *et al.*, 2019). For a more global recording of rodent social spontaneous behaviours, Benbouzid and collaborators did a video monitoring in home cage during

6 hours (Benbouzid *et al.*, 2008). In this case the SI was performed with littermates instead of a juvenile congener.

The number of studies using the SI as a measure of anxiety-like behaviours in pain conditions is quite limited. Yet, when conducted in neuropathic pain models, a decrease in SI has been observed at 4 (Benbouzid *et al.*, 2008) and 6 (Hisaoka-Nakashima *et al.*, 2019) weeks post-surgery (**Table 1, Figure 4**). The studies conducted by Maldonado-Bouchard (Maldonado-Bouchard *et al.*, 2016) or Gregoire (Gregoire *et al.*, 2012) only tested animals before 3 weeks post-surgery, which might explain the absence of decrease in SI (**Table 1, Figure 4**). Indeed, the work conducted by Benbouzid and collaborators even report an increase in time dedicated to social contact at 2 post-operative weeks (Benbouzid *et al.*, 2008). Regarding the sole study conducted in an inflammatory model (Gregoire *et al.*, 2014), a decrease in SI was observed 2-3 weeks after CFA injection.

4.1.6. Marble burying test

Originally used to assess anxiety-like behaviours because of its sensitivity to anxiolytic drugs such as diazepam or buspirone (Njung'e & Handley, 1991), the marble burying test (MB) is now thought to also be a potential test for the detection of compulsive behaviours (Thomas *et al.*, 2009; Angoa-Perez *et al.*, 2013). MB is performed in cages (same dimension as the home cages) containing 3-5 cm of fine sawdust. Twelve to 25 glass marbles (1 cm diameter) are evenly spaced on top of the sawdust. Animals are placed individually into the cages and left undisturbed for 15-30 min. After this period animals are removed, and buried marbles are counted. Marbles are considered buried if two thirds or more of their surface is covered by sawdust. The number of buried marbles is considered as a measure of animal anxiety and/or compulsive behaviour (Jimenez-Gomez *et al.*, 2011).

When used in neuropathic pain models, the MB highlights compulsive/anxiety-like behaviours at time-points between 28 to 46 days post-surgery (Benbouzid *et al.*, 2008; Yalcin *et al.*, 2011; Guida *et al.*, 2015; Aguilar-Avila *et al.*, 2019) (**Table 1, Figure 4**). According to D'Aniello and collaborators, the changes seen in burying behaviours, at least in the SNI model, can last up to 1 year (D'Aniello *et al.*, 2017) (**Table 1, Figure 4**). In an inflammatory pain model induced by intraplantar CFA injection, the increase in buried marbles occurred within 5 weeks post CFA injection (Urban *et al.*, 2011).

4.1.7. Hole-board test

While the hole-board test (HB) can also give an insight into anxiety-like behaviours, it is less commonly used in the study of pain and mood disorder comorbidity. The HB device consists of a square plate (around 40x40 cm dimension) surrounded by walls and containing 9 (Sieberg *et al.*, 2018) or 16 holes (Montserrat-de la Paz *et al.*, 2015), around 3 cm diameter each, equally spaced on 3 to 4 rows. Animals are placed in the periphery (Sieberg *et al.*, 2018) or in the centre (Montserrat-de la Paz *et al.*, 2015) of the arena, and let free to explore the apparatus for 5 to 15 minutes (Montserrat-de la Paz *et al.*, 2015; Sieberg *et al.*, 2018). The number of nose-pokes, recorded by infrared photocells in the hole, is used as a measure of anxiety-like behavior since diazepam or chlordiazepoxide administration increase nosepoke numbers while anxiogenic compounds (FG7142, beta-CCM; inverse agonists of the benzodiazepine site of GABAa receptors) decrease it (Takeda *et al.*, 1998). A decrease in the number of nose-pokes then reflects anxiogenic condition. Besides, the time spent in the centre of the HB is also recorded as a measure of anxiety (like in the OF), and the total distance travelled is an indicator of locomotor activity and thus serves as an internal control for motor function (Sieberg *et al.*, 2018).

In a neuropathic pain model, a decrease in nose-poke activity has been observed at 4-6 post-operative weeks (Sieberg *et al.*, 2018). In a fibromyalgia model, this effect is already present at 3 post-induction days (Montserrat-de la Paz *et al.*, 2015).

4.1.8. Burrowing test

This test was first introduced by Deacon and collaborators in 2001, and relies on the natural burrowing behaviour of rodents (Deacon *et al.*, 2001; Deacon, 2012). The burrowing test (BT) was proposed as a measurement of laboratory animals well-being since burrowing deficit are among the first behaviours to be detectable when rodents undergo stressful condition (Jirkof, 2014). The testing takes place in new cages similar to animal's home cages. Hollow plastic tubes (32 cm long, 10 cm diameter for rats) sealed at one end and opened at the other end, are filled with gravel and disposed 6 cm above the ground to avoid loss of gravel (Andrews *et al.*, 2012; Huang *et al.*, 2013). Test sessions are usually 2 hours long and latency to start burrowing and the amount of gravel displaced are recorded. In the BT, an increase in latency to burrow and a decreased amount of material displaced suggests the development of anxiety-like behaviours. Interestingly BT can be repeated on the same animals over time and thus gives the opportunity to conduct longitudinal studies. Note that several other protocols exist for burrowing assessment in rodent, and notably some using food pellet instead of gravel (for a review see (Jirkof, 2014)).

In a model of inflammatory pain, burrowing behaviour deficits were seen at 10 post-induction days (Andrews *et al.*, 2012). Regarding neuropathic pain models, a decrease in burrowing has been observed at 10 post-operative days in SNL and PSNL (Andrews *et al.*, 2012) and between 21 (Huang *et al.*, 2013) and 77 days (Andrews *et al.*, 2012) in TNT (**Table 1, Figure 4**). Notably, a standardization of the procedure and a comparison across laboratories have been recently done (Muralidharan *et al.*, 2016; Wodarski *et al.*, 2016), making this test particularly interesting and reinforcing its validity for studying pain-related deficits.

4.2. Depression-like behaviours

4.2.1. Novelty-suppressed feeding test

The novelty-suppressed feeding (NSF) test can be used to assess both anxiety- and depressive-like behaviours, as demonstrated by its sensitivity to both anxiolytic (lorazepam, buspirone) and antidepressant drugs (imipramine, fluoxetine, amitriptyline) (Dulawa & Hen, 2005). The NSF consists in a 40x40x30 cm plastic box with the floor covered with 2 cm of sawdust. Animals are usually food-restricted for twenty-four hours prior to the test. At the time of testing, a single pellet of food is placed on a paper in the centre of the box. An animal is then placed facing a corner of the box and the latency to first contact and onset of eating the pellet is recorded within a 5 minutes period. This test induces a conflict between the drive to eat the pellet and the fear of venturing in the centre of the box. The increase in the latency to eat suggests anxiodepressive-like behaviours.

In each neuropathic pain model used so far, an increase in the latency to feed has been observed, mainly between 2 to 9 weeks post-surgery (Yalcin *et al.*, 2011; Mutso *et al.*, 2012; Barthas *et al.*, 2015; Barthas *et al.*, 2017; Jiang *et al.*, 2018; Poupon *et al.*, 2018; Sellmeijer *et al.*, 2018; Hisaoka-Nakashima *et al.*, 2019; Jiang *et al.*, 2019) (**Table 1, Figure 5 & 6**). In a model of chemotherapy-induced neuropathy, Hache and collaborators showed an earlier onset of anxiodepressive-like behaviours compared to traumatic models (Hache *et al.*, 2015) (**Table 1, Figure 5 & 6**). In the biogenic amine depletion model of fibromyalgia, an increase in the latency to feed was seen 4 to 5 post-induction days (Blasco-Serra *et al.*, 2015).

4.2.2. Forced swim test

A more common test to assess depressive-like behaviours in rodents is the forced swim test (FST), initially developed by Porsolt and collaborators in rats (Porsolt *et al.*, 1977b) and mice (Porsolt *et al.*, 1977a) in order to rapidly screen antidepressant drugs. Indeed, it was shown that immobility in

the FST was decreased by tricyclic antidepressants, such as imipramine or amitriptyline (Porsolt *et al.*, 1977b). From this initial validation and use as a simple drug-screening test, the FST has since been more widely used to also study depressive-like behaviours. In rats, a pre-test phase is required. Animals are gently lowered in an inescapable cylinder (height 50 cm, diameter 20 cm) containing 30 cm of water (23-25°C) for 15 minutes. The following day the rat is placed once again in the same apparatus and the duration of immobility phase is scored during 5 minutes (Alba-Delgado *et al.*, 2013). For mice, there is no need to expose them to the pre-test, so animals are directly lowered into an inescapable cylinder (height 20-46 cm, diameter 10-25 cm) containing 14-20 cm of water (21-25°C) (Dimitrov *et al.*, 2014; Gai *et al.*, 2014; Descalzi *et al.*, 2017; Yang *et al.*, 2019a). Here the test duration is 6 minutes, and since little immobility is generally observed during the first 2 minutes, the duration of immobility is quantified over the last 4 minutes of the 6 minutes test (Yalcin *et al.*, 2011). The animals are considered immobile when they float in the water, in an upright position, and made only small movements to keep their head above water. In this paradigm, the impossibility to escape an aversive situation creates a despair state in the animals, reflected by immobility time, thus an increase in immobility time is considered as a depressive-like behaviour. Besides immobility time, differentiating active behaviours between climbing, defined as forepaw vigorous upward movements in and out of the water, and swimming can also be recorded (Hu *et al.*, 2009; Alba-Delgado *et al.*, 2013). This distinction will then allow a finest assessment of despair behaviour since it has been shown that climbing behaviour was increased by norepinephrine-targeting antidepressant drugs, while swimming was modified by serotonin-targeted antidepressant drugs (Detke & Lucki, 1996).

For most of the studies using FST to assess neuropathic pain-induced depression, an increased immobility time was observed at 4 weeks (Hu *et al.*, 2010; Gai *et al.*, 2014; Bruning *et al.*, 2015; Wang *et al.*, 2015b; Chung *et al.*, 2017; Wang *et al.*, 2017; Poupon *et al.*, 2018) and 8 weeks (Suzuki *et al.*, 2007; Goncalves *et al.*, 2008; Descalzi *et al.*, 2017; Boadas-Vaello *et al.*, 2018; Hisaoka-Nakashima *et al.*, 2019) post-surgery (**Table 1, Figure 5 & 6**). Interestingly, in the SNI and CCI models a shift to an earlier development of depressive-like behaviours can be observed. Indeed, over the 15 studies reporting an increase in immobility time in CCI, 8 showed it at or even before 2 weeks post-surgery (Fukuhara *et al.*, 2012; Li *et al.*, 2014; Garg *et al.*, 2017; Li *et al.*, 2019) (see also **Table 1, Figure 5 & 6**). For the SNI, among the 17 studies presenting depressive-like behaviour, 11 observed the development of deficits in active behaviour in this test before 2 weeks post-surgery (Stratinaki *et al.*, 2013; Zhou *et al.*, 2015; Laumet *et al.*, 2017; Xu *et*

al., 2017; Pan *et al.*, 2018; Yang *et al.*, 2019b) (see also **Table 1, Figure 5 & 6**). This timing could however be related to the severity of the model(s), and the fact that pain related to paw might by itself also affect motor (swimming) capacity, thus interfering with FST. In the CCI model, fluctuation in the time-dependency of depressive-like behaviours could also be explained by the inter-individual variability in pain induction that may be present in this model. Similarly, in a chemotherapy-induced neuropathy an early onset of depressive-like behaviour has been reported (Redivo *et al.*, 2016; Toma *et al.*, 2017). Regarding inflammatory pain models, increased immobility time in FST has been detected between 7 and 35 post-induction days in CFA injected animals (Urban *et al.*, 2011; Kim *et al.*, 2012; Maciel *et al.*, 2013; Borges *et al.*, 2014; Le *et al.*, 2014; Hamann *et al.*, 2016; Zhang *et al.*, 2016) and at 4 post-induction weeks in kaolin/carrageenan injected animals (Amorim *et al.*, 2014). Finally, when conducted in an acid injection-induced model of fibromyalgia, a decrease in immobility time was observed after 19-20 post-operative days (Liu *et al.*, 2014), after 10-14 days in an intermittent cold stress model (Nasu *et al.*, 2019), and within few days in biogenic amine depletion models (Nagakura *et al.*, 2009; Arora & Chopra, 2013; de Souza *et al.*, 2014; Klein *et al.*, 2014; Siemian *et al.*, 2019).

4.2.3. Tail-suspension test

A variant of the FST, also developed for antidepressant drug screening (Steru *et al.*, 1985) and based on behavioural despair, is the tail suspension test (TST) in mice. It is sensitive to desipramine and amitriptyline (Steru *et al.*, 1985). In TST, mice are suspended by the tail from a bar, 50 cm above the floor using an adhesive tape (1-2 cm from the proximal tail tip) (D'Aniello *et al.*, 2017; Jiang *et al.*, 2018). The test duration is 6 minutes and the immobility is measured during the whole test. Mice are considered as immobile when they hung down motionless (Gai *et al.*, 2014). An increase immobility time is thought to represent depressive-like behaviour.

As for the FST, when the TST is used in CCI or SNI an early development of depressive-like behaviour (around 1 to 2 weeks) is observed (Zhao *et al.*, 2014a; Zhao *et al.*, 2014b; Jiang *et al.*, 2018; Yang *et al.*, 2019a). Similar results were found when using a chemotherapy-induced neuropathic pain model (Hache *et al.*, 2015). For other neuropathic pain models, increased in immobility time was observed between 4 weeks and 2 months (Gai *et al.*, 2014; Wu *et al.*, 2014; Guida *et al.*, 2015; Ferreira-Chamorro *et al.*, 2018; Aguilar-Avila *et al.*, 2019; Zhang *et al.*, 2019) (**Table 1, Figure 5 & 6**). For inflammatory pain models, depressive-like behaviours have been highlighted by the TST 7 to 14 days after CFA injection (Kim *et al.*, 2012; Maciel *et al.*, 2013;

Omorogbe *et al.*, 2018) and at 41 weeks in an osteoarthritis model (Griffin *et al.*, 2010). Finally, in a fibromyalgia model, an increase in immobility time was observed within 3 post-induction days (Klein *et al.*, 2014).

4.2.4. Sucrose preference test

The sucrose or saccharine preference test (SPT) was first described by Katz in 1982 (Katz, 1982), and pharmacologically validated five years later by Willner and collaborators using the tricyclic antidepressant desipramine (Willner *et al.*, 1987). The purpose of this test is to assess in animals the decrease ability to feel pleasure, also called anhedonia, often reported in patients suffering from depression. Animals are individually housed for the duration of the test and are free to choose between water and sweet solution. An index of sweet solution preference is then calculated as the ratio of the sweet solution intake over total liquid intake. A decrease in this index suggests depressive-like behaviour (Dellarole *et al.*, 2014; Xie *et al.*, 2017). Today, a multitude of protocols are used to assess anhedonia in rodents. The sweet solution is mainly obtained using sucrose at a concentration varying from 0.5% (Gambeta *et al.*, 2018) to 20% (Liu *et al.*, 2014), but concentrations of 1% or 2% are the most used (Bura *et al.*, 2013; Wang *et al.*, 2015b; La Porta *et al.*, 2016; Zhu *et al.*, 2017; Martinez-Navarro *et al.*, 2019). To avoid a potential bias due to sucrose caloric value, it can be replaced by saccharine; the concentrations used are then comprised between 0.25 and 0.3% (Wu *et al.*, 2014; Refsgaard *et al.*, 2016). Usually, a period of habituation is required prior testing. During this period, from 2 h (Zong *et al.*, 2018) to 10 days (Wang *et al.*, 2011), the bottles of water and sweet solution are often interchanged to prevent any side preference. Before the test session, a water deprivation is sometimes done with a duration varying between 2 (Bura *et al.*, 2013) to 24 hours (Yang *et al.*, 2019a). Finally, when considering the test duration, it varies from 15 minutes (Liu *et al.*, 2014; Ji *et al.*, 2017) to 48 hours (Urban *et al.*, 2011; Wu *et al.*, 2014), but test sessions of 24 hours were the most commonly used (La Porta *et al.*, 2016; Li *et al.*, 2017; Xie *et al.*, 2017; Gong *et al.*, 2018; Pan *et al.*, 2018; Wu *et al.*, 2018; Martinez-Navarro *et al.*, 2019).

Despite all these protocol variations, the majority of reported studies could asses a presence of anhedonia between one week (Goffer *et al.*, 2013; Xu *et al.*, 2017; Zhu *et al.*, 2017; Wu *et al.*, 2018; Fang *et al.*, 2019b; Martinez-Navarro *et al.*, 2019) to 10-11 weeks (Wu *et al.*, 2014; Fu *et al.*, 2018; Thompson *et al.*, 2018; Fang *et al.*, 2019a) after neuropathic pain induction (see also **Figure 5 & 6** and **Table 1**). However, this time window depends on the considered model.

Regarding the CCI model, anhedonia tends to arise at 4 post-surgery weeks (Dellarole *et al.*, 2014; Li *et al.*, 2017; Wang *et al.*, 2019). Thus the lack of such behavioural deficit in the Gregoire and collaborator study could result from the fact that the test was performed at an earlier time point (Gregoire *et al.*, 2012). Furthermore, two studies conducted in the SNI model showed the presence of individual differences (in pro-inflammatory cytokines or in gut microbiota) between animals that are resilient or sensitive to chronic pain induced-depression (Xie *et al.*, 2017; Yang *et al.*, 2019a). These inter-individual differences might explain that effect in the SPT is sometimes cohort-dependant. In inflammatory pain models, a decrease in sucrose consumption was observed at 2 days post-induction (Refsgaard *et al.*, 2016) and lasted at least for 4 weeks (Amorim *et al.*, 2014). Finally, in a fibromyalgia model, Liu and collaborators observed anhedonia-like behaviour at 19-20 post-induction days (Liu *et al.*, 2014).

4.2.5. Nesting test

Nesting is an innate behaviour in rodents, which allows them to shelter from environment, maintain a certain heat and reproduce (Jirkof, 2014). As for the burrowing test described before, a deficit in nesting is an early sign of decreased well-being that can be rescued with chronic fluoxetine treatment (Farooq *et al.*, 2018). In the study of Toma and collaborators, mice were individually housed with all the previous nesting material removed from the cage and placed in a dark room for an acclimation period of 30 minutes. Then, a compressed cotton nestlet was weighted and cut into 6 pieces placed on the top of the wire cage lid, evenly spaced. After 120 minutes the nestlet pieces remaining on the cage lid were weighted and a score given to the nest constructed. A score of 0 was given if no nest was formed, a score of 1 if the mice build a partial nest and a score of 2 if the nest was completely constructed. A poor nest score and a high amount of remaining nestlet on the cage lid are thought to indicate depressive-like behaviours. With this nesting protocol, no nesting deficit was found in a paclitaxel-induced neuropathic pain model (Toma *et al.*, 2017).

If one wants to assess the nesting behaviour more precisely, other protocols have been used in mood disorder-related studies (see (Jirkof, 2014) for a review); the most common protocol being the one described by Deacon in 2003, with a score from 0 (no nest formed) to 4 (established nest). This protocol also takes into account the shape of the nest (flat or dome shaped), the position in the cage (in the centre or at a corner) and is performed overnight (Deacon, 2006a; Deacon, 2012). When using the nest test to assess depressive-like behaviour it is essential to make sure that

the chosen protocol fits with the strain and sex of the animals used in the study. Indeed, differences in nest quality have been reported between males and females and between mice strains (Gaskill *et al.*, 2012) or even between sub-strains (Sluyter *et al.*, 1999).

4.2.6. Splash Test

The splash test (ST) is based on grooming, which is an important aspect of rodent behaviour and is often altered in animal models of depression (Santarelli *et al.*, 2003; Yalcin *et al.*, 2011). Animals are placed in a new cage with 1 cm of sawdust and a solution of 10% sucrose is sprayed on their back. The time spent for grooming as well as the grooming location (head or body) are measured for 5 minutes. A grooming deficit in this test is thought to be related to the loss of interest in performing self-oriented minor tasks, thus indicating the development of depressive-like behaviours. Moreover, the administration of antidepressant drugs, such as imipramine, desipramine, fluoxetine or maprotiline, rescued the grooming deficits in the unpredictable chronic mild stress mouse model of depression (Yalcin *et al.*, 2008). When studied in a neuropathic pain model, more particularly in the cuff model, grooming deficits were reported between 6 and 9 post-operative weeks (Yalcin *et al.*, 2011; Barthas *et al.*, 2015; Sellmeijer *et al.*, 2018) (**Table 1, Figure 5 & 6**). Interestingly, Sellmeijer and collaborators studied the long term effect of neuropathic pain on affective behaviours and found that grooming deficits were still present at 14 post-operative weeks but no more at 16 weeks. In this study the extinction of depressive-like behaviours seemed to follow the recovery of ongoing pain.

5. Discussion

For this review, we found and analysed 144 articles related to the study of anxiodepressive-like disorders induced by chronic pain. The first articles on the topic were published shortly before the 2000s, but there has been a sharp increase in the number of scientific publications in the recent years, pointing out the growing interest in the comorbidity between pain and anxiety and depression. While most published studies demonstrated the possibility to model anxiodepressive-like consequences of chronic pain in animals (and potentially highlighted the essential role of time in the development of these symptoms), contradictory results can still be observed. Beside the time factor, these differences between studies may be due to the chosen animal models and tests, as well as to the protocols used to perform the tests. Rather than relying on a single parameter in animal models, it may thus be important to prefer strategies that would include behavioural

profiling based on performing several tests evaluating anxiety and depression (Yalcin *et al.*, 2011; Sellmeijer *et al.*, 2018). In this respect, choosing the appropriate tests and control condition is one of the critical steps to assess the affective consequences of chronic pain. For example, most of the tests measuring anxiety and depression in rodent depend on motor activity of animals (exploration of a novel environment, swimming), which might be altered by pain models and lead to bias in interpreting the results. It is thus critical to take into consideration the limit of each test. For instance FST is one of the most common paradigm used to detect depressive-like behaviours, despite the fact that besides antidepressants most psychostimulants could also decrease the immobility time (Bogdanova *et al.*, 2013). Similarly when using the NSF, nesting, burrowing and marble burying tests, it should be kept in mind that these tests can in fact reflect various behavioural alterations at the same time, such as anxiety- or depressive-like behaviours for NSF (Dulawa & Hen, 2005), as well as obsessive compulsive- and autism-like behaviours for marble burying (Deacon, 2006b; Angoa-Perez *et al.*, 2013). Furthermore, the experimenter should be careful with the order of tests when using several tests on the same animals. Indeed, some tests are anxiogenic *per se*, like the FST or TST, and should preferably be performed at the end of the experiments to avoid risks of interactions with other tests. In addition, tests based on the fear generated by novelty can often only be done once (EPM, NSF, EZM). On the other hand, tests based on ethologically relevant rodent behaviours, such as grooming, nesting or burrowing assessment, are potentially less anxiogenic. These tests, together with social interaction and the sucrose preference test, have the advantage to be repeatable and thus useful for a longitudinal follow-up of the animals (Thomas *et al.*, 2009; Kaidanovich-Beilin *et al.*, 2011). For chronic pain studies, such longitudinal testing strategy allows evaluating emotional state before pain induction and at various time points afterwards, thus using the animal as its own control. However, the development of new devices, such as PhenoWorld, can reinforce the possibility of testing animals in their habitual environment in automatic fashion, with limited interaction with the experimenter and on long term periods (Castelhano-Carlos *et al.*, 2014). In addition, apparatuses combining multiple tests (EPM, LDB and OF) in one testing paradigm (Ramos, 2008) can also be a good alternative.

In this issue, we aimed at describing anxiodepressive tests that are already used for studying the comorbidity of chronic pain and mood disorders, but it is worth to mention that other paradigms such as intracranial self-stimulation (ICSS), sexual behaviours, electroencephalography or

circadian rhythm analysis (Castagne *et al.*, 2009) can also be used to address motivation, anhedonia and sleep pattern which are frequently altered in chronic pain.

The diversity of tests has already enable notable breakthrough in the understanding of mood disorders and chronic pain comorbidity in animal models. However, in order to homogenize and increase the reproducibility of results, it is critical that the description of the parameters used for the testing is detailed in articles' methods. Indeed, important information such as handling and housing conditions or habituation to the testing room are often missing and thus prevent to conclude on the best practices to adopt. For example, as already mentioned previously light setting in tests like OF, EPM, or EZM are rarely specified although the use of a too bright light can induces anxiety-like behaviours even in control animals. Indeed, creating more relevant procedures and standardization of some of the most variable procedures (such as OF and SPT) among laboratories would be of great interest for the field. NIMH proposed a Research Domain Criteria system (RDoC) defining the good practices when evaluating psychopathologies in animal models that might be of great use for achieving this goal (Anderzhanova *et al.*, 2017). Moreover, an effort is still needed in developing new methods to measure pain that are not based on nociceptive reflex response. Indeed, no study so far could show a correlation between the degree of nociceptive hypersensitivity and the anxiodepressive-like consequences. Thus, animals with or without anxiety- and/or depression-like phenotype can show similar mechanical or thermal withdrawal thresholds in animal models of pain (Gui *et al.*, 2016; Xie *et al.*, 2017; Yang *et al.*, 2019a). Conversely, a recent study showed that rats that do not develop mechanical allodynia after SNI can still develop anxiodepressive-like behaviours similarly to painful rats (Guimaraes *et al.*, 2019). There is thus no correlation in rodent models of chronic pain between the nociceptive response and the development of anxiodepressive disorders, which is similar to clinical reports (Dickens *et al.*, 2002; Jensen *et al.*, 2010; Keltner *et al.*, 2012; Bagnato *et al.*, 2015).

The above results may apparently question the causality relation between pain and emotional/cognitive disturbances. However, a causal link between pain and anxiodepressive consequences should not necessarily imply direct correlation between the intensity of nociceptive and anxiodepressive symptoms. Some observations suggest a temporal dissociation and partly independent mechanisms between these aspects of chronic pain (Zhou *et al.*, 2015; Gui *et al.*, 2016; Guimaraes *et al.*, 2019). As example, in a model of sciatic nerve compression, mechanical hypersensitivity is no longer present 2 to 3 months after the surgery, while anxiodepressive-like behaviours can persist after the recovery of hypersensivity (Dimitrov *et al.*, 2014; Sellmeijer *et al.*,

2018). Interestingly, one of these studies showed that ongoing pain can also persist beyond the recovery of nociceptive hypersensitivity (Sellmeijer *et al.*, 2018), suggesting that reflex responses might not always be the best marker of pain.

Another limitation in the field relates to the fact that most published data used trauma models of neuropathic pain. While the cause of neuropathic pain is peripheral in a large set of patients, recent studies on anxiodepressive consequences of pain showed the potential involvement of distinct mechanisms with different neuropathic pain aetiologies, *i.e.* diabetic *vs.* trauma (Alba-Delgado *et al.*, 2016). For mechanistic aspects, it will thus be necessary to study these comorbidities in the context of the considered aetiologies, and in particular distinguish neuropathy, inflammation and fibromyalgia; and within neuropathic pain also consider metabolic diseases or neurotoxicity beyond the mostly used lesion models. Indeed, only three preclinical articles so far focused on the anxiodepressive-like aspects in chemotherapy-induced murine models of neuropathic pain (Hache *et al.*, 2015; Toma *et al.*, 2017; Poupon *et al.*, 2018). Similarly, models mimicking neuropathic pain following viral infection (HIV or varicella zoster virus) have been poorly studied in regard to anxiodepressive-like symptoms. The study of central neuropathic pain also requires improvements. Indeed, preclinical studies using spinal cord injury either failed in showing anxiodepressive phenotype or reported a lack of reproducibility, whereas the comorbidity is clinically well established (Haythornthwaite & Benrud-Larson, 2000; Attal *et al.*, 2011; Lim *et al.*, 2017). Studies testing similar mechanistic hypotheses in models relying on different aetiologies would likely be important in the field in order to identify shared mechanistic features (which may illustrate core or converging mechanisms of anxiety or of depression) and distinct mechanistic features (which may be relevant to individualised medicine).

Despite their imperfections, animal models have proved to be useful in dissecting the mechanisms underlying the comorbidity between chronic pain and mood disorders. Thus, the involvement of several brain structures, such as the prefrontal cortex (PFC) including the anterior cingulate cortex, the hippocampus, the amygdala, the nucleus accumbens (NAc), the lateral habenula, the ventral tegmental area, or the locus coeruleus (LC) has been shown (Yalcin *et al.*, 2014; Doan *et al.*, 2015; Humo *et al.*, 2019). Not only morphological, structural and functional modifications have been observed in these brain structures, but the implication of several neurotransmitter systems was also identified. For example, there is an increase in glutamatergic transmission in PFC, NAc, LC and amygdala (Goffer *et al.*, 2013; Gonzalez-Sepulveda *et al.*, 2016; Llorca-Torralba *et al.*, 2018; Martinez-Navarro *et al.*, 2019) leading to hyperactivities in

these brain structures. Besides the glutamatergic system, the implication of the endocannabinoid system (Hasnie *et al.*, 2007a; Wallace *et al.*, 2007c; Jiang *et al.*, 2019), and of serotoninergic, noradrenergic and opioidergic transmissions have also been identified in structures such as the LC, the amygdala, the striatum or the anterior cingulate cortex (ACC) (Narita *et al.*, 2006b; Ji *et al.*, 2017; Alba-Delgado *et al.*, 2018; Sang *et al.*, 2018; Thompson *et al.*, 2018).

Beyond these anatomical and neurotransmitter-related information, animal studies on neuropathic pain also reported an implication of inflammatory mechanisms such as microglia activation (Galan-Arriero *et al.*, 2014; Sawada *et al.*, 2014; Wu *et al.*, 2014; Galan-Arriero *et al.*, 2015; Xu *et al.*, 2017; Ferreira-Chamorro *et al.*, 2018) and/or pro-inflammatory cytokine production (Norman *et al.*, 2010; Dellarole *et al.*, 2014; Gonzalez-Sepulveda *et al.*, 2016) in mood disorders accompanying chronic pain. At intracellular level, changes in the mitogen-activated protein kinases (MAPK) and indoleamine 2, 3-dioxygenase 1 (IDO1) were also reported (Sawada *et al.*, 2014; Zhou *et al.*, 2015; Barthas *et al.*, 2017). Looking at the mechanisms down to epigenetic level, the animal models and tests also allowed showing the recruitment of histone deacetylases (HDAC) (Descalzi *et al.*, 2017) and of dimethyl-3-transferase (DM3T) (Wang *et al.*, 2019). From anatomy to neural transmission and cellular, molecular and epigenetic changes, the animal models and tests thus provided major contributions to our understanding of the mechanisms linking pain and mood (for review: (Yalcin & Barrot, 2014; Yalcin *et al.*, 2014; Leite-Almeida *et al.*, 2015; Humo *et al.*, 2019).

In conclusion, despite their drawbacks that are highlighted in this review, preclinical models so far allowed exploring the anxiodepressive-like consequences of chronic pain. However, translational studies combining animal models and human condition, as well as side by side comparison of different animal models, should help us further improving the existing tests and guide us in developing new approaches to model this comorbidity in animals. Moreover, not all the patients suffering from chronic pain develop mood disorders. To better understand the mechanisms underlying the comorbidity between pain and mood disorders, it would thus also be critical to develop studies on such resiliency/susceptibility in animal models. In parallel, an effort is still needed in developing other measurements than the behavioural testing, such as the neuroimaging or biochemical biomarkers, in order to better characterize the anxiodepressive consequences of chronic pain.

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Pain model	Species	Behavioural Test	Results	References
PSNL	Mouse	EPM; LD	ALB at PO day 28	(Narita *et al.*, 2006a; Narita *et al.*, 2006b)
PSNL	Rat	OF	No ALB at PO day 14	(Hasnie *et al.*, 2007a)
PSNL	Mouse	EPM;OF; TST	No ALB at PO days 7, 14, 28 No DLB at PO days 8, 15, 29	(Hasnie *et al.*, 2007b)
PSNL	Rat	OF	ALB at PO day 14	(Wallace *et al.*, 2007c)
PSNL	Mouse	EPM; LD	ALB at PO day 27	(Matsuzawa-Yanagida *et al.*, 2008)
PSNL	Rat	EPM	No ALB at PO week 4	(Roeska *et al.*, 2008)
PSNL	Mouse	OF	No ALB at PO day 10	(Kodama *et al.*, 2011)
PSNL	Rat	BT	Burrowing behaviour deficits at PO day 14	(Andrews *et al.*, 2012)
PSNL	Mouse	SPT	DLB at PO day 16	(Bura *et al.*, 2013)
PSNL	Mouse	EPM	ALB at PO day 28	(Sawada *et al.*, 2014)
PSNL	Mouse	FST; TST	DLB at PO week 4	(Gai *et al.*, 2014)
PSNL	Rat	EPM; OF; FST; SPT	ALB at PO day 28; No DLB at PO day 28	(Wang *et al.*, 2015b)
PSNL	Mouse	FST	DLB at PO week 4	(Bruning *et al.*, 2015)
PSNL	Mouse	EPM TST; MB	ALB at PO days 5 to 47; DLB at post-surgery days 20 to 62	(Gonzalez-Sepulveda *et al.*, 2016)
PSNL	Mouse	EPM; FST; SPT	ALB at PO weeks 1, 3; DLB at PO week 3	(La Porta *et al.*, 2016)
PSNL	Mouse	EPM; OF FST	ALB and DLB at PO day 30	(Wang *et al.*, 2017)
PSNL	Mouse	EPM SPT	ALB at PO day 15; DLB at PO day 10	(Martinez-Navarro *et al.*, 2019)
PSNL	Mouse	SI FST; NSF	ALB at PO week 6; DLB at PO week 8	(Hisaoka-Nakashima *et al.*, 2019)
PSNL	Mouse	FST; ST	DLB at PO day 28	(Birmann *et al.*, 2019)
SNL	Rat	EPM; OF; LD	No ALB at PO day 14	(Kontinen *et al.*, 1999)
SNL	Mouse	EPM; OF; LD; FST	ALB at PO days 30, 56; DLB at PO days 15, 30, 56	(Suzuki *et al.*, 2007)
SNL	Rat	OF	ALB at PO day 14	(Hasnie *et al.*, 2007a)
SNL	Rat	FST	DLB at PO day 29	(Hu *et al.*, 2010)

SNL	Rat	BT	Burrowing behaviour deficits at PO day 14	(Andrews *et al.*, 2012)
SNL	Rat	EPM; OF	ALB at PO day 10	(Jiang *et al.*, 2014)
SNL	Rat	OF; FST	No ALB at PO day 20 DLB at PO day 23	(Chung *et al.*, 2017)
SNL	Rat	EPM; SPT	ALB and DLB at PO week 4	(Ji *et al.*, 2017)
SNL	Mouse	OF; FST; SPT	ALB at PO day 7, 14; DLB at PO day 7, 14, 21	(Zhu *et al.*, 2017)
SNL	Rat	EPM; FST	ALB and DLB at PO week 4	(Ji *et al.*, 2018)
SNL	Mouse	FST; SPT	DLB at PO day 14	(Wu *et al.*, 2018)
SNL	Rat	FST; TST; SPT	DLB at PO day 15	(Zong *et al.*, 2018)
CCI	Rat	FST; HST	DLB at PO days 3, 7	(Zeng *et al.*, 2008)
CCI	Rat	EPM	ALB at PO week 4	(Roeska *et al.*, 2008)
CCI	Rat	EPM	ALB at PO day 36	(Roeska *et al.*, 2009)
CCI	Rat	FST	DLB at PO days 21-28	(Hu *et al.*, 2009)
CCI	Mouse	EPM; OF; MB	No ALB at PO day 3 to week 7	(Urban *et al.*, 2011)
CCI	Rat	FST	DLB at PO days 14-21	(Fukuhara *et al.*, 2012)
CCI	Rat	EPM; OF; SI; SPT	No ALB and no DLB at PO days 14-21	(Gregoire *et al.*, 2012)
CCI	Rat	EZM; FST	ALB and DLB at PO day 28	(Alba-Delgado *et al.*, 2013)
CCI	Rat	EPM; FST	ALB at PO day 25; DLB at PO day 32	(Caspani *et al.*, 2014)
CCI	Rat	EPM; FST	ALB and DLB at PO days 7, 21	(Li *et al.*, 2014)
CCI	Mouse	FST; TST	DLB at PO weeks 2, 4, 6	(Zhao *et al.*, 2014a)
CCI	Mouse	FST	DLB at PO weeks 2-5	(Zhao *et al.*, 2014b)
CCI	Mouse	SPT	DLB at PO weeks 4-10	(Dellarole *et al.*, 2014)
CCI	Rat	OF; EZM	ALB at PO week 4	(Alba-Delgado *et al.*, 2016)
CCI	Rat	BT	Burrowing behaviour at PO days 3-14	(Muralidharan *et al.*, 2016)
CCI	Mouse	OF	ALB at PO week 2	(Missig *et al.*, 2017)
CCI	Rat	FST	DLB at PO days 7, 14, 21, 28	(Garg *et al.*, 2017)
CCI	Rat	FST; SPT	DLB at PO day 28	(Li *et al.*, 2017)
CCI	Mouse	FST; TST	DLB at PO days 7-34	(Jiang *et al.*, 2018)

CCI	Rat	EZM; FST	ALB and DLB at PO weeks 4, 6	(Alba-Delgado *et al.*, 2018)
CCI	Mouse	EPM; TST	ALB and DLB at PO day 28	(Ferreira-Chamorro *et al.*, 2018)
CCI	Rat	EZM	ALB at PO week 4	(Llorca-Torralba *et al.*, 2018)
CCI	Rat	FST; NSF	DLB at PO day 29	(Jiang *et al.*, 2019)
CCI	Mouse	FST; SPT	DLB at PO days 35-42	(Wang *et al.*, 2019)
CCI	Rat	FST	DLB at PO week 2	(Li *et al.*, 2019)
SNI	Rat	EPM; OF; FST	No ALB at PO week 7; DLB at PO week 7	(Goncalves *et al.*, 2008)
SNI	Rat	EPM; OF; FST	ALB and DLB at PO day 28	(Leite-Almeida *et al.*, 2009)
SNI	Rat	EPM	ALB at PO weeks 19, 24	(Seminowicz *et al.*, 2009)
SNI	Mouse	OF; FST	No ALB at PO day 6; DLB at PO day 7	(Norman *et al.*, 2010)
SNI	Rat	FST; SPT	DLB at PO day 14, 56	(Wang *et al.*, 2011)
SNI	Mouse	OF; EZM; SI; MB; FST; SPT	No ALB and DLB at PO day 3 to week 7	(Urban *et al.*, 2011)
SNI	Rat	EPM	ALB cohort-dependent at PO day 28	(Leite-Almeida *et al.*, 2012)
SNI	Mouse	LD; NSF	ALB at PO day 12	(Mutso *et al.*, 2012)
SNI	Rat	FST; SPT	DLB at PO day 14	(Goffer *et al.*, 2013)
SNI	Mouse	FST	DLB at PO day 15	(Stratinaki *et al.*, 2013)
SNI	Rat	FST	DLB at PO day 14	(Le *et al.*, 2014)
SNI	Rat	OF	ALB at PO day 21	(Avila-Martin *et al.*, 2015)
SNI	Mouse	TST; MB	DLB at PO day 30	(Guida *et al.*, 2015)
SNI	Rat	OF	ALB at PO 21	(Galan-Arriero *et al.*, 2015)
SNI	Mice	FST	DLB at PO day 7	(Zhou *et al.*, 2015)
SNI	Rat	EPM; OF	No ALB at PO weeks 2, 5, 9, 14, 19	(Hubbard *et al.*, 2015)
SNI	Mouse	EPM; OF; FST; SPT	ALB at PO month 2 DLB at PO week 9	(Descalzi *et al.*, 2017)
SNI	Mouse	EPM; OF	ALB at PO day 28	(Zhang *et al.*, 2017)

SNI	Mouse	FST	DLB at PO day 7	(Laumet *et al.*, 2017)
SNI	Rat	FST; SPT	DLB cohort-dependent at PO days 14, 21	(Xie *et al.*, 2017)
SNI	Mouse	TST; MB	DLB at PO year 1	(D'Aniello *et al.*, 2017)
SNI	Rat	FST; SPT	DLB at PO day 14	(Xu *et al.*, 2017)
SNI	Rat	EPM; OF; SPT	ALB at PO days 20-40 DLB at PO day 45	(Gong *et al.*, 2018)
SNI	Rat	EPM; OF	ALB at PO weeks 4, 8	(Sang *et al.*, 2018)
SNI	Rat	EPM; OF; LD; SPT	ALB at PO week 3 No DLB at PO week 3	(Chen *et al.*, 2018)
SNI	Mouse	EPM; LD; HB	ALB at PO weeks 4-6	(Sieberg *et al.*, 2018)
SNI	Rat	SPT	DLB at PO week 11	(Thompson *et al.*, 2018)
SNI	Rat	OF; FST; SPT	DLB at PO days 14, 18	(Pan *et al.*, 2018)
SNI	Rat	FST; SPT	DLB at PO days 42, 56	(Fu *et al.*, 2018)
SNI	Mouse	EPM; LD; FST	No ALB and DLB at PO days 3-97	(Pitzer *et al.*, 2019)
SNI	Rat	LD	ALB at PO day 14	(Chen *et al.*, 2019)
SNI	Rat	FST; TST; SPT	DLB at PO day 25	(Zhang *et al.*, 2019)
SNI	Mouse	SPT	Anhedonia cohort-dependent at PO days 5, 12, 19	(Yang *et al.*, 2019a)
SNI	Rat	FST	DLB at PO day 14	(Yang *et al.*, 2019b)
SNI	Rat	FST; SPT	DLB at PO day 42	(Fang *et al.*, 2019a)
SNI	Rat	SPT	DLB cohort-dependent at PO day 12, 19	(Fang *et al.*, 2019b)
SNI	Mouse	OF; EPM; TST; SPT	ALB and DLB at PO week 6	(Zhou *et al.*, 2019)
Cuff	Mouse	EPM; SI; MB; TST	ALB at PO days 30, 41 No DLB at PO days 23, 35	(Benbouzid *et al.*, 2008)
Cuff	Mouse	LD; MB; FST; NSF; ST	ALB at PO weeks 4-9 ; DLB at PO weeks 6-9	(Yalcin *et al.*, 2011)
Cuff	Mouse	OF; EZM; FST	ALB at PO day 35; DLB at PO day 40	(Dimitrov *et al.*, 2014)
Cuff	Mouse	FST; NSF;	DLB at PO weeks 6-8	(Barthas *et al.*, 2015)

		ST		
Cuff	Mouse	LD; FST; NSF; ST	ALB at PO week 8; DLB at PO weeks 8-17	(Barthas *et al.*, 2017)
Cuff	Mouse	LD; FST; NSF; ST	ALB at PO week 8; DLB at PO weeks 7, 8	(Sellmeijer *et al.*, 2018)
Cuff	Mouse	LD; FST	ALB at PO week 8; DLB at PO week 8	(Liu *et al.*, 2019)
TNT	Rat	BT	Burrowing behaviour deficits at PO days 56-77	(Andrews *et al.*, 2012)
SCI	Rat	OF	No ALB at PO day 42	(Galan-Arriero *et al.*, 2014)
SCI	Mouse	TST; SPT	DLB at PO week 10	(Wu *et al.*, 2014)
SCI	Rat	OF; SI; FST; SPT	ALB and DLB cohort dependent at PO 10, 21	(Maldonado-Bouchard *et al.*, 2016)
SCI	Mouse	OF; LD; FST	No ALB at PO weeks 1, 4, 8; DLB at PO week 8	(Boadas-Vaello *et al.*, 2018)
Oxaliplatin	Mouse	TST; NSF	ALB and DLB at PI day 7	(Hache *et al.*, 2015)
Oxaliplatin	Mouse	FST; NSF	DLB at PI day 28	(Poupon *et al.*, 2018)
Paclitaxel	Mouse	FST; SPT; NSF; Nest test	ALB at PI weeks 3-9; DLB at PI weeks 2, 3	(Toma *et al.*, 2017)
Streptozotocin	Rat	OF; EZM	ALB at PI week 4	(Alba-Delgado *et al.*, 2016)
Streptozotocin	Rat	FST	DLB at PI weeks 2, 4	(Redivo *et al.*, 2016)
Streptozotocin	Mouse	FST; TST; MB	DLB at PI day 46	(Aguilar-Avila *et al.*, 2019)
CION	Rat	EPM; LD; FST; SPT	ALB at PO day 15; No DLB at PO day 14-46	(Gambeta *et al.*, 2018)
TIC	Mouse	EPM; OF; LD	ALB at PO week 8	(Lyons *et al.*, 2015)
TIC	Mouse	LD	ALB at PO week 8	(Lyons *et al.*, 2018)
Antiretroviral	Rat	BT	Burrowing behaviour at PI day 21	(Huang *et al.*, 2013)
gp120	Rat	OF	ALB at PI 14	(Wallace *et al.*, 2007a; Wallace *et al.*, 2007b)
VZV	Rat	OF	ALB at PI day 14	(Hasnie *et al.*, 2007a)

Table 1. Summary of studies on the affective consequences of neuropathic pain.

ALB, anxiety-like behaviour; BT, burrowing test; CCI, chronic constriction injury; CION, infraorbital nerve constriction; DLB, depression-like behaviour; EPM, elevated-plus maze; EZM, elevated zero maze; FST, forced swimming test; gp120, immunodeficiency virus type 1 envelope glycoprotein 120; HB, hole-board test; HST, horizontal suspension test; LD, light-dark test, MB, marble burying test; NSF, novelty-suppressed feeding; OF, open field; PI, post-induction; PO, post-operative; PSNL, partial sciatic nerve ligation; SCI, spinal cord injury; SI, social interaction; SNI, spared nerve injury; SNL, sciatic nerve ligation; SPT, sucrose or saccharin preference test; ST, splash test; TIC, trigeminal inflammatory compression; TNT, tibial nerve transection; TST, tail suspension test; VZV, varicella zoster virus.

Pain model	Species	Behavioural Test	Results	References
CFA	Mouse	EPM; LD	ALB at PI day 28	(Narita *et al.*, 2006a; Narita *et al.*, 2006b)
CFA	Mouse	OF; EZM; MB; SI; FST; SPT	No ALB and DLB at PI days 7-35	(Urban *et al.*, 2011)
CFA	Rat	OF; FST; TST; SPT	ALB at PI days 7, 14; DLB at PI day 14	(Kim *et al.*, 2012)
CFA	Rat	EPM; OF; LD; SPT	ALB at PI day 28	(Parent *et al.*, 2012)
CFA	Rat	BT	Burrowing behaviour at PI day 10	(Andrews *et al.*, 2012)
CFA	Mouse	EPM; OF	ALB at PI days 3, 7	(Chen *et al.*, 2013)
CFA	Mouse	FST; TST	DLB at PI days 7-21	(Maciel *et al.*, 2013)
CFA	Rat	EPM; LD	ALB at PI days 1, 3, 10	(do Nascimento & Leite-Panissi, 2014)
CFA	Rat	EPM; FST	ALB and DLB at PI day 28	(Borges *et al.*, 2014)
CFA	Rat	OF; SI; SPT	ALB and DLB at PI weeks 2-3	(Gregoire *et al.*, 2014)
CFA	Rat	FST	DLB at PI day 7	(Le *et al.*, 2014)
CFA	Mouse	EPM	ALB at PI day 21	(Wang *et al.*, 2015a)
CFA	Rat	FST	DLB at PI day 7	(Hamann *et al.*, 2016)
CFA	Rat	FST; SPT	DLB at PI days 7-14	(Zhang *et al.*, 2016)
CFA	Mouse	EPM; OF	ALB at day 21	(Guo *et al.*, 2016)
CFA	Mouse	EZM; SPT	ALB at PI day 1; DLB at PI day 2	(Refsgaard *et al.*, 2016)
CFA	Mouse	EPM; OF	ALB at PI day 21	(Sun *et al.*, 2016)
CFA	Rat	BT	Burrowing behaviour at PI days 2-10	(Muralidharan *et al.*, 2016)
CFA	Mouse	EPM; OF	ALB at PI week 2	(Tian *et al.*, 2017)
CFA	Mouse	LD; TST	ALB and DLB at PI day 14	(Omorogbe *et al.*, 2018)
CFA	Mouse	EPM; OF	ALB at PI week 1	(Yue *et al.*, 2018)
CFA	Mouse	EPM; OF; LD; FST	No ALB and DLB at PI days 1-22	(Pitzer *et al.*, 2019)
CFA	Mouse	OF; EPM; TST; SPT	ALB and DLB at PO week 3	(Zhou *et al.*, 2019)
K/C	Rat	EPM	ALB at PI hours 5-6	(Ji *et al.*, 2007)
K/C	Rat	EPM; OF; FST; SPT	ALB and DLB at PI week 4	(Amorim *et al.*, 2014)

Uric acid	Rat	EPM; MB	ALB at PI hour 3	(Fernandez-Guasti *et al.*, 2005)
Osteoarthritis	Mouse	EZM; TST	ALB and DLB at PI week 41	(Griffin *et al.*, 2010)

Table 2. Summary of studies on the affective consequences of inflammatory pain.

ALB, anxiety-like behaviour; BT, burrowing test; CFA, complete Freund's adjuvant; DLB, depression-like behaviour; EPM, elevated-plus maze; EZM, elevated zero maze; FST, forced swimming test; HB, hole-board test; K/C, kaolin/carrageenan; LD, light-dark test; MB, marble burying test; NSF, novelty-suppressed feeding; OF, open field; PI, post-induction; SI, social interaction; SPT, sucrose or saccharin preference test; ST, splash test; TST, tail suspension test.

Pain model	Species	Behavioural Test	Results	References
USS	Rat	EPM	ALB at PI day 14	(Green *et al.*, 2011)
BAD	Rat	FST	DLB at PI day 5	(Nagakura *et al.*, 2009)
BAD	Rat	FST	DLB at PI day 2	(Arora & Chopra, 2013)
BAD	Mouse	FST; TST	DLB at PI day 3	(Klein *et al.*, 2014)
BAD	Mouse	FST	DLB at PI day 4	(de Souza *et al.*, 2014)
BAD	Rat	NSF	DLB at PI days 4-5	(Blasco-Serra *et al.*, 2015)
BAD	Rat	OF; EZM	ALB at PI day 5	(Wu *et al.*, 2017)
BAD	Rat	FST	DLB at PI day 3	(Siemian *et al.*, 2019)
Acid-induced hyperalgesia	Rat	OF; EPM FST; SPT	ALB at PI day 13; DLB at PI days 19-20	(Liu *et al.*, 2014)
ICS	Mouse	HB	DLB at PI day 3	(Montserrat-de la Paz *et al.*, 2015)
RCS	Rat	FST	DLB at PI days 10-14	(Nasu *et al.*, 2019)
SSS	Rat	EPM	ALB at PI week 1	(Nazeri *et al.*, 2018)

Table 3. Summary of studies on the affective consequences of fibromyalgia.

ALB, anxiety-like behaviour; BAD, biogenic amine depletion; DLB, depression-like behaviour; EPM, elevated-plus maze; FST, forced swimming test; HB, hole-board test; ICS, intermittent cold stress; NSF, novelty-suppressed feeding; OF, open field; PI, post-induction day; RCS, repeated cold stress; SPT, sucrose preference test; SSS, subchronic swim stress; TST, tail suspension test; USS, unpredictable sound stress.

Terms	Definitions
Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. (IASP)
Allodynia	Pain due to a stimulus that does not normally provoke pain. (IASP)
Analgesia	Absence of pain in response to stimulation which would normally be painful. (IASP)
Arthritis	An informal way of referring to joint pain or joint disease. (COFER)
Dysesthesia	An unpleasant abnormal sensation, whether spontaneous or evoked. (IASP)
Fibromylagia	Syndrome characterized by chronic widespread pain at multiple tender points, joint stiffness, and systemic symptoms (e.g. mood disorders, fatigue, cognitive dysfunction and insomnia) without a well-defined underlying organic disease. (ICD)
Hyperalgesia	Increased pain from a stimulus that normally provokes pain. (IASP)
Hyperpathia	A painful syndrome characterized by an abnormally painful reaction to a stimulus, especially a repetitive stimulus, as well as an increased threshold. (IASP)
Hypoalgesia	Diminished pain in response to a normally painful stimulus. (IASP)
Inflammatory pain	Inflammatory nociceptive pain is associated with tissue damage and the resulting inflammatory process. (COFER)
Monoarthritis	Inflammation of one joint (arthritis) at a time (ICD)
Neuropathic pain	Pain caused by a lesion or disease of the somatosensory nervous system. (IASP)
Nociception	The neural process of encoding noxious stimuli. (IASP)
Nociceptive pain	Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors. (IASP)
Nociceptive stimulus	An actually or potentially tissue-damaging event transduced and encoded by nociceptors. (IASP)
Nociceptor	A high-threshold sensory receptor of the peripheral somatosensory nervous system that is capable of transducing and encoding noxious stimuli. (IASP)
Osteoarthritis	Group of distinct, but overlapping diseases, which may have different etiologies, but similar biological, morphological, and clinical outcomes affecting the articular cartilage, subchondral bone, ligaments, joint capsule, synovial membrane and periarticular muscles. (ICD)

Pain threshold	The minimum intensity of a stimulus that is perceived as painful. (IASP)
Paraesthesia	An abnormal sensation, whether spontaneous or evoked. (IASP)
Rheumatoid arthritis	Persistent and/or erosive disease that is defined as the confirmed presence of synovitis in at least 1 joint, absence of an alternative diagnosis that better explains the synovitis, and achievement of a total score of 6 or greater (of a possible 10) from the individual scores in 4 domains: number and site of involved joints, serologic abnormality, elevated acute-phase response, and symptom duration. (ICD)
Sensitization	Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally subthreshold inputs. (IASP)

Box1. Definition and assessment of sensory symptoms or signs in pain.

COFER, Collège français des enseignants en rhumatologie; IASP, international association for the study of pain; ICD, international classification of diseases.

Figure legends

Figure 1. Experimental traumatic models of neuropathic pain.
(1) Partial sciatic nerve ligation (PSNL; Seltzer et al., 1990); (2) Sciatic nerve ligation (SNL; Kim and Chung, 1992); (3) L5 spinal nerve ligation (variant of the SNL model; LaBuda and Little, 2005); (4) Tibial nerve transection (TNT; Lee and al., 2000); (5) Chronic constriction injury (CCI; Bennett and Xie, 1988); (6) Sciatic nerve cuffing (Cuff; Mosconi and Kruger, 1996; Benbouzid *et al.*, 2008); (7) Spared nerve injury (SNI; Decosterd and Woolf, 2000); (8) Spinal cord injury (SCI; Behrmann *et al.*, 1992). The level of insertion of the nerve roots and therefore the associated dorsal root ganglia may vary according to the animals' strain hence the double level numbering on the dorsal root ganglia.

Figure 2. Anxiety-like behaviours in animal models of neuropathic pain.
"n" displayed in the figure corresponds to the number of publications relative to the test (see **Table 1** for more details and references). EPM, elevated-plus maze; EZM, elevated zero maze.

Figure 3. The impact of time on the anxiety-like behaviour in animal models of neuropathic pain.
"n" displayed in the figure corresponds to the number of publications relative to the test (see **Table 1** for more details and references). EPM, elevated-plus maze; EZM, elevated zero maze; LD, light-dark test; OF, open field.

Figure 4. The impact of time on well-being in animal models of neuropathic pain.
"n" displayed in the figure corresponds to the number of publications relative to the test (see **Table 1** for more details and references). SI, social interaction.

Figure 5. Depressive-like behaviours in animal models of neuropathic pain.
"n" displayed in the figure corresponds to the number of publications relative to the test (see **Table 1** for more details and references). FST, forced swimming test; HST, horizontal suspension test; NSF, novelty-suppressed feeding; TST, tail suspension test.

Figure 6. The impact of time on depressive-like behaviour in animal models of neuropathic pain.
"n" displayed in the figure corresponds to the number of publications relative to the test (see **Table 1** for more details and references). FST, forced swimming test; NSF, novelty-suppressed feeding; TST, tail suspension test.

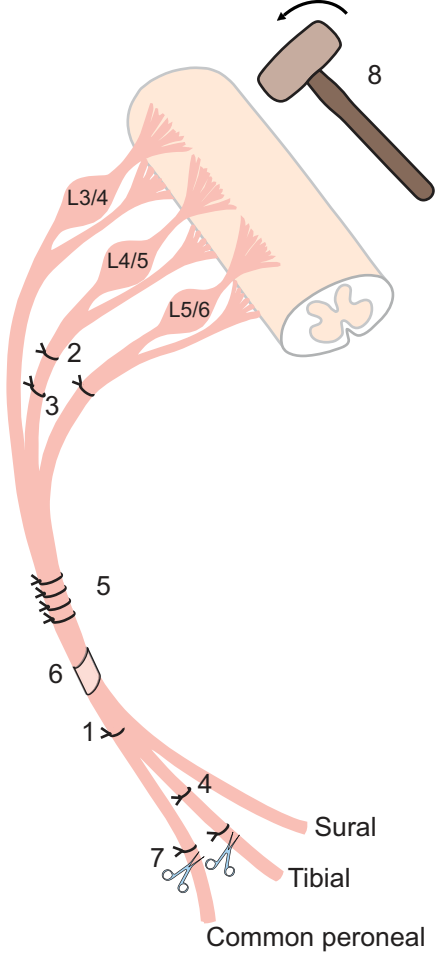

Figure 1.

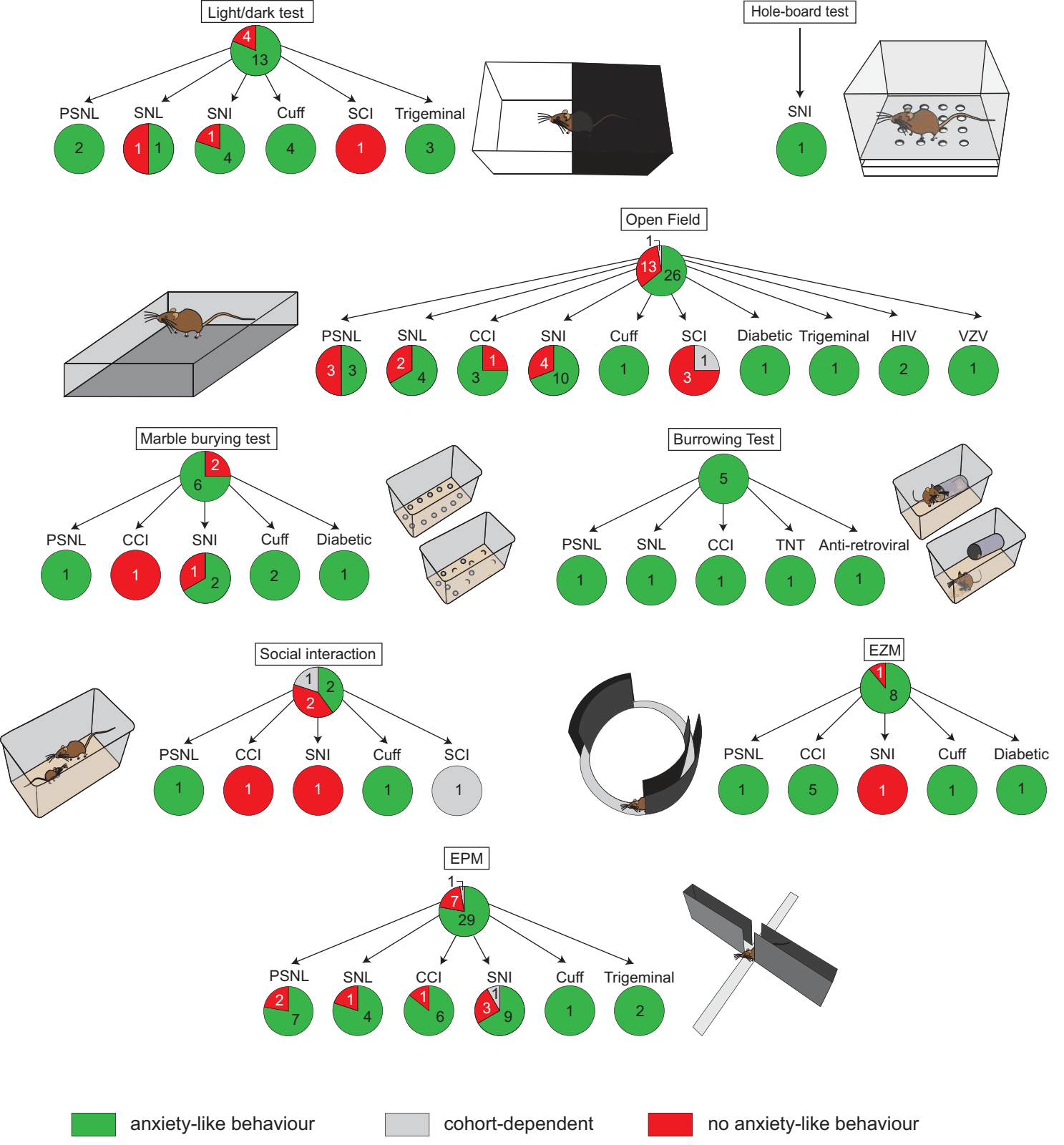
Light/dark test
4
13
PSNL
SNL
SNI
Cuff
SCI
Trigeminal
2
1
1
1
4
4
1
3
Hole-board test
SNI
1
Open Field
1
13
26
PSNL
SNL
CCI
SNI
Cuff
SCI
Diabetic
Trigeminal
HIV
VZV
3
3
2
4
3
1
4
10
1
3
1
1
1
2
1
Marble burying test
2
6
PSNL
CCI
SNI
Cuff
Diabetic
1
1
1
2
2
1
Burrowing Test
5
PSNL
SNL
CCI
TNT
Anti-retroviral
1
1
1
1
1
Social interaction
1
2
2
PSNL
CCI
SNI
Cuff
SCI
1
1
1
1
1
EZM
1
8
PSNL
CCI
SNI
Cuff
Diabetic
1
5
1
1
1
EPM
1
7
29
PSNL
SNL
CCI
SNI
Cuff
Trigeminal
2
7
1
4
1
6
1
3
9
1
2
anxiety-like behaviour
cohort-dependent
no anxiety-like behaviour

Figure 2.

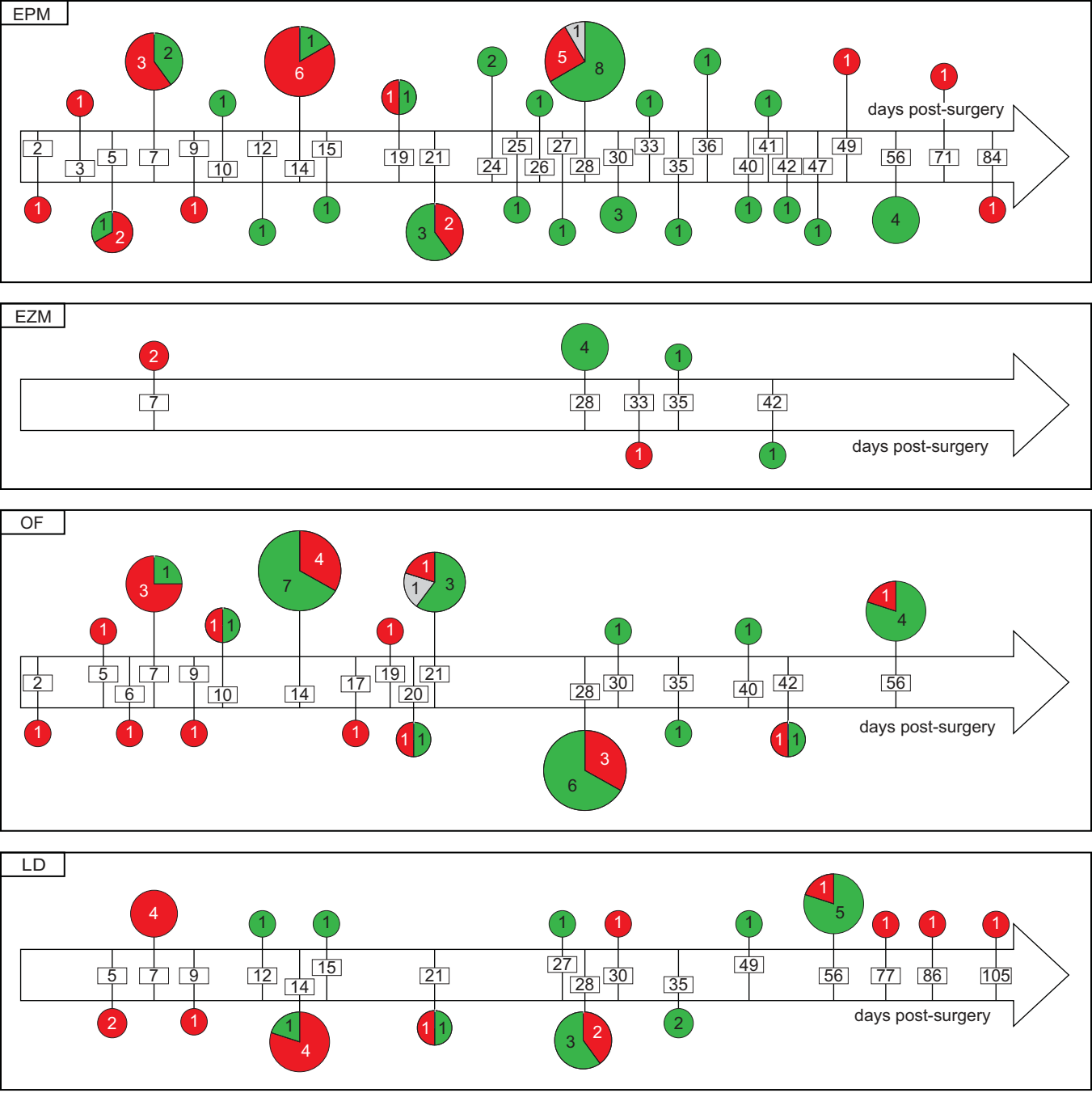
EPM
days post-surgery
EZM
days post-surgery
OF
days post-surgery
LD
days post-surgery
anxiety-like behaviour
cohort-dependent
no anxiety-like behaviour

Figure 3.

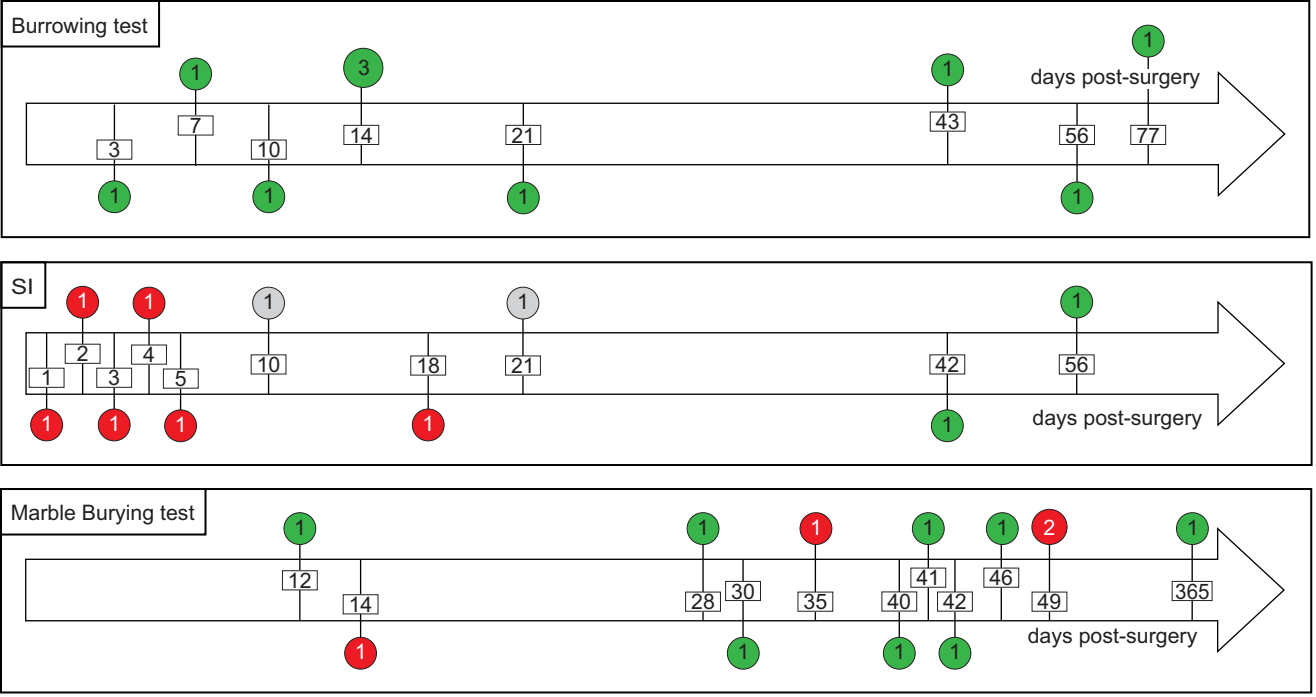
Burrowing test
days post-surgery
SI
days post-surgery
Marble Burying test
days post-surgery
deficit
cohort-dependent
no deficit

Figure 4.

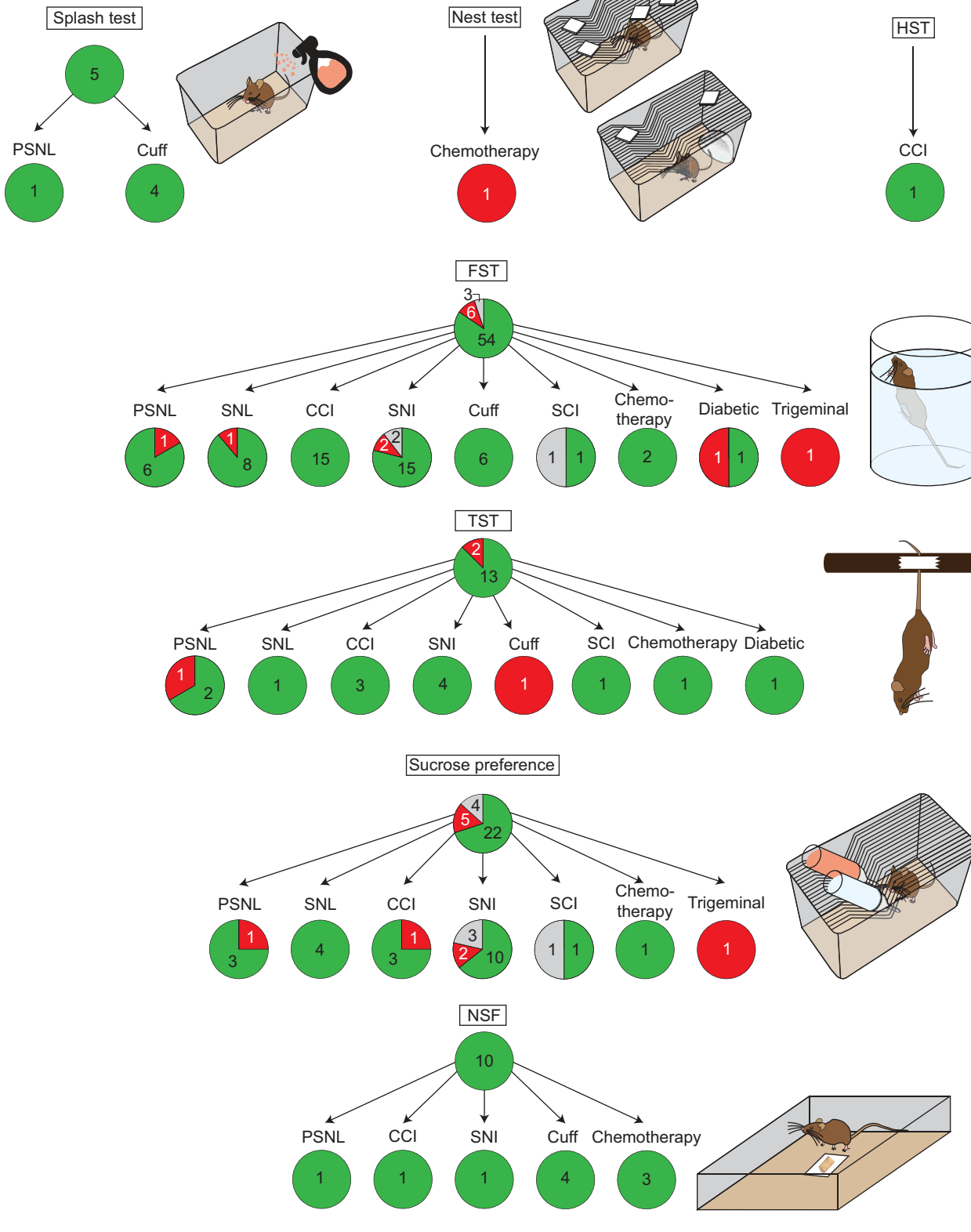
Splash test
5
PSNL
Cuff
1
4
Nest test
Chemotherapy
1
HST
CCI
1
FST
3
6
54
PSNL
SNL
CCI
SNI
Cuff
SCI
Chemo-
therapy
Diabetic
Trigeminal
1
6
1
8
15
2
2
15
6
1
1
2
1
1
1
TST
2
13
PSNL
SNL
CCI
SNI
Cuff
SCI
Chemotherapy
Diabetic
1
2
1
3
4
1
1
1
1
Sucrose preference
4
5
22
PSNL
SNL
CCI
SNI
SCI
Chemo-
therapy
Trigeminal
1
3
4
1
3
3
2
10
1
1
1
1
NSF
10
PSNL
CCI
SNI
Cuff
Chemotherapy
1
1
1
4
3
depression-like behaviour
cohort-dependent
no depression-like behaviour

Figure 5.

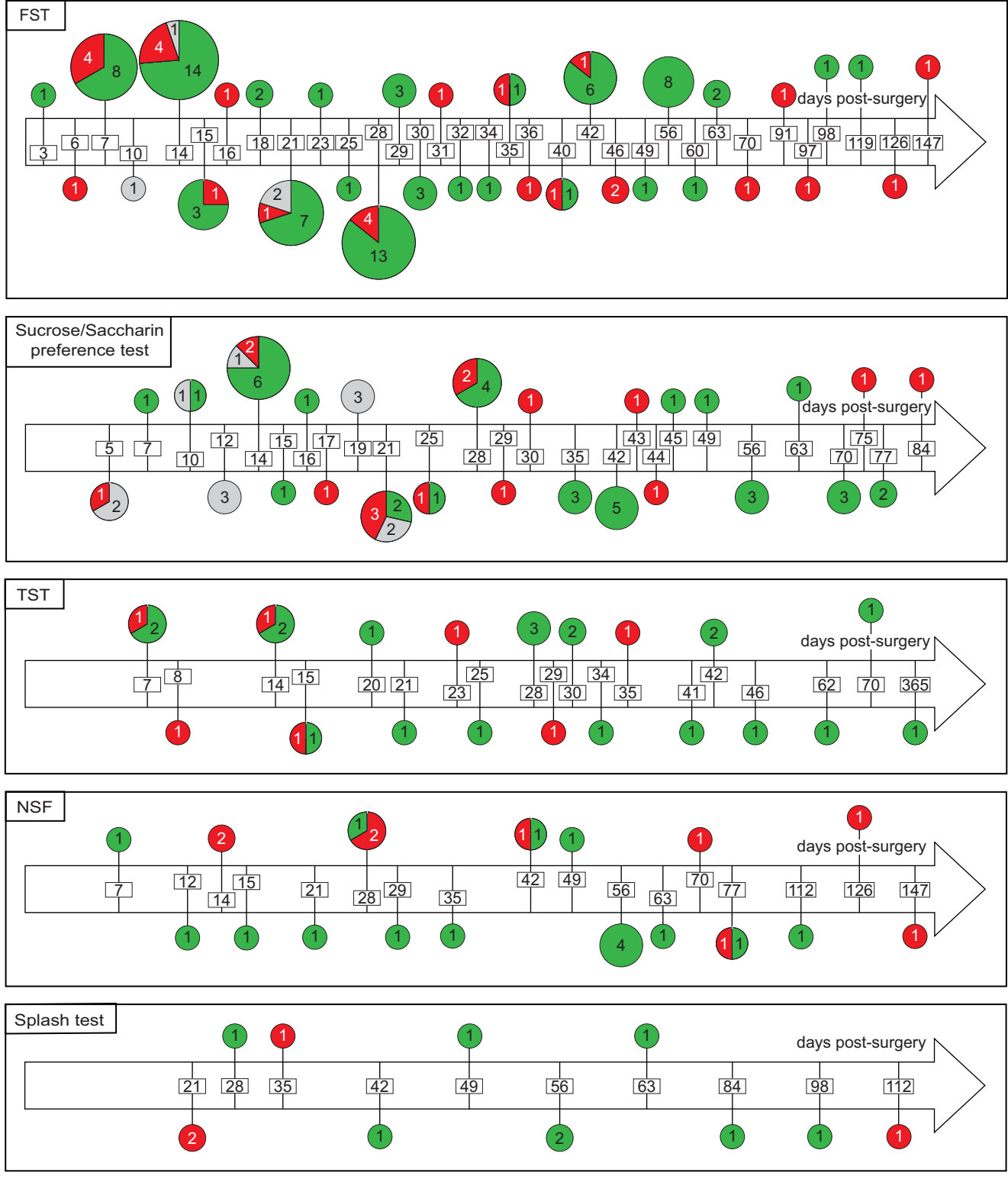
FST
days post-surgery
Sucrose/Saccharin preference test
days post-surgery
TST
days post-surgery
NSF
days post-surgery
Splash test
days post-surgery
depression-like behaviour
cohort-dependent
no depression-like behaviour

Figure 6.