Neuroplasticity of Supraspinal Structures Associated with Pathological Pain

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ABSTRACT

Peripheral nerve and spinal cord injuries, along with other painful syndromes such as fibromyalgia, diabetic neuropathy, chemotherapeutic neuropathy, trigeminal neuralgia, complex regional pain syndrome, and/or irritable bowel syndrome, cause several neuroplasticity changes in the nervous system along its entire axis affecting the different neuronal nuclei. This paper reviews these changes, focusing on the supraspinal structures that are involved in the modulation and processing of pain, including the periaqueductal gray matter, red nucleus, locus coeruleus, rostral ventromedial medulla, thalamus, hypothalamus, basal ganglia, cerebellum, habenula, primary and secondary somatosensory cortex, motor cortex, mammillary bodies, hippocampus, septum, amygdala, cingulated and prefrontal cortex. Hyperexcitability caused by the modification of postsynaptic receptor expression, central sensitization and potentiation of presynaptic delivery of neurotransmitters, as well as the reduction of inhibitory inputs, changes in dendritic spine, neural circuit remodeling, alteration of gray matter, and upregulation of pro-inflammatory mediators (e.g. cytokines) by reactivation of astrocytes and microglial cells are the main functional, structural and molecular neuroplasticity changes observed in the above supraspinal structures, associated with pathological pain. Studying these changes in greater depth may lead to the implementation and improvement of new therapeutic strategies against pathological pain.

Key words: Supraspinal Structures, Neuroplasticity, Inflammation Pain, Neuropathic Pain, Painful Syndromes

INTRODUCTION

Traumatic injuries in the peripheral and central nervous system may lead to the development of a specific kind of pain called 'neuropathic pain'. The inflammation of several tissues including skin, joint, bone, muscle, muscular fascia, and the visceral wall may also cause the development of pain classifiable as inflammatory pain. Other conditions (diabetes mellitus, obesity, cancer, cerebrovascular diseases) and several treatments (e.g. chemotherapy and retroviral treatments) also develop pain responses. All these painful conditions and treatments may be included under the classification of painful syndromes. Overall, injuries or conditions affecting the somatosensory system may trigger the onset of pathological pain.

Neural plasticity, also called neuroplasticity, is the phenomenon by which the central nervous system (CNS), whether healthy or damaged, can adapt to new experiences by changing its function and structure (Westlake and Byl 2013). A fact of paramount importance is that the CNS maintains a capacity for functional and structural changes throughout life (Pascual-Leone et al 2005). Neuropathic pain and inflammatory pain (as well as other painful syndromes comprised within the concept of pathological pain) are a frequent source of chronic pain, which causes several significant changes in the CNS, inducing neural plasticity of the areas involved in the processing of pain. Following traumatic injuries, both the neural plasticity of the spinal cord (Dickenson et al 2002, Ro and Chang 2005, Baron 2009, Jarvis et al 2009, Wrigley et al 2009, Vranken 2009, 2012; Boadas-Vaello et al 2016) and ascending and descending pathways (Ro and Chang 2005, Baron 2009, Boadas-Vaello et al 2016) have been thoroughly reviewed. On another note, the neural plasticity of the spinal cord after inflammatory pain has also been reviewed (Brierley and Linden 2014, Demir et al 2015). In general, neural plasticity in the spinal cord has been broadly studied, as the spinal cord is in fact the first site of pain processing. More

specifically, aberrant afferent innervation of the dorsal horn, reactivation of endogenous glial cells with the production of pro-hyperalgesic factors, central sensitization and hyperexcitability of dorsal horn neurons, and reduction of intrinsic and descending inhibitory signals are the main changes reported after traumatic and/or inflammatory injuries in the somatosensory nociceptive nervous system leading to neuropathic pain (Boadas-Vaello et al 2016, Vranken 2009, 2012). All together these structural, functional and biochemical changes in the dorsal horn of the spinal cord facilitate the generation and conduction of action potentials by the ascending pathways up to supraspinal structures including brainstem, thalamus, habenula, amygdala, hypothalamus, cerebellum, basal ganglia, somatosensory cortex, insular cortex and limbic cortex, causing more pain. Structural, functional and biochemical changes in all these supraspinal structures involved in the modulation of pain have been reported after injuries and/or conditions of the somatosensory nervous system. The neural plasticity of these supraspinal structures related with pain is thoroughly reviewed in this paper.

PLASTICITY IN BRAINSTEM STRUCTURES ASSOCIATED WITH THE MODULATION OF PAIN

Several nuclei from the brainstem are related with the processing of pain, including periaqueductal gray matter (PAG), red nucleus (RN), locus coeruleus (LC), and rostral ventromedial medulla (RVM) (Fig. 1). Following neuropathic and inflammatory pain, neural plastic changes have been reported in all of the aforementioned nuclei.

Periaqueductal gray matter

After chronic constriction injury (CCI), glial reactivity (Mor et al 2010, Ni et al 2016) and upregulation of phospho-p38 MAPK were seen in PAG (Ni et al 2016), and the immunohistochemistry analysis showed that protein levels of tumor necrosis factor (TNF)-alpha, interleukin (IL)-1 beta, and IL-6 were significantly increased in the PAG of CCI rats (Chu et al 2012). In addition, the PAG of CCI rats significantly increased the expression of glucocorticoid receptor (GR) mRNA and protein. Consequently, PAG neurons are sensitive to the increase in corticosterone occurring after CCI (Mor and Keay 2013), whereas a decrease in cannabinoid receptor type 1 (CB1) was observed in both CCI rats (Palazzo et al 2012) and SCI rats (Knerlich-Lukoschus et al 2011), despite the fact that the concentrations of endocannabinoids increased in PAG after CCI (Petrosino et al 2007), suggesting a downregulation of the endocannabinoid system that modulates pain at PAG. On another note, peripheral nerve ligation-induced chronic pain was associated with an increased NMDA/non-NMDA ratio in serotonergic neurons of PAG. Moreover, the upregulation of NR2B subunit expression in non-serotonergic/non-GABAergic neurons was also reported after peripheral nerve ligation. These changes in the expression of NMDA receptor in PAG result in an alteration of the descending modulation of nociception, which might be an underlying mechanism for peripheral nerve injury-evoked persistent pain (Terashima et al 2012). Lastly, the protein expression of P2X3 receptors in the plasma membrane of the dorsolateral PAG of STZ-treated rats decreased significantly. This decrease in the membrane expression of P2X3 receptors in the PAG of diabetic rats is likely to impair the descending inhibitory system in modulating pain transmission, contributing thereby to the development of mechanical allodynia in diabetic patients (Guo et al 2015). Likewise, diabetic neuropathy is accompanied by a progressive increase in spontaneous neuronal activity in the spinal cord and PAG (Morgado et al 2010). Overall, these studies highlight the cellular and

molecular changes in PAG after neuropathic pain interfering with their descending modulatory role (Fig. 2).

Red nucleus

Neuropathic pain also causes neural plasticity in the red nucleus (RN). Pro-inflammatory cytokines TNF-α and IL-1β, as well as NGF, were clearly increased in the RN of rats with spared nerve injury (SNI). Microinjections of anti-TNF-α, anti-IL-1β or anti-NGF antibodies alleviated the mechanical allodynia induced by SNI, suggesting that TNF-α, IL-1β, and NGF in RN are involved in the development of neuropathic pain (Li et al 2008, Wang et al 2008, Jing et al 2009). After spinal cord hemisection, an increase in the expression of nitric oxide synthase I and microglia reactivity was reported in RN (Xu et al 1998). Microglial reactivity was also found after lower thoracic rubrospinal tractotomy (Tseng et al 1996). Taken as a whole, these findings suggest that neural injuries causing neuropathic pain induce gliosis and liberation of pro-inflammatory mediators that facilitate the development and/or persistence of pain in the RN.

Locus coeruleus

A microdialysis-based study indicates that after ligation of the L5-L6 spinal nerve (SNL) in an experimental model of neuropathic pain, basal GABA concentrations in the locus coeruleus (LC) increase, whereas a decrease is reported in the spinal cord. Quantitatively, GAD67 immunoreactivity in the LC was significantly higher in tissue from SNL compared to normal rats, but the effect of SNL on GAD67 immunoreactivity in the spinal dorsal horn was opposite to the effect observed in the LC. These findings indicate that injuries in the peripheral nerve induce

GABAergic neuronal plasticity in the LC and the spinal dorsal horn, increasing both the expression and release of GABA in the LC, but decreasing them in the spinal cord (Yoshizumi et al 2012). The corticotropin-releasing factor (CRF) is a stress-related neuropeptide that modulates LC activity. In an inflammatory chronic pain model (complete Freund's adjuvant-induced monoarthritis model), the microinjection of CRF in the LC has been reported to cause nociceptive and anxiety-like behaviors, while increasing the levels of phosphorylated extracellular signal-regulated kinases 1/2 in both the LC and paraventricular nucleus, although the expression of CRF receptors remained unaltered. These findings suggest that, after inflammatory pain, pain-induced anxiety is mediated by CRF neurotransmission in the LC through extracellular signal-regulated kinases 1/2 signaling cascade (Borges et al 2015) (Fig. 2).

Rostral ventromedial medulla

Experimental models of neuropathic and inflammatory pain showed that the hyperexcitation of specific nociceptive and wide dynamic range (WDR) neurons in the spinal cord causes the hyperexcitability and sensitization of the neurons from the rostral ventromedial medulla (RVM) that facilitate the descendent pain signaling towards a dorsal horn level in the spinal cord. In particular, in the RVM nucleus, a strengthening of the 'ON' neuron response and a weakening of the 'OFF' neuron response have been observed. 'ON' cells exert a pro-nociceptive effect, whereas 'OFF' cells produce an antinociceptive effect. The preferential activation of 'ON' cells located in the RVM causes hyperalgesia, whereas hypoalgesia is achieved by the activation of 'OFF' RVM cells (Heinricher and Tortorici 1994, Carlson et al 2007, Khasabov et al 2012). In addition, the hyperexcitability of nociceptive ascending neurons also causes a sensitization of 'ON' RVM neurons through the overexpression of NMDA/AMPA,

Trk-B and NK1 receptors, whereas mu opioid receptor expression decreases. Under these circumstances, 'ON' RVM neurons do not respond to inhibitory signals from PAG, whilst they are highly stimulated by ascending inputs (Guo et al 2006, Miki et al 2002, Lagraize et al 2010, Khasabov et al 2012, Noguchi and Ruda 1992). These neural plasticity changes consequently potentiate the descending facilitating pathway over pain transmission in the dorsal horn of the spinal cord. On another note, a strong increase in the levels of both anandamide and 2-arachidonoylglycerol (2-AG) was observed in RVM after 7 days (when thermal hyperalgesia and mechanical allodynia are maximal) following chronic constriction injury of the sciatic nerve. These findings strongly support that anandamide and 2-AG are upregulated during CCI of the sciatic nerve (Petrosino et al 2007). It is well-known that RVM neurons express cannabinoid receptors. 'OFF' cells display a measurable increase in their activity after local infusion of a CB1 agonist in RVM (Heinricher and Ingram 2009). However, it has been reported that CCI causes a decrease in the expression of CB1 receptors in RVM neurons (Palazzo et al 2012). All these neural plasticity changes observed after CCI make the compensatory increase of endocannabinoids ineffective for relieving neuropathic pain, as there is a simultaneous reduction in the CB1 expression from 'OFF' cells. Overall, these findings suggest that neuropathic pain and inflammatory pain cause molecular neural plasticity that promotes the facilitating descending pathway from RVM, while the inhibiting descending pathway from RVM is blocked (Fig. 2).

PLASTIC CHANGES IN THE DIENCEPHALIC STRUCTURES INVOLVED IN THE PROCESSING OF PAIN

Several diencephalic structures are associated with the control, processing and modulation of pain, including the thalamus (Fig. 3-4) and hypothalamus. Changes in neuroplasticity related to pain have been reported within these structures.

Thalamus

Neural plasticity of several thalamic nuclei has been reported after various experimental models of neuropathic pain. Spinal cord injury (SCI) causes suppression of activity in the GABAergic nucleus of the zona incerta (ZI), and concomitantly increases the activity in one of its main targets: the posterior nucleus of the thalamus (PO). This increased activity in the PO correlates with the persistence and the expression of hyperalgesia after SCI (Masri et al 2009). SCI also causes a similar pathological increase in other thalamic nuclei regulated by ZI, specifically the mediodorsal thalamus (MD), involved in emotional-affective aspects of pain (Whitt et al 2013). The activity of neurons recorded in the two ventral posteromedial (VPM) nuclei of the thalamus also increases in rats subjected to chronic constriction injury (CCI) (Vos et al 2000) (Fig. 4). In addition, other experimental studies have revealed that neuropathic pain causes central sensitization of neurons from the ventral posterolateral (VPL) nucleus of the thalamus (Gerke et al 2003, Hains et al 2005, 2006), which are responsible for this hyperexcitability to neural injuries among thalamic neurons. Hyperexcitability of thalamic neurons has also been linked to a reduction of inhibitory inputs (Hoot et al 2011, Mòdol et al 2014).

Other neural plasticity changes in the thalamus following neuropathic pain have also been reported. In humans, several neuroimaging studies have revealed anomalies in the gray matter (GM) within different areas of the brain among patients with neuropathic pain. SCI patients with

neuropathic pain showed consistent decreased GM in bilateral thalamus (Pan et al 2015, Jutzeler et al 2015), as well as a significant reduction in cerebral blood flow (CBF) and in both the N-acetylaspartate and gamma amino butyric acid content in the thalamus (Gustin et al 2014). Lastly, in rats subjected to sciatic chronic constriction injuries, thermal hyperalgesia and microglial reactivity in VPL thalamic nucleus were observed. Microinjection of minocycline in VPL attenuated hyperalgesia and reduced microglial reactivity (LeBlanc et al 2011). Chemokine expression was increased in the thalamus of rats subjected to spinal cord contusion (Knerlich-Lukoschus et al 2011).

On the other hand, high-frequency stimulation (HFS) in the sciatic nerve at intensities recruiting C-fibers induces long-term potentiation (LTP) in the dorsal horn of the spinal cord during 4 to 9 hours (Liu and Sandkühler 1995). Spinal LTP could be at the origin of chronic pain arising after an initial painful event (Ruscheweyh et al 2011). In addition, this higher use-dependent synaptic strength between primary afferent-C-fibers and second order neurons in the superficial spinal dorsal horn is related to plastic changes associated with central hyperalgesia and sensitization (Sandkühler et al 2000). HFS in the sciatic nerve also causes supraspinal modifications perceptible through the development of enhanced and long-lasting neuron excitability in the ventral posterolateral nucleus (VPL) and cortical synchronization (Sanoja et al 2013), and it also enhances the excitability of neurons from the posterior triangular nucleus (PoT) of the thalamus. The PoT is one of the main targets of spinal and trigeminal lamina I neurons (Gauriau and Bernard 2004); PoT neurons project to the posterior insular cortex involved in pain perception in humans (Isnard et al 2011, Garcia-Larrea 2012a,b) and nociceptive processing in rodents (Coffeen et al 2011, Benison et al 2011).

Injuries in the nervous system causing neuropathic pain lead to several neural plastic changes in the thalamus, including reduction of inhibitory inputs, sensitization and hyperexcitability of thalamic neurons, glial reactivation, and overproduction of inflammatory mediators (e.g. chemokines). In addition, spinal long-term potentiation causes hyperexcitability of nociceptive neurons from the thalamus.

Hypothalamus

Experimental studies have shown that neurons from the hypothalamus change under conditions of neuropathic pain: after chronic constriction injury (CCI), synaptic cleft widths in neurons from the hypothalamic paraventricular nucleus were significantly larger compared to control animals, and postsynaptic density size decreased significantly in CCI rats. Compared with the control group, the active zone lengths in CCI rats also decreased significantly (Xu et al 2013). Under this same experimental paradigm and compared to the normal control group, AChE activity in the hypothalamic arcuate nucleus (ARC), the supraoptic nucleus (SON) regions, and also the paraventricular nucleus (PVN) were significantly downregulated in CCI rats (Wang et al 2012). All these findings suggest that CCI causes synaptic plasticity in neurons from the hypothalamus.

A hypothalamic nucleus particularly involved in the modulation of pain at the dorsal horn is the paraventricular nucleus (PVN). It is well-known that oxytocin (OT), synthesized and secreted by paraventricular nucleus neurons with spinal projection, modulates nociceptive information in the dorsal horn (Rojas-Piloni et al 2008, 2010, Condés-Lara et al 2009). More specifically, PVN neurons send collaterals at least to the superficial cervical and lumbar segments of the dorsal horn of the spinal cord (Condés-Lara et al 2007). Furthermore, OT

secreted by the hypothalamo-spinal projection exerts antinociceptive effects in the dorsal horn by binding with OT receptors expressed mainly in neurons' cell bodies and in non-peptidergic C-fibers (Moreno-López et al 2013). These antinociceptive effects of OT were minor in normal rats, but higher in rats subjected to spinal nerve ligation, suggesting that the central sensitization of OT receptors in the dorsal horn following neuropathic pain facilitates the antinociceptive effects of descending OT (Condés-Lara et al 2005). In addition, at spinal levels, OT also enhances GABA release from spinal interneurons located in the substantia gelatinosa (Rojas-Piloni et al 2007, Jiang et al 2014). Intraplantar injection of carrageenan causes the activation of oxytocinergic neurons in the PVN and leads to an elevation of spinal-located OT, producing local synthesis of allopregnanolone which, in turn, increases the GABAA receptor-mediated inhibitory tone (Juif et al 2013). Lastly, either PVN stimulation or intrathecal OT reduced or prevented the ability of the spinal LTP to selectively facilitate nociceptive-evoked responses of spinal wide dynamic range (WDR) neurons recorded in anesthetized rats (DeLa Torre et al 2009). Recently, blood concentrations of OT have been reported to also modulate nociception, windup plasticity and pain responses (Juif and Poisbeau 2013). Overall, these findings suggest that the hypothalamic paraventricular nucleus may be considered part of an integrated homeostatic analgesic system that modulates the transmission of pain in the dorsal horn by releasing oxytocin. As previously described, synaptic transmission at PVN was compromised after CCI (Xu et al 2013); these findings consequently suggest that this homeostatic analgesic system may be altered following CCI.

Chronic pain conditions such as rheumatoid arthritis and fibromyalgia are associated with profound dysfunction in the hypothalamic–pituitary–adrenal (HPA) axis, which may exacerbate the symptoms of chronic pain (Blackburn-Munro 2004). HPA axis dysfunction has also been

well-documented in animal models of chronic inflammatory pain (Bomholt et al 2004). On the contrary, in models of neuropathic pain after CCI, the basal HPA axis function remains unchanged (Bomholt et al 2005), and the increased nociceptive sensitivity during CCI-associated pain is linked to alterations in the limbic system, but it is nonetheless dissociated from HPA axis activation (Ulrich-Lai et al 2006). In this sense, plasma ACTH and corticosterone levels increased in CCI rats after 20 minutes of restraint stress compared with baseline, but the magnitude of the increase did not differ from sham rats. Furthermore, the temporal profile of ACTH release over the 60-minute period after termination of restraint was similar between CCI and sham rats, suggesting normal glucocorticoid-mediated feedback (Bomholt et al 2005). In addition, plasma ACTH and corticosterone levels were unaltered in CCI rats after restraint stress. However, CCI increased CRH mRNA expression in the central amygdala (CeA), but the expression of CRH mRNA in the paraventricular nucleus of the hypothalamus (PVN) and the fusiform and oval subregions of the bed nucleus of the stria terminalis (BST) were not affected by CCI. The CCI also increased the mRNA expression of the glucocorticoid receptor (GR) in the medial amygdala (MeA) and central amygdala (CeA), whereas GR mRNA expression was decreased by CCI in the CA1, CA3, and dentate gyrus subregions of the hippocampus. CCI did not affect GR mRNA expression in the PVN. These findings indicate that the mRNA expression of the glucocorticoid receptor in CCI rats is increased in the medial and central amygdala, unaffected in the paraventricular nucleus, and decreased in the hippocampus, suggesting that increased nociceptive sensitivity during chronic pain is associated with alterations in the limbic system, without HPA axis activation (Ulrich-Lai et al 2006). On the other hand, in the animal model of adjuvant-induced arthritis (AA), associated with hyperalgesia and allodynia in response to hind paw sensory stimulation, the HPA axis displayed dysfunction characterized by increased

basal plasma levels of ACTH and corticosterone (Harbuz et al 1993, Windle et al 2001). After intraplantar injection of carrageenan, the HPA axis was also altered with an over-secretion of corticosterone (Juif et al 2012). Lastly, clinical studies have reported hyperactive HPA-axis responses and diurnal variation in the loss of cortisol with elevated evening cortisol levels among patients with fibromyalgia (McCain and Tilbe 1989, Crofford et al 1994). However, the majority of clinical studies found reduced activity and impaired feedback sensitivity of the HPA axis in chronic pain conditions, mostly characterized by low basal levels of cortisol as well as a blunted cortisol response to a variety of stressors and dynamic tests (Maletic and Raison 2009, Macedo et al 2008, McBeth et al 2005, 2007, Turner-Cobb et al 2010). More recently, no associations with HPA-axis function have been found for either pain intensity or pain disability among persons with chronic multi-site musculoskeletal pain, in contrast to the hypothesis stating that HPA-axis dysregulation is associated with pain severity. In spite of these results, patients with chronic multi-site musculoskeletal pain and without depressive and/or anxiety disorders displayed significantly lower cortisol levels at awakening, lower evening levels, and a blunted diurnal slope. Interestingly, hypercortisolemia has been reported in patients with chronic pain and depressive/anxiety disorders, suggesting that the association between cortisol levels and chronic multi-site musculoskeletal pain appears to be partly masked (Generaal et al 2014). All the aforementioned findings suggest that several pains are associated with changes in the hypothalamus affecting the HPA axis, whereas other pains do not cause any functional changes on the HPA axis, but nonetheless affect the limbic structures involved in the processing of pain and the hypothalamus function (Fig. 4).

NEUROPLASTICITY OF THE BASAL GANGLIA AND CEREBELLUM IN THE CONTROL OF PAIN

There is clinical and experimental evidence supporting the fact that the basal ganglia and cerebellum, two structures involved in the control of motor activities, also participate in the control of pain; in this respect, plastic changes have been reported in both (Fig. 5).

Basal ganglia

Neural plasticity changes have been reported in the basal ganglia after neuropathic pain and inflammatory pain. One of the critical brain regions associated with the development of chronic back pain is the striatum, an area that participates in the formation of coherent behavioral responses by integrating three different functions: sensorimotor, emotional, and motivational (Haber 2003, Baliki et al 2010, Baliki et al 2012). Striatal function is strongly regulated by dopaminergic projections from the midbrain. Midbrain activity has been linked to pain control mechanisms, including endogenous opioid, μ-opioid receptor (MOR)-mediated antinociception (Morgan and Franklin 1990, Gear et al 1999, Schmidt et al 2002). The effects of striatal dopamine (DA) on pain are thought to be mediated by the DA D-2 receptor (D2R), since the striatal administration of selective D2R agonists reduced pain responses in animal models of persistent pain, whilst D2R antagonists enhanced this effect (Morgan and Franklin 1991, Magnusson and Fisher 2000, Taylor et al 2003). In addition, the development of an experimental chronic pain state in animal models found parallel reductions in both D2R expression and the excitatory drive in D2R-expressing neurons in the nucleus accumbens (Chang et al 2014, Schwartz et al 2014). In patients with chronic back pain, a decrease in baseline D2R/D3R was observed in the right ventral striatum: this reduction in the ventral striatum positively correlates with a reduction of μ-opioid receptors (MOR) in the amygdala. These findings indicate that, in

humans, changes in the neurotransmission of dopamine in the ventral striatum occur after chronic pain (Martikainen et al 2015).

In rats, functional magnetic resonance imaging (fMRI) scans of spared nerve injury (SNI) have shown a decrease in functional connectivity in the NAc core. These rats with SNI had behavioral signs of persistent neuropathic pain, including tactile allodynia after SNI. Moreover, peripheral nerve injury induced significant time-dependent changes in the expression of several important genes within the NAc (e.g. cannabinoid receptor 1, l-opioid receptor 1, serotonin1a receptor, D1 and D2 receptor) (Chang et al 2014). Changes in the expression of D1 and D2 in NAc were also reported after chronic constriction injury (Austin et al 2010). In addition, the upregulation of TNF-α (which is upregulated in NAc following SNI) reduced DA levels and enhanced the dopamine transporter in NAc (Wu et al 2014). Likewise, SNI also increases GluA1 (a subunit of the AMPA receptor) expression at NAc synapses, leading to the formation of Ca^{2+}-permeable AMPA receptors (CPARs). These CPARs, in turn, exert powerful control on the depressive symptoms of chronic pain (Goffer et al 2013).

MicroRNAs (miRNAs) are endogenous small non-coding RNAs that regulate gene expression through the modulation of target messenger RNAs (mRNAs). Sciatic nerve ligation (SNL) induces a drastic decrease in the expression of miR200b and miR429 in NAc neurons. Consequently, a SNL-based injury causes changes in the gene expression of NAc neurons via miRNAs (Imai et al 2011).

A decrease in ventral striatal dopamine, associated with a concomitant rise in the content of norepinephrine, has been linked to a decrease in mechanical withdrawal thresholds (indicative of neuropathic pain -cuff- in animals): mechanical thresholds shifted from being correlated with dopamine to norepinephrine in neuropathic pain, which suggests adaptations in ventral striatal

neurochemistry that may underlie the pathological pain associated with nerve injury (Taylor et al 2014).

Cerebellum

The fluorodeoxyglucose micro-positron emission tomography (FDG micro-PET) imaging technique has revealed a decrease in connections in the cerebellum and certain prefrontal regions in rats with spinal nerve ligation (SNL), suggesting a potential association between neuropathic pain and connectional plasticity of the resting-state brain (Kim et al 2014). After tibial and sural nerve transection (TST) in model rats, rats with neuropathic pain showed increased mechanical sensitivity of the injured hind paw. In the micro-PET scan, the cerebellum was gradually activated (initially starting from the anisoform lobule) from the third to the eighth week in all image acquisitions. The longitudinal micro-PET scan study of brains from neuropathic pain rat models showed sequential cerebellar activity that was in accordance with results from behavioral test responses, thus supporting a role for the cerebellum in the development of neuropathic pain (Kim et al 2015).

Several experimental studies indicate that CCI causes an upregulation of nitric-oxide synthase (NOS) expression in the cerebellum, related with pain responses, suggesting that neuropathic pain causes changes in the levels of nitric oxide in the cerebellum, subsequently affecting pain modulation (Önal et al 2003, Farghaly et al 2012).

In addition, a reduction in the volume of gray matter was observed in the cerebellum of patients with trigeminal neuralgia (TN) (Obermann et al 2013). A clinical study also revealed that, among patients with neuropathic pain who are more sensitive to both thermal and

mechanical stimuli applied to the same region of the face (V2 or the maxillary division of the trigeminal nerve), heat pain induced activation of the cerebellar regions involved in sensorimotor processing (anterior lobe, lobules III–V, and lobules VI and VIIIA), as well as areas involved in cognitive processing (lobule CRI). The activation pattern was not very different from heat in healthy subjects. For brush-induced allodynia, activation in the cerebellum was observed in sensorimotor regions in lobules III to V, putative secondary somatosensory regions (lobule VIII), vestibular regions (lobule IX), cognitive regions (lobules VIIB, CRI, CRII), and prominent dentate nucleus activation: this pattern was nonetheless different from neuropathic and healthy subjects. Innocuous brush stimuli in healthy subjects produced decreased cerebellar activation in the lobules involved in somatosensory processing. These findings suggest that neuropathic pain causes functional changes in the cerebellum related with the modulation of emotional and cognitive experiences, distinguishing the perception of pain from the appreciation of innocuous sensory stimulation (Borsook et al 2008).

EPITHALAMIC STRUCTURES RELATED WITH PAIN

The habenula and the pineal gland are the two main structures in the epithalamus: they are both associated with the modulation of nociceptive inputs and pain sensitivity, but plastic changes have only been reported in the habenula.

Habenula

Few studies have reported changes in the neural plasticity of neurons from the habenula, and they all are related with their activation. Excitotoxic injury of the dorsal spinal cord, by

means of injection of quisqualic acid (QUIS), causes significant activation of the habenular complex (HBC) (Paulson et al 2005). After chronic constriction injury, similar patterns were observed (Paulson et al 2000). Neonatal rats subjected to LPS injections showed hyperalgesia to formalin test and also activation of the HBC (Zouikr et al 2014). In contrast, streptozotocin-diabetic rats showed thermal hyperalgesia but no HBC activation (Paulson et al 2007). These results suggest that neuropathic pain and inflammatory pain cause activation of neurons located in the HBC, whereas other painful syndromes do not.

About two thirds of the neurons in the lateral habenula respond to peripheral noxious stimuli, according to the extracellular electrical recordings of single units in the anaesthetized rat (Benabid and Jeaugey 1989). The firing pattern of lateral habenula cells is either excitatory (75%) or inhibitory (24%), and it is also related to the intensity of the stimulus, and the receptive field is large and bilateral. Most of these cells do not respond to non-noxious stimuli (Benabid and Jeaugey 1989). Lesions of the habenular nuclei increase pain sensitivity whilst any lesion of the fasciculus retroflexus, a pathway connecting the habenular nuclei with the interpeduncular nucleus, also enhances pain sensitivity (Mészáros et al 1985).

NEUROPLASTICITY OF THE CORTEX WITH NEUROPATHIC PAIN AND INFLAMMATORY PAIN

Functional imaging studies in humans, as well as anatomical and physiological studies in animals, have shown the activation of multiple cortical areas after painful stimuli; these areas included the primary and secondary somatosensory cortex, motor cortex, insular cortex, anterior cingulate cortex and prefrontal cortex (Treede et al 1999). Clinical and experimental studies showed neuroplasticity in almost all of these cortical areas (Fig. 6).

Somatosensory and motor cortices

Peripheral nerve injury triggers maladaptive plastic changes along the somatosensory system, altering nociceptive signal processing (Costigan et al 2009, Melzack et al 2001, Devor 2006). In functional brain imaging studies, nerve-injured patients and animals showed enhanced excitation, somatotopic reorganization, and changes in cortical thickness in the SI, the amount of which highly correlates with the degree of allodynia (Peyron et al 2004, DaSilva et al 2008, Cha et al 2009). The injury based on partial sciatic nerve ligation (PSL) markedly increased the mechanical sensitivity of the injured paw: the increase was detected within the very first day, peaking on day 6, and persisting for at least 1 month. Simultaneously, somatosensory-evoked potentials significantly increased in PSL animals, and spine density had increased significantly after the first 6 days post-lesion. These results suggest that peripheral nerve injury induces rapid and selective remodeling of cortical synapses, which is associated with the development of neuropathic pain (Kim and Nabekura 2011). PSL injury also induces cortical excitability changes related with neuropathic pain development (Cha et al 2009).

Structural changes have also been reported in patients with trigeminal neuralgia (TN): these patients experience a reduction in the volume of gray matter in the primary somatosensory and orbitofrontal cortices, as well as in the secondary somatosensory cortex, thalamus, insula, anterior cingulate cortex (ACC), cerebellum, and dorsolateral prefrontal cortex (Obermann et al 2013).

Phantom limb pain (PLP) is a condition characterized by experiencing sensations of pain in the missing limb. It is usually more common at early stages post-amputation (Jensen and Rasmussen 1995). It has been reported that PLP causes enhanced plasticity in both the motor and

somatosensory systems, consisting in a reorganization of the cortical map with hyperexcitability of these areas (Karl et al 2001). Traumatic amputations accompanied by PLP show a shift of the cortical areas adjacent to the amputation area towards the representation of the deafferented body part (Montoya et al 1998).

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder defined by symptoms of chronically recurring abdominal pain associated with alterations in bowel habits. IBS-affected patients show a pattern of alteration in both white matter and the microstructure of subcortical gray matter consistent with impairment of the corticothalamic-basal ganglia-cortical loops involved in the processing of pain-related signals (Ellingson et al 2013).

Changes in the topographical organization of the primary sensory and motor cortices are induced after deafferentation due to spinal cord injury (SCI) (Moxon et al 2014). In addition, SCI patients with persistent neuropathic pain below the level of the injury show reorganization of the primary somatosensory cortex that correlates with the intensity of pain (Wrigley et al 2009). There is an association between spinal cord atrophy and the presence of neuropathic pain (NP) in SCI patients with neuropathic pain. The magnitude of atrophy above the neurological level of the lesion is associated with the presence of below-level NP in individuals with paraplegia: thus, individuals with greater cord atrophy are more likely to exhibit below-level NP regardless of the neurological level of the lesion. Likewise, in individuals with SCI, below-level NP is accompanied with reduced gray matter volume in SI and the thalamus, as well as increased gray matter in the primary motor cortex (MI) and ACC (Jutzeler et al 2016).

Insular cortex

Injuries in the insular cortex prior to inflammatory pain (plantar injection of carrageenan) or neuropathic pain (ligature of the sciatic nerve; CCI) in rats produce a significant decrease in pain-related behaviors, suggesting the important role that the insular cortex could play in the modulation of both inflammatory and neuropathic pain (Coffeen et al 2011). Pharmacological evidence suggests that the activation of D2 or the blockade of D1 dopaminergic receptors elicit antinociception after neuropathic pain in the insular cortex (Coffeen et al 2008). Following inflammatory nociception, dynamic neurotransmitter response was observed in the insular cortex; a gradual decrease in the release of dopamine accompanied with an increase in D2-receptors and a decrease in D1-receptors mRNA was observed in this experimental model of pain (Coffeen et al 2010).

Long-term potentiation of glutamatergic transmission has been observed after either physiological learning or pathological injuries in various brain regions, including the spinal cord, hippocampus, amygdala, and cortices. In the insular cortex the expression of AMPARs is enhanced after nerve injury by a pathway involving adenylyl cyclase subtype 1 (AC1), A-kinase anchoring protein 79/150 (AKAP79/150), and protein kinase A (PKA). This enhancement may (at least in part) contribute to behavioral sensitization together with other cortical regions, such as the anterior cingulate and the prefrontal cortices (Qiu et al 2014). Moreover, an increase in synaptic NMDA receptors in the insular cortex also contributes to neuropathic pain after peripheral nerve injury (Qiu et al 2013).

Complex regional pain syndrome (CRPS) is a neurological illness characterized by spontaneous pain that extends beyond the sensory distribution of any single nerve; it is also disproportionate to the inciting event. Swelling (edema), temperature changes, and excess sweating are commonly observed, distinguishing CRPS from other possible neuropathic pain

disorders (Birklein et al 2000). Several studies have reported that CRPS patients show decreased gray matter volume in several pain-affected regions (dorsal insula, left orbitofrontal cortex, and several aspects of the cingulate cortex), whereas greater gray matter volume has been observed in the bilateral dorsal putamen and the right hypothalamus (Barad et al 2014). Among children with CRPS, reduced gray matter is also reported in the primary motor cortex, premotor cortex, supplementary motor area, midcingulate cortex, orbitofrontal cortex, dorsolateral prefrontal cortex (dlPFC), posterior cingulate cortex, precuneus, basal ganglia, thalamus, and hippocampus (Erpelding et al 2016).

Primary dysmenorrhea (PDM) is the most prevalent gynecological disorder for women of reproductive age. PDM patients suffer from lower abdominal pain starting with the onset of menstrual flow. Prolonged nociceptive inputs to the central nervous system can induce functional and structural alterations throughout the nervous system. More specifically, PDM patients showed increased regional gray matter volumes in the right posterior hippocampus/parahippocampus, anterior/dorsal posterior cingulate cortex along the cingulate gyrus, dorsal midbrain (PAG), hypothalamus, left ventral portion of precuneus, left superior/middle temporal gyrus, and right cerebellar tonsil, whilst decreases in regional gray matter volume were reported in the right medial frontal gyrus within medial prefrontal cortex (mPFC), right central portion of precuneus, right ventral portion of precuneus, bilateral secondary somatosensory cortices (SII), insula, right culmen, and left cerebellar tonsil (Tu et al 2010).

As for patients with fibromyalgia, a reduction affecting regional gray matter in the left parahippocampal gyrus, bilateral mid/posterior cingulate gyrus, left insula and medial frontal cortex has been reported (Kuchinad et al 2007). Moreover, pain in patients affected by

fibromyalgia correlated with (i) reduced connectivity between PAG and anterior insula, (ii) reduced connectivity between SII and primary somatosensory, visual, and auditory cortices, and (iii) increased connectivity between SII and the default mode network (Pujol et al 2014).

Burning mouth syndrome (BMS) is characterized by a burning sensation in the oral cavity, which appears without stimulation and for which no medical cause has been found yet. The burning sensation frequently appears on the tongue, but can also involve the hard palate, the lips and the alveolar ridges, whereas the buccal mucosa and the floor of the mouth are less frequently affected. In BMS patients, modification of gray matter concentration has been found, affecting the anterior and posterior cingulate gyrus, lobules of the cerebellum, insula/frontal operculum, inferior temporal area, primary motor cortex and dorsolateral prefrontal cortex (Sinding et al 2016). In addition, in BMS patients, lower gray matter volumes were identified in the insula, cingulate, amygdala, hippocampus, putamen, and frontal regions, whereas greater gray matter volumes were observed in the SI (Labus et al 2014).

In patients with chronic neuropathic pain after SCI, significant structural and functional abnormalities in several brain regions associated with nociceptive processing have been observed. The aforementioned structural and metabolic abnormalities found in cortical areas of the anterior insula, ACC, and prefrontal regions might be associated with failures in pain modulation. In contrast, the changes in white matter affecting the internal capsule, cerebral peduncle, and superficial white matter of the pre- and post-central cortex and prefrontal area seem to be associated with both abnormal pain modulation and/or motor impairment (Yoon et al 2013).

Anterior cingulate cortex

Neuronal hyperexcitability in the anterior cingulate cortex (ACC) is considered one of the most important pathological changes responsible for the chronification of neuropathic pain. In this sense, several electrophysiological studies have indicated that increased excitability of ACC layer 2/3 neurons mainly results from the increased excitatory afferent activity altered by long-term peripheral sensitization in the nociceptive system (Basbaum et al 2009, Costigan et al 2009). Recently, the firing activity of layer V ACC neurons by whole-cell current-clamp recordings in brain slices following chronic constriction injury has been carried out with the aim of assessing the effect of neuropathic pain in the brain. Data stemming from these studies provide strong evidence supporting the fact that mGluR1 is upregulated and activated after peripheral nerve injury, inducing neuronal hyperexcitability through the inhibition of HCN1 in ACC neurons (Gao et al 2016). Along similar lines, another study also reported that CCI nerve injury causes strengthening of the intrinsic excitability of pyramidal neurons in ACC (Blom et al 2014). Neuropathic pain by chronic constriction injury (CCI) is accompanied by an increase in the rates of spontaneous oscillations of ACC neurons. This change may be critical not only for the development of neuropathic pain, but also for pain hypersensitivity and spontaneous pain (Ning et al 2013). Electrophysiological studies have also shown that inflammatory pain enhances presynaptic glutamate release in ACC neurons, mediated by an increase in neuronal cAMP (Wu et al 2008).

Peripheral nerve injury also causes molecular changes in ACC neurons. Specifically, a decrease in dopamine D1 and D2 receptor expression (Ortega-Legaspi et al 2011) and muscarinic-1 and -2 receptors (M1R, M2R) (Ortega-Legaspi et al 2010) were reported in ACC after an animal model of neuropathic pain. Similarly, inflammatory pain also causes a reduction of NMDA receptors in ACC neurons (Chen et al 2008). However, the ligation of the common

peroneal nerve (CPN), an experimental model of neuropathic pain, increases the postsynaptic expression of the AMPA receptor in pyramidal neurons in layer V of the anterior cingulate cortex (Chen et al 2014).

Moreover, astrocyte activation has been observed in the ACC in models of chronic, neuropathic and inflammatory pain (Chen et al 2012, Kuzumaki et al 2007, Lu et al 2011, Yamashita et al 2014) and also for paclitaxel-induced neuropathic pain (Masocha 2015). Likewise, BDNF is upregulated in the ACC and the primary sensory cortex (SI) in rats with inflammatory pain, causing neuronal hyperexcitability (Thibault et al 2014).

Prefrontal cortex

Neuropathic pain induced by spared nerve injury (SNI) is associated with mechanical and thermal hypersensitivity, as well as depression-like behaviors, cognitive impairments, and obsessive-compulsive activities. These changes are related with an enhancement of glutamate release in the medial prefrontal cortex (mPFC) that is linked to increased synaptic vesicle proteins and amino acid levels, and the activation of the ERK1/2- and CaMKII-synapsin signaling cascade in presynaptic axonal terminals. Enhanced supraspinal glutamate levels following nerve injury are associated with pathophysiological mechanisms responsible for neuropathic pain (Guida et al 2015, Hung et al 2014).

Chronic back pain (CBP) is one of the most frequent pain disorders in the general population. Roughly 70 to 85% of all people have experienced back pain at some point in their lifetime. Brain atrophy (e.g. dorsolateral prefrontal cortices) has been reported in patients with CBP (Apkarian et al 2004, Schmidt-Wilcke et al 2006).

Patch-clamp recordings and anatomical analyses of layer II/III pyramidal neurons in the contralateral medial prefrontal cortex of SNI and sham-operated rats have been made in order to assess the effect of neuropathic pain in the brain. Results showed that neuropathic pain is associated with morphological and functional changes. Morphologically, the neurons from SNI in animals showed increased dendritic complexity and spine density in basal dendrites compared to the sham-operated group. From a functional point of view, SNI neurons showed a great increase in the NMDA/AMPA ratio in currents synaptically evoked by layer V stimulation, whereas the basic electrical properties of neurons did not differ between both groups. These findings provide evidence of pain-related morphological and functional changes in the cortex (Metz et al 2009). In addition, the firing activity of layer V prelimbic medial prefrontal cortex (mPFC) neurons by whole-cell current-clamp recordings in brain slices following peripheral injection of complete Freund's adjuvant (CFA), a well-characterized inflammatory pain model, has been carried out with the aim of assessing the effects of inflammatory pain in the brain. Results suggest that the electrophysiological properties of pyramidal cells in layer V prelimbic mPFC are significantly altered under peripheral inflammatory pain conditions (Wu et al 2016).

Reduced connectivity of the prefrontal cortex (mPFC) and mediodorsal thalamus (MD) is associated with spatial working memory impairment in rats with inflammatory pain (Cardoso-Cruz et al 2013a). Similarly to basal ganglia, changes in miRNA expression were also reported in the prefrontal cortex. More specifically, significantly increased levels of miR-155 and miR-223 were detected in the prefrontal cortex of carrageenan-injected mice (Poh et al 2011).

In summary, the above paragraphs lead to the conclusion that acute pain and chronic pain cause structural, functional and molecular plasticity in several cortical areas of the brain, and also in other subcortical structures of the CNS.

NEURAL PLASTIC CHANGES OF THE LIMBIC SYSTEM

The limbic system includes the hypothalamus, mammillary bodies, hippocampus, septum, amygdala, cingulated and prefrontal cortex. Neural changes in these structures have been reported after neuropathic and inflammatory pain. Some of these changes affecting specific structures have already been analyzed in previous sections. The present section focuses on explaining the plastic changes in the amygdala, septum, hippocampus and mammillary bodies (Fig. 7).

Amygdala

Rats with spared nerve injury (SNI) displayed signs of depressive-like behavior accompanied by an increase in amygdalar volume. No alterations were found in the dendritic arborizations of the neurons in the amygdala, but the amygdalar hypertrophy was associated with an increased cell proliferation in the central (CeA) and basolateral (BLA) amygdaloid nuclei. These findings suggest that neuropathic pain promotes the generation of new neurons in the amygdala. These neuroplastic changes might contribute to the development of depressive-like symptoms frequently present in prolonged pain syndromes (Gonçalves et al 2008).

Using the formalin test as a mouse model of persistent inflammatory pain, the activation of ERK in the amygdala has been reported to be both necessary and sufficient to induce long-lasting peripheral hypersensitivity to tactile stimulation. The blockade of inflammation-induced ERK activation in the amygdala significantly reduces long-lasting peripheral hypersensitivity

associated with persistent inflammation, while the pharmacological activation of ERK in the amygdala induces peripheral hypersensitivity in the absence of inflammation (Carrasquillo and Gereau 2007). Likewise, after carrageenan-induced inflammatory pain in the rat, BLA slow-firing neurons (supposed GABAergic) with decreased activity and BLA fast-firing neurons (supposed glutamatergic) remain hyperactive after 4 hours following intraplantar microinjection of carrageenan.

Cortex pyramidal neurons responding with excitation to BLA electrical stimulation or mechanical paw pressure were inhibited by inflammation. In addition, complete firing suppression of cortical neurons responding with inhibition after BLA electrical stimulation was also seen. This inhibition could be due to glutamatergic neuron hyperactivity in the BLA leading to GABA increase in the mPFC. These findings suggest that carrageenan-induced inflammatory pain could be associated with changes in BLA mGluR1 or mGluR5 expression and with an increased GABA release in the mPFC which may, in turn, induce neural deactivation following intra-paw carrageenan (Luongo et al 2013). On the other hand, it has been reported that chronic pain (complete Freund's adjuvant, sciatic nerve ligation) has an anxiogenic effect in mice, which may be associated with changes in the opioidergic function in the amygdala (Narita et al 2006).

Pain-related neuroplasticity in the amygdala has been established in electrophysiological and biochemical studies in brain slice preparations obtained from animals after the induction of different pain states, suggesting that brain changes persist regardless of continued afferent inputs, at least in part (Neugebauer 2015).

In humans, pediatric patients with complex regional pain syndrome (CRPS) showed changes in the functional connectivity of the amygdala with the cortical and subcortical regions (Simons et al 2014).

The aforementioned findings as a whole suggest that inflammatory pain and neuropathic pain cause neuroplasticity changes in the amygdala.

Septum

After spared nerve injury, an increase in the metabolism of the prefrontal-limbic-brainstem areas has been reported, including the septal area and also the anterior olfactory nucleus, insular cortex, piriform cortex, basal forebrain/preoptic area, amygdala, hypothalamus, rostral ventromedial medulla and ventral midbrain (Kim et al 2014). Along the same lines, an increase in enkephalin mRNA and protein expression was reported in the amygdala and the lateral septum after intraplantar injection of the inflammatory agent carrageenan (Victoria et al 2013). Therefore, the implication of all these findings is twofold: (i) the potential involvement of the septum in pain modulation and (ii) that injuries related with pain from the nervous system cause plastic changes in the septum.

Hippocampus

Hippocampal changes have been reported after neuropathic, inflammatory and painful syndromes. The formalin model of inflammatory pain causes a decrease in the number of Fos-positive cells in whole CA1, CA3 and dentate gyrus, with a more significant effect in the posterior–ventral regions of the hippocampus (Khanna et al 2004). Inflammatory models of pain (e.g. formalin, complete Freund's adjuvant) downregulate the expression of both the NK-1 receptor and BDNF genes in the hippocampus (Duric and McCarson 2005). Neuropathic pain models (e.g. chronic constriction injury, spared nerve injury) cause a robust expression of IL-1β

in the hippocampus contralateral to the lesion site that correlates with neuropathic pain behavior (del Rey et al 2011, 2012).

N-acetylaspartate (NAA) is a metabolite recognized as a marker of neuronal structure and function. Levels of NAA decrease in the hippocampus of patients with fibromyalgia. These findings suggest a neuronal abnormality in the hippocampus of fibromyalgia-affected patients (Aoki et al 2013).

A weak but widespread increase concerning hippocampal connectivity has been observed in patients with back pain, compared with control subjects. This hyperconnectivity causes a disruption in the normal network of the hippocampus that may have an impact on its standard functions in learning, memory, and emotional regulation (Mutso et al 2014).

Evidence from both animal neurophysiological recordings and human brain imaging studies shows that neural activity of the medial prefrontal cortex (mPFC) and the hippocampus correlates with the retention of information over a brief period of time, a function that is crucial for a wide range of cognitive tasks (Stern et al 2001). Impaired working memory is observed in several clinical conditions including chronic pain (Ling et al 2007, Luerding et al 2008). In rats, spared nerve injury (SNI) causing chronic neuropathic pain affects fronto-hippocampal functional connectivity, impairing spatial memory performance in these animals (Cardoso-Cruz et al 2013b).

Mammillary bodies

Despite the fact that mammillary bodies have not been directly associated with pain and painful syndromes, it is well-known that a bilateral injection of Zoplicone in mammillary bodies

produces a significant increase in punished responses (0.1-second electrical shock to the paws). In addition, the mammillary body is a potential site of antianxiety action for benzodiazepines (Kataoka et al 1982, Yamashita et al 1989). Likewise, several studies have highlighted the involvement of mammillary bodies in behaviors of anxiety and defense (Silveira et al 1993, Beck and Fibiger 1995), and the acquisition and expression of contextual fear share common brain regions involved in fear, anxiety, and defensive behavior, such as the periaqueductal gray, the hippocampus, the mammillary bodies and the habenula (González-Pardo et al 2012). Periaqueductal gray matter, hippocampus and habenula are CNS structures also involved in pain processing and modulation. The involvement of mammillary bodies in these pathways is highly likely, although further studies to ascertain this potential involvement should be conducted.

CONCLUSIONS

The development of pathological pain, i.e. pain caused by traumatic or inflammatory injury to the nervous system, triggers a series of plastic changes in the central nervous system itself that are responsible for the enhancement and perpetuation of pain. This review shows the impact of these changes at structural (remodeling of synapses and neural circuits) and functional (changes of synapses, neuronal excitability and neural circuits) levels. The reason behind these changes is that injuries cause genetic and molecular changes in the affected neurons, leading to observable structural and functional changes. Although the trigger for pain injury only affects the peripheral nervous system, changes are transmitted throughout the central nervous system, inducing multiple plastic changes in all the spinal and supraspinal structures involved in the processing and modulation of pain. These changes are not confined to neurons, but also affect

the glial cells surrounding them, and especially neuron-glia interaction. As noted in this review, pathological pain interferes with multiple tasks such as cognition, orientation, and emotional states. Knowledge of these plastic changes may enable the development of new therapies to improve the quality of life of patients suffering from painful conditions.

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FIGURE LEGENDS

Figure 1. Brainstem and diencephalic structures associated with the modulation of pain. Anatomical sagittal **[A]** and frontal **[B]** sections of head from two fresh-frozen adult cadavers, obtained from the body donation program of the University of Girona, showing several anatomical structures related with pain modulation. *1. Thalamus; 2. Anterior commissure; 3. Stria medullaris; 4. Habenula; 5. Mammillary body; 6. Posterior commissure; 7. Mesencephalon; 8. Pons; 9. Medulla oblongata; 10. Fourth ventricle; 11. Fornix; 12. Red nucleus; 13. Hippocampus; 14. Caudate nucleus; 15. Putamen; 16. Subthalamic nuclei; 17. Substantia nigra*. **[C]** Schematic representation of afferent inputs related with locus coeruleus

(LC). LC receives inputs from prefrontal cortex (Arnsten and Goldman-Rakic 1984), bed nucleus of the stria terminalis (Van Bockstaele et al 1999a), hypothalamic nuclei (Peyron et al 1998), raphe nuclei (Pickel et al 1977), amygdala (Van Bockstaele et al 1998), solitary nucleus (Van Bockstaele et al 1999b), nucleus paragigantocellularis, periaqueductal gray matter, nucleus prepositus hypoglossus, insular and perirhinal cortices, and the intermediate zone of the spinal cord (Aston-Jones et al 1991), indicating that it integrates information from the autonomic nervous system, neuroendocrine nuclei, stress and limbic circuitry, as well as higher order cognitive centers. There is also evidence of input from spinal cord lamina I cells (Craig 1992), suggesting that LC also integrates nociceptive information. **[D]** Schematic representation of the descending pain modulation pathway. Periaqueductal gray (PAG) receives inputs from neurons located in lamina I, and also from neurons of the reticular regions of laminae IV-V, laminae VI-VIII and lamina X in rats. The axons of these spinal cord neurons constitute the spinomesencephalic pathway (Lima 2009). In addition, PAG also receives afferent inputs from prefrontal and agranular insular cortices as well as from the amygdala and hypothalamus. Other brainstem inputs to the PAG include the nucleus of tractus solitarius (NTS), adjacent nucleus cuneiformis (ANC), pontine reticular formation (PRF), locus coeruleus (LC) and other catecholaminergic nuclei (Heinricher and Ingram 2009). The main descending projection from PAG is the rostral ventral medulla (RVM) and the dorsomedial nucleus of the hypothalamus (DMH). However, RVM neurons are also likely to receive spinothalamic inputs, and inputs from noradrenergic neurons in the pons, particularly the A7 cell group (Heinricher and Ingram 2009). In turn, RVM neurons project to the dorsal horn through the dorsolateral funiculus, forming synapses with spinal cord neurons of the dorsal horn, in both superficial and deep layers (Heinricher and Ingram 2009, Heinricher et al 2009). On the other hand, in the cat and monkey it

is generally agreed that afferents from the sensorimotor cortex terminate throughout most of the red nucleus, including the magnocellular region which gives rise to the rubrospinal tract (Rinvik and Walberg 1963, Mabuchi and Kusama 1966, Kuypers and Lawrence 1967, Padel and Smith 1971). In the rat, however, the corticorubral projection terminates entirely within the parvocellular part of the nucleus that does not project down the spinal cord (Gwyn and Flumerfelt 1974). In the cat and rat, RN also receives afferent inputs from the cerebellum (Angaut et al 1986, Daniel et al 1987, Condé 1988), limbic structures (Morecraft and Van Hoesen 1998), thalamus (Roger and Cadusseau 1987, Mitrofanis 2002) and peripheral primary afferent fibers by passing both the cerebellum and the cerebral cortex (Padel et al 1986).

Figure 2. Brainstem, nociceptive modulation and neural plastic changes in PAG-RMV system. **[A]** Sagittal anatomical section from fresh-frozen adult cadaver showing the diencephalon and human brainstem (midbrain, pons and medulla oblongata) in detail. **[B]** Horizontal anatomical section from adult cadaver through the mesencephalic region. *1. Septum pellucidum; 2. Thalamus; 3. Hypothalamus; 4. Anterior commissure; 5. Septal area; 6. Lamina terminalis; 7. Mammillary body; 8. Fornix; 9. Stria medullaris; 10. Habenula; 11. Posterior commissure; 12. Ventral tegmental area; 13. Red nucleus; 14. Substantia nigra (pars reticular); 15. Substantia nigra (pars compacta) pus; 16. Cerebral aqueduct; 17. Periaqueductal substance*. **[C]** Neuroplasticity changes were reported in PAG-RVM system neurons. The hyperexcitability of these PAG-RVM neurons by ascending pathways causes input of calcium ions (Ca^{2+}), and probably the generation of second messengers. Both intracellular mediators are able to facilitate the transcription of target genes that result in downregulation of cannabinoid receptors (CBr) and mu opioid receptors (MOR), but an upregulation of NMDA and AMPA receptors. It is also

possible that the reduction of CBr and MOR receptors observed in PAG-RVM neurons may be caused by internalization of both receptors (see text for details). **[D]** Schematic representation of ascending and descending pain pathways by brainstem. Peripheral nerve injury by chronic constriction injury (CCI) or inflammation causes hyperexcitability of afferent nociceptive nerve fibers that, at the dorsal horn of spinal cord, cause excitability of dorsal horn (DH) neurons. Consequently, these DH neurons generate more action potentials that propagate by spinothalamic pathway but also by other ascending pathways including spinobulbar pathway [i], which projects to neurons located in the ventrolateral reticular formation, dorsal reticular nucleus, nucleus tractus solitari and rostral ventromedial medulla (RVM), the spinopontine pathway that projects to neurons from the parabranchial nuclei and locus coeruleus (LC) [ii], and the spinomesencephalic pathways that project to neurons of periaqueductal gray matter (PAG) [iii] (Lima 2009). PAG neurons project their descending axons to neurons located in LC and RVM. Neurons located in the RVM and LC directly project their axons to the spinal DH. PAG-RVM system represents the main descending modulatory pathway of pain transmission at the dorsal horn of the spinal cord (Heinricher and Ingram 2009), despite the fact that other brainstem nuclei located in the caudal medulla such as the dorsal reticular nucleus (DRt) and ventrolateral medulla (VLM) also project to the spinal cord for modulating their pain transmission (Heinricher et al 2009). Under physiological conditions, descending PAG-RVM system causes the liberation of serotonin (5-NT) and norepinephrine (NE) over DH neurons inducing the hyperpolarization of these neurons via potassium channels (K^+). However, after CCI and/or inflammatory conditions that generate acute and/or chronic pain, the physiology of PAG-RVM system changes (see text for details).

Figure 3. The thalamus and its projections. [A] Anatomical detail of diencephalon. Midsagittal view from an adult cadaver. *1. Thalamus 2. Septal area; 3. Anterior commissure; 4. Lamina terminalis; 5. Tuber cinereum; 6. Mammilary body; 7. Stria medullaris; 8. Habenula; 9. Pineal gland; 10. Posterior commissure; 11. Cerebral aqueduct; 12. Periaqueductal substance; h1. Hypothalamus, preoptic area; h2. Hypothalamus, anterior region; h3. Hypothalamus, tuberal region; h4. Hypothalamus, posterior region*. **[B]** Main thalamic nuclei and spinothalamic and thalamocortical projections. The nociceptive areas of the spinal cord dorsal horn (lamina I, V and deep) project to several nuclei in the lateral thalamus including ventral posterior lateral nucleus (VPL), ventral posterior medial nucleus (VPM), ventral posterior inferior nucleus (VPI), posterior part of the ventromedial nucleus (VMpo) and in the medial thalamus such as ventrocaudal part of medial dorsal nucleus (MDvc), parafascicular nucleus (Pf) and centrolateral nucleus. In turn, neurons from all these thalamic nuclei project to several cortical areas including primary and secondary somatosensory cortex (SI, SII), insula (IC) and anterior cingulate cortex (ACC) (Treede et al 1999).

Figure 4. Neuroplasticity changes in the thalamus and hypothalamus. Plastic changes of the thalamus and hypothalamus after chronic constriction injury (CCI) and/or inflammation. Intracellular recording in neurons from ventral posterior lateral nucleus (VPL) and ventral posterior medial nucleus (VPM) nuclei of thalamus showed hyperexcitability after CCI and/or inflammation (see text for details). In addition, changes in the hypothalamic-pituitary-adrenal (HPA) axis were also reported after CCI/inflammation. Under physiological conditions, the hypothalamus releases corticotropin-releasing hormone (CRH). In turn, this hypothalamic factor regulates the release of adrenocorticotropic hormone (ACTH) into systemic circulation. The

main target for circulating ACTH is the adrenal cortex, where it stimulates glucocorticoid synthesis. However, in response to stress such as acute and/or chronic pain, neurons in the paraventricular nucleus (PVN) of the hypothalamus synthesize and secrete corticotropin-releasing factor (CRF), the main regulator of the HPA axis. CRF is released into hypophysial portal vessels that access the anterior pituitary gland. Binding of CRF to its receptor on pituitary corticotropes induces an over-synthesis and release of ACTH into systemic circulation and in turn this hormone causes also upregulation of glucocorticoids in adrenal gland (Smith and Vale 2006). In addition, neuropathic pain and peripheral inflammation cause upregulation of glucocorticoid receptors (GCRs) in neurons located in several central nervous system (CNS) nuclei associated with pain processing and/or modulation. Consequently, the uprelease of glucocorticoids under stress/pain also potentiates neuropathic/inflammatory pain. Likewise, GCRs also were increased in glial cells after neuropathic pain, and glucocorticoids improved the inflammatory response of microglia and astrocytes with higher levels of pro-inflammatory cytokines and chemokines that stimulate nociceptive neurons (Madalena and Lerch 2016).

Figure 5. Neuroplasticity changes of basal ganglia, cerebellum and habenula after neuropathic and/or inflammatory pain. [A] Anatomical horizontal section through the basal ganglia from an adult human specimen. *1. Caudate; 2. Claustrum; 3. Putamen; 4. Globus pallidus (external segment); 5. Globus pallidus (internal segment); 6. Thalamus; 7. Interthalamic adhesion; 8. Pulvinar; 9. Insular cortex; 10. Habenula; 11. Pineal gland; 12. Fornix (anterior column)*. **[B]** Neuropathic pain and inflammation pain cause downregulation of D1 and D2 receptors in neurons of basal ganglia, whereas AMPA/GluA1 receptors increase in

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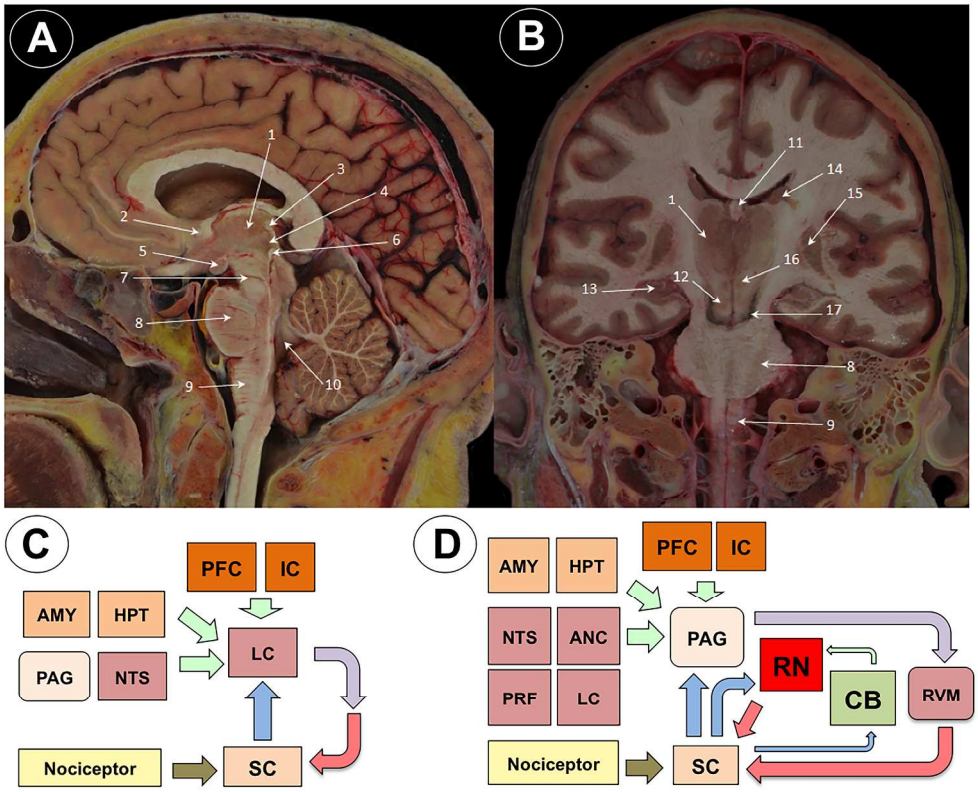
Figure 6. Neuroplasticity changes of cortical neurons. Anatomical lateral view **[A]** and midsagittal view **[B]** from an adult human encephalon, showing cortical areas related to neuroplasticity changes in neuropathic and/or inflammatory pain. *1. Prefrontal cortex; 2. Primary somatosensorial cortex; 3. Anterior cingular cortex.* **[C]** The main plastic changes observed in cortical neurons of several areas such as somatosensory cortices, insula cortex, anterior cingulated cortex, and prefrontal cortex, are hyperexcitability and changes in expression of several post-synaptic receptors. Specifically, there is upregulation of AMPA and NMDA receptors that causes depolarization, but a decrease in the density of post-synaptic dopaminergic (D1/D2) and muscarinic (M1/M2) receptors, involved in the hyperpolarization of cortical neurons (see text for details).

Figure 7. Plastic changes in the limbic system: amygdala and hippocampus. **[A]** Coronal section from a fresh-frozen human adult encephalon showing the amygdala (1) and its relation with the hippocampus (2).**[B]** Neuropathic pain causes structural changes in both cortical structures. In the amygdala, neuropathic pain induces proliferation of neurons, whereas it causes an increase of connectivity within the hippocampus. The functional alterations reported in both cortical structures may be related with these morphological changes (see text for details).



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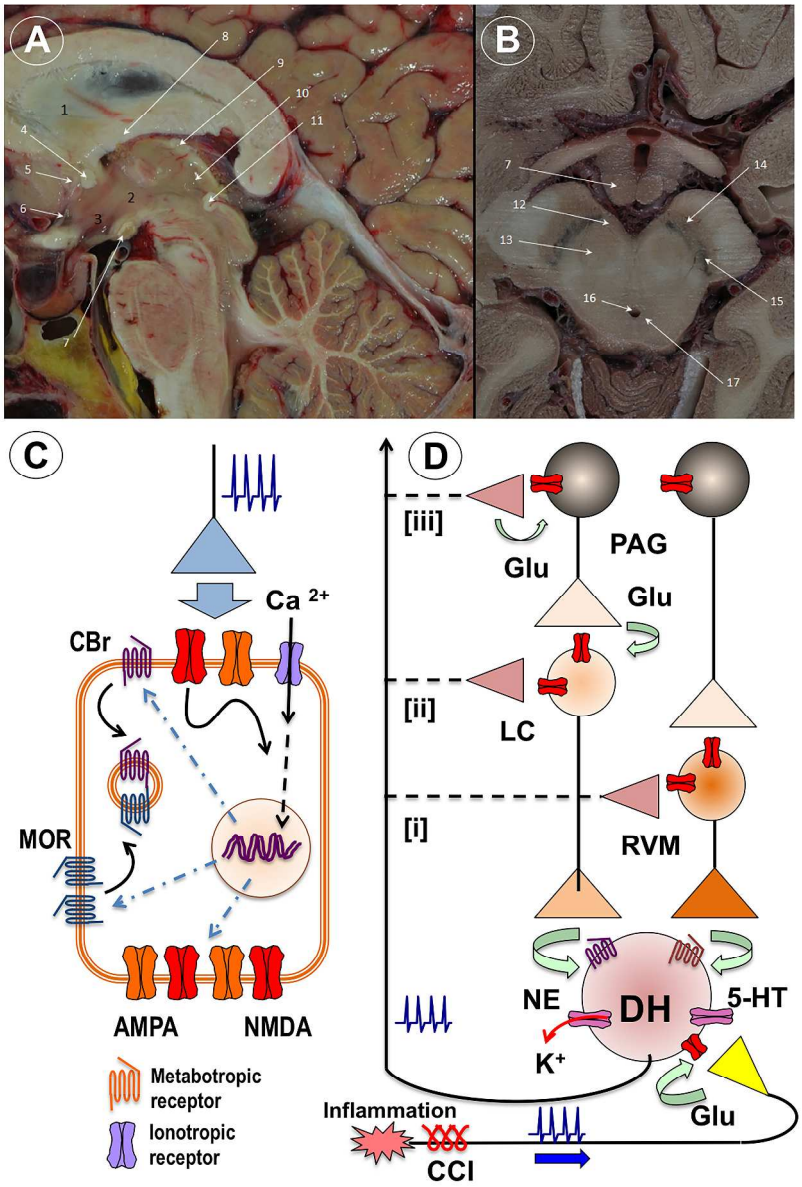

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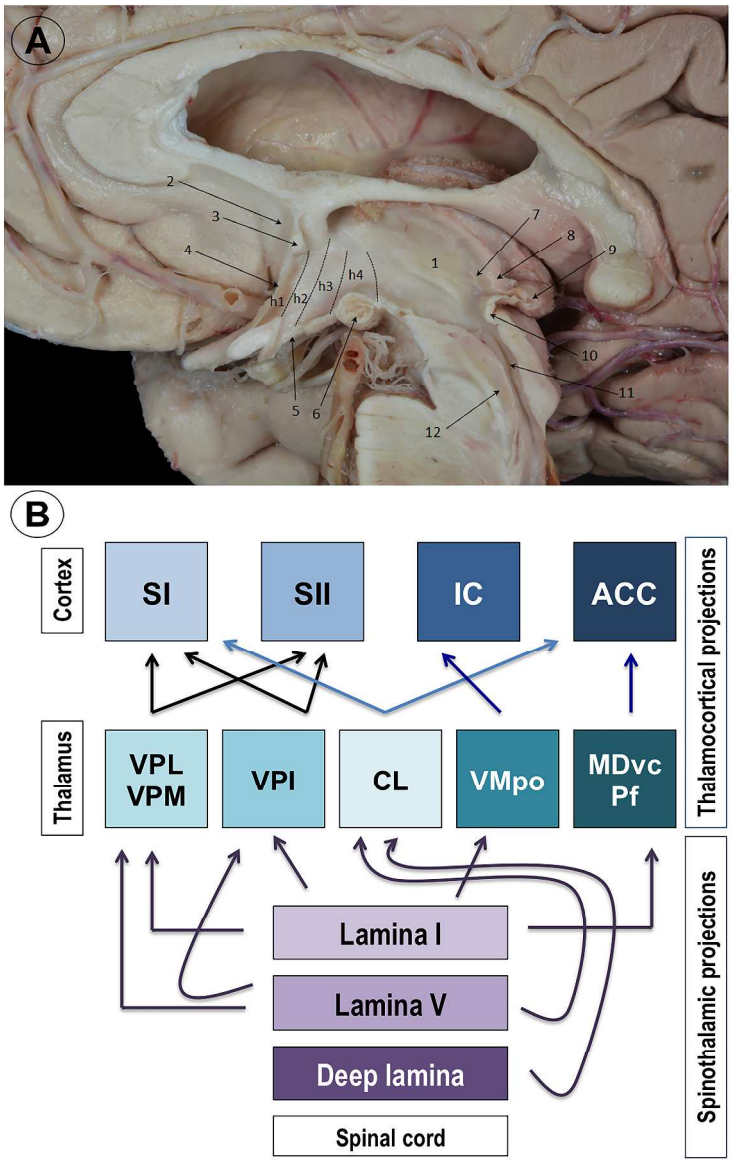

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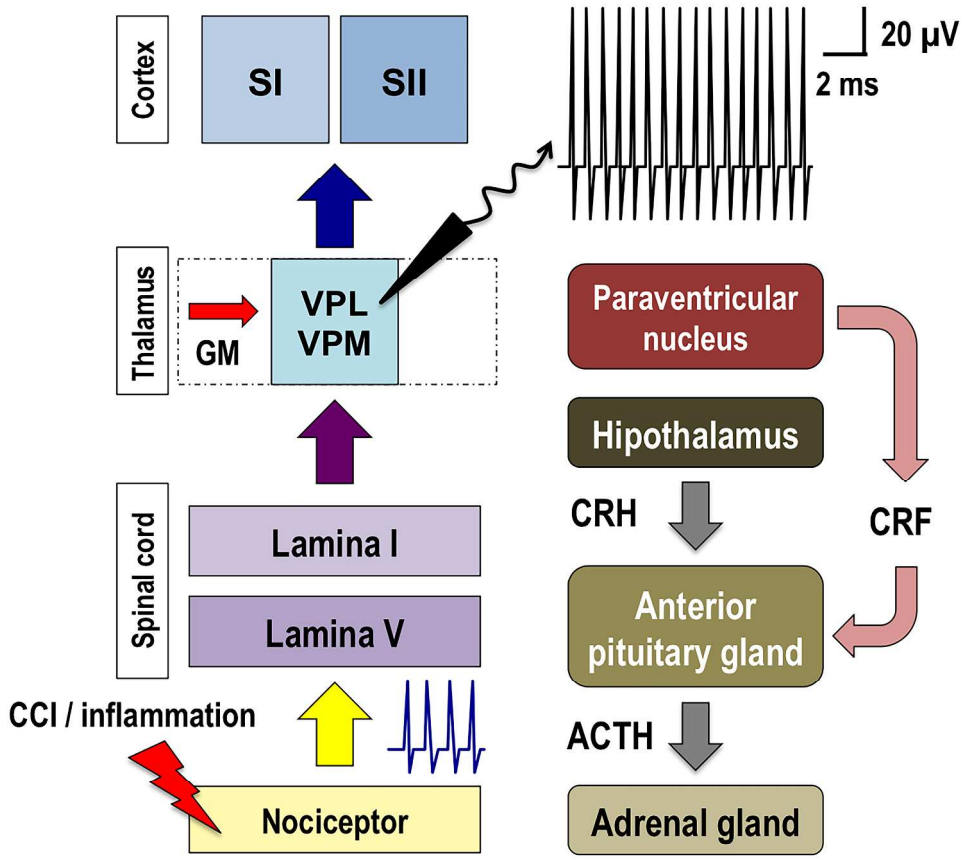

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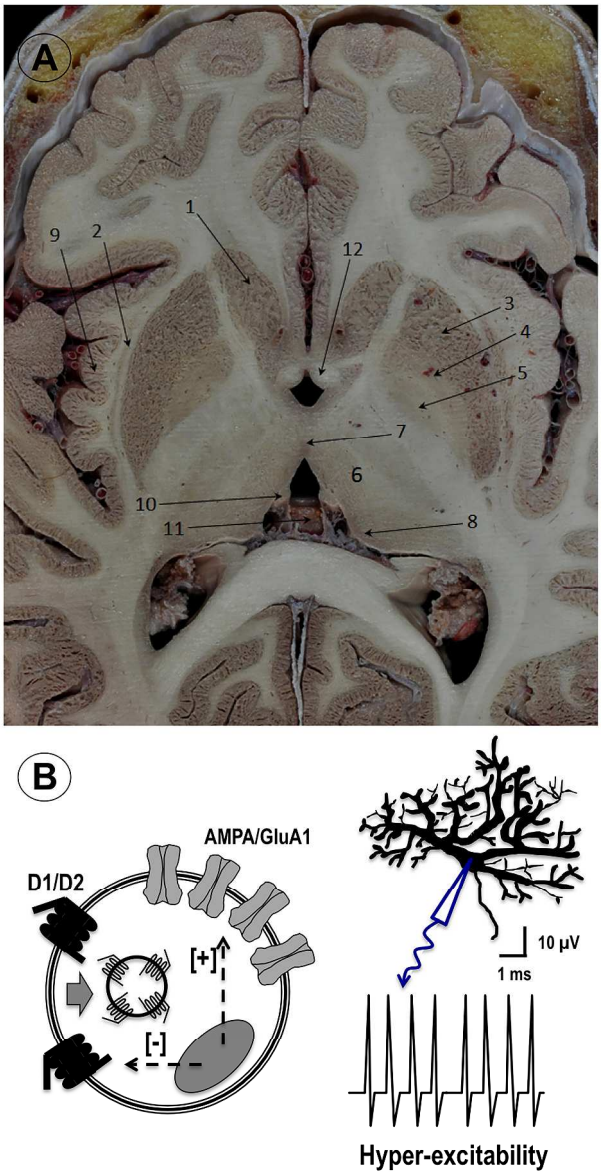

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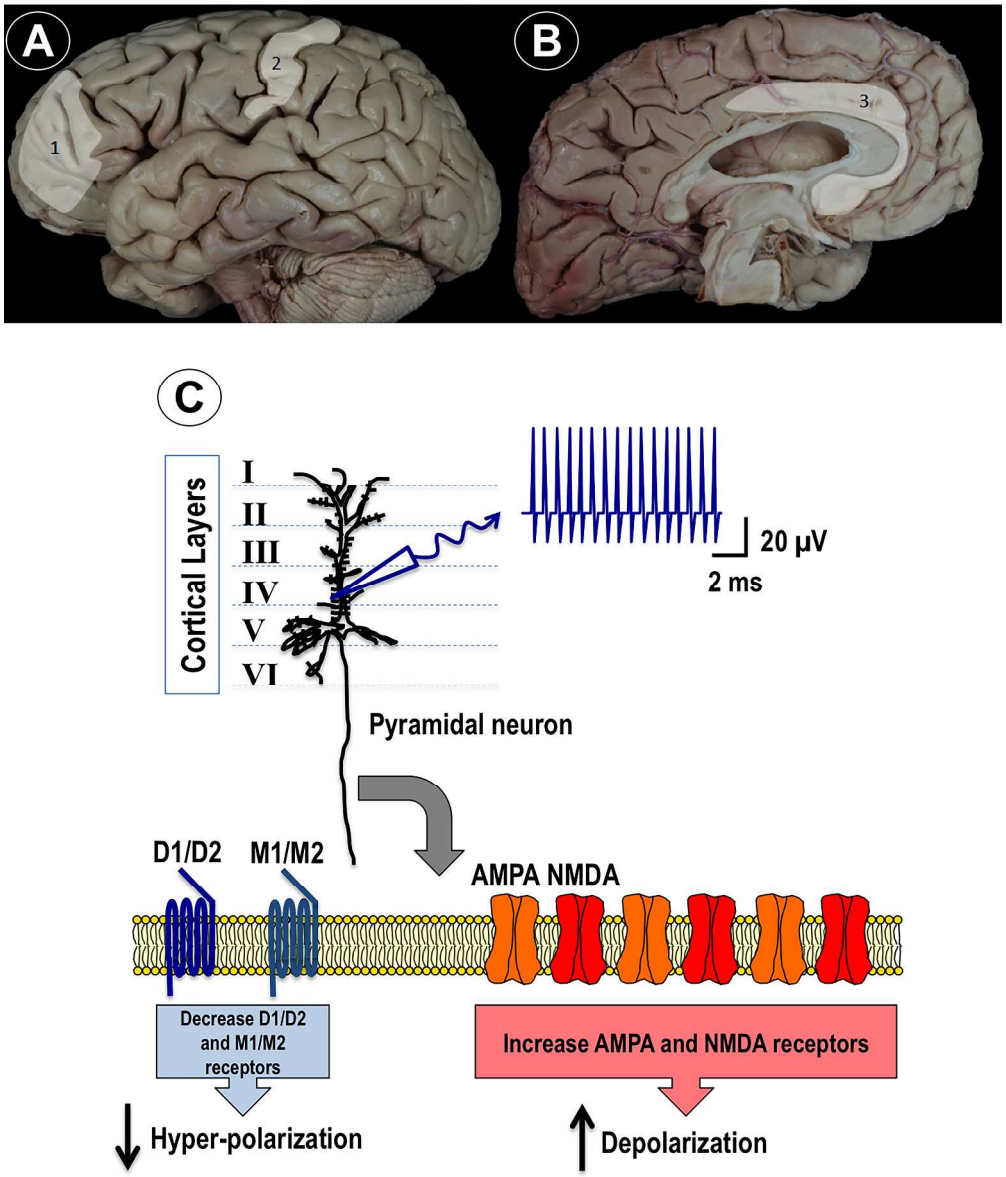

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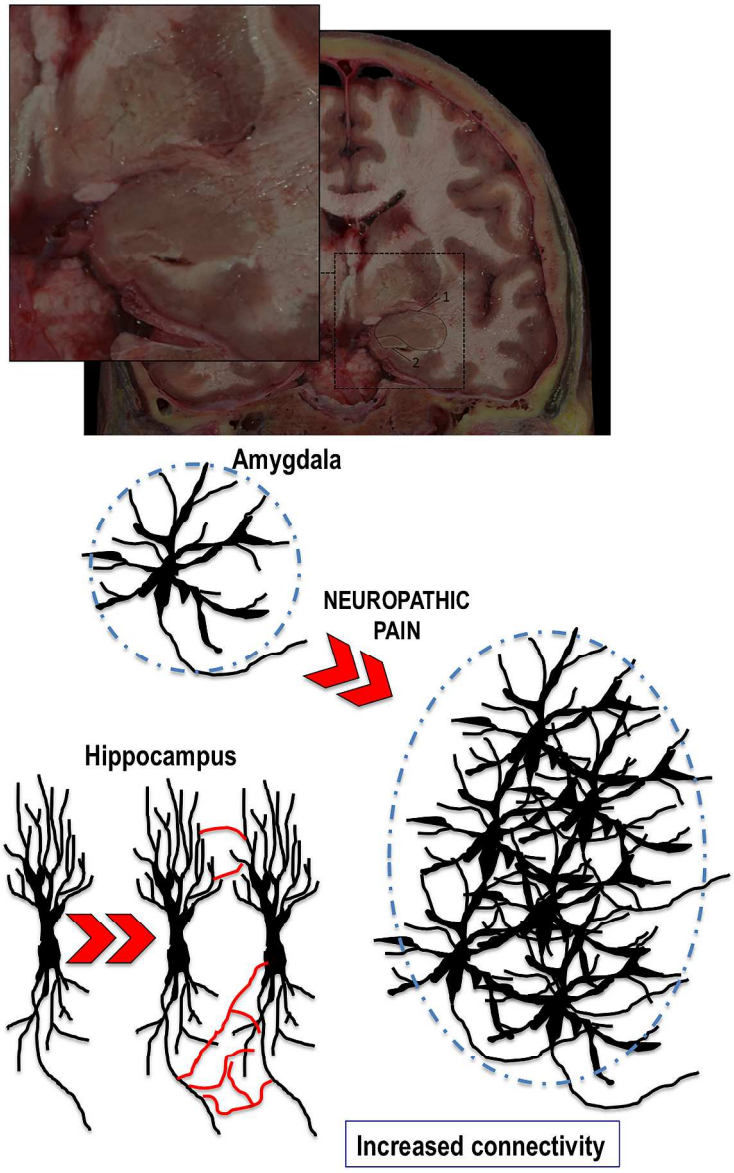

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