

The neurobiology of pain perception in normal and persistent pain

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Practice points

- The perception of pain arises through a complex interconnection of nervous system sites, beginning with peripheral receptors and continuing through relay synapses in the spinal cord, medulla, hindbrain, thalamus and multiple cortical sites.
- Deregulation of nerve endings can lead to pain in the absence of continued stimulation; these terminals can be targeted by peripherally acting medications.
- Changes in the pattern of neuron firing in the spinal cord and brainstem can produce unregulated pain signals. These neurons and their receptors can be targeted by different medications.
- Modulation of specific areas of cortical activity through medical, psychological, surgical or external stimulation techniques holds potential to significantly improve persistent pain in many cases.

SUMMARY Pain is a significant national burden in terms of patient suffering, expenditure and lost productivity. Understanding pain is fundamental to improving evaluation, treatment and innovation in the management of acute and persistent pain syndromes. Pain perception begins in the periphery, and then ascends in several tracts, relaying at different levels. Pain signals arrive in the thalamus and midbrain structures which form the pain neuromatrix, a constantly shifting set of networks and connections that determine conscious perception. Several cortical regions become active simultaneously during pain perception; activity in the cortical pain matrix evolves over time to produce a complex pain perception network. Dysfunction at any level has the potential to produce unregulated, persistent pain.

Pain has been highlighted by several important governmental bodies as being of particular importance to clinicians and researchers [1]. In addition to the significant suffering and personal toll, chronic pain produces a wide range of economic problems. This is both for the patient who can no longer work and for society as a whole which now must support them. One of the biggest challenges in chronic pain is to understand the underlying neurobiology. This would allow the development of new more effective treatments and limit the side effects that typically accompany adequate medical pain relief. Identifying and understanding the underlying pain process can be validating and therapeutic for the patient. Likewise, lack of this validation can lead to prolonged and worsening pain.

The perception of pain arises through a complex cascade of peripheral signaling, central processing, cortical activation and finally behavioral response. Because the appropriate response to a painful

KEYWORDS

- chronic pain
- neuroscience • pain • pain perception

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stimulus is highly dependent on the situation, such a complex array helps to ensure that the correct behavior is applied. In addition, withdrawal from a noxious environment or stimulus is one of the key evolutionary steps in the development of complex life, and thus nociception in humans is built upon several previously evolved pain perception pathways.

Acute pain from injuries or other obvious organic cause is generally well received by patients and clinicians. The full range of medical care and emotional empathy is available to patients with acute pain from injuries or other obvious problems causing pain. Chronic pain or pain without clear etiology is much more sinister as these patients can be mislabeled with a factitious disorder or somatization. This renders these patients a severe disservice, since pain by definition is a subjective complaint [2]. Just because the clinician is unable to determine the source of the pain does not make it any less real.

The objective of this review article is to describe the underlying neurobiology of the pain experience, with a special emphasis on potential sites for the development of chronic or persistent pain. The mechanisms that can lead to persistent pain are many and varied. It is possible that the pain perception pathways can become dysfunctional at any one particular location or at several sites simultaneously. Most of the possible pathologies described here would not be detectable using typical diagnostic techniques available to the clinician. Some may not even be discoverable by a research laboratory and can only be inferred based on animal studies. With a better understanding of the potential mechanisms underlying chronic pain, there is hope that clinicians may become more empathetic and validate a population of patients in desperate need of support and assistance.

• Peripheral nociception

Pain is a protective mechanism, allowing the organism to detect and respond to injury and threats to its survival coming from the environment. Necessarily most damage sensing mechanisms occur in the skin, which is the transition from the external world to the homeostasis of the living organism. Receptor activation at nerve terminals is transmitted by A-delta and C-fibers through peripheral nerves to the spinal cord, where modulated synapses relay the signal of peripheral damage up to the CNS.

Nociception begins at the terminal end of pain sensitive neurons, which project from the spinal cord to the periphery [3]. The A-delta and C-fibers have a wide range of receptors on their terminals. These receptors are responsible for translating potentially damaging events into neural signals that travel up the information ladder of the nervous system to reach consciousness and produce an appropriate behavioral response. Transient receptor potential cation channels include several known subtypes, each of which activates in the presence of different types of stimuli: including cold, heat, toxins or mechanical stimulation [4]. A transient, local action potential is generated by these receptors in response to appropriate receptor binding. This action potential can then be either up- or down-regulated by other ligands and receptors at the peripheral nerve terminus. Amplification of the signal occurs through a regenerative potential of sodium channels; inhibition occurs through the recruitment of potassium channels.

C-fibers are slower conducting compared with the A-delta and are responsible for prolonged burning sensations. Comparatively, the A-delta fibers are faster and transmit sharp or intense sensations. The C-fibers are responsible for the pain experienced after removing the noxious stimuli, classically described as a burning pain. A subgroup of C-fibers is only active under specific conditions. These C-fibers can be categorized into mechanosensitive or mechanoinensitive nociceptors. The mechanoinensitive nociceptors are often referred to as silent nociceptors due to their lack of response following mechanical or electrical stimuli [5].

• Spinal cord processing

The cell bodies of peripheral nerves located in the dorsal root ganglia are responsible for conduction of the generated signal toward the CNS. Postsynaptic signaling from the peripheral neuron to spinal nerves occurs in the spinal cord at appropriate levels. Lissauer's tract allows for localized connections at the dorsal root level up or down the adjacent dermatome. Nociception specific projection neurons receive the peripheral A-delta and C-fiber signals exclusively and then ascend in the neospinothalamic tract. This tract crosses immediately and ascends to the thalamus (ventroposterolateral nucleus) and then on to somatosensory cortex. Polymodal nonspecific neurons in layer V receive non-nociceptive peripheral input, but

can respond to peripheral nociceptors. These neurons also receive visceral afferents, leading to the referred pain from internal organs onto the somatotopic body map (Figure 1, left panel). These nonspecific neurons can also project centrally in the paleospinothalamic tract (Figure 1, right panel). This tract carries crossed and uncrossed fibers up to synapse in the hindbrain (periaqueductal gray [PAG], reticular formation, tegmentum) and then project to the thalamus, secondary somatosensory cortex, cingulate and insula. The archispinothalamic tract carries crossed and uncrossed fibers from lamina II, synapsing on lamina IV and VII cells. These ascend through a diffuse multisynaptic pathway through the PAG, hypothalamus, thalamus, and finally limbic cortex (anterior cingulate, insula, secondary somatosensory, similar to Figure 1 right panel). The latter two pathways can carry visceral pain sensations as well as autonomic nerve impulses.

• Pain processing in the hindbrain

As a defensive stimulus, pain involves deep brain centers in the medulla. Due to the well-protected location of these centers in the base of the skull, determining the role of these regions in pain processing in humans is technically quite challenging. However, a number of acute and chronic pain studies in animal models provide useful insight into how these regions contribute to the pain experience [6].

The rostra ventromedial medulla (RVM) is typically considered as a single unit and represents an important relay in the descending modulation of pain perception [7]. The RVM lies deep in the medulla, near the midline, at about the level of the olive. It comprises three categories of neurons: on-cells, off-cells and neutral cells. Off-cells decrease firing just before nociception and are considered inhibitory to pain perception. On-cells act oppositely, facilitating the perception of noxious stimuli. These cells express μ -opioid receptors (MOR) and cholecystokinin (CCK) receptors and can be blocked by lidocaine. The RVM is the main region of origin of serotonergic descending pain modulating pathways.

Lying on the caudal aspect of the floor of the 4th ventricle, the Cuneate and Gracile nuclei are the termination of the dorsal columns, which generally carry proprioception and fine touch sensation. They are part of the archispinothalamic pathway, which can carry pain sensation.

• Midbrain pain processing

The ventral tegmentum

The ventral tegmental area (VTA) of the midbrain is located near the red nucleus (RN), just above the level of the pons and PAG. It is adjacent to the substantia nigra, but can be distinguished by having more limbic afferents. The VTA has been related to salient sensory and emotional coding, which are related to reward based learning and addiction [8]. Projections from the VTA ascend in the mesocortical pathway to the prefrontal cortex, and in the mesolimbic pathway to nucleus accumbens, amygdala and cingulate cortex. Connections to the VTA form feedback loops, receiving projections primarily via excitatory glutaminergic synapses. These are implicated in the unregulated reward induced by drugs of abuse. Current evidence divides this region into anterior and posterior divisions, with pain sensitivity and depression related behaviors mediated by the posterior division. The posterior tegmentum and posterior rostromedial tegmental nucleus are primarily dopamine releasing neurons, but have receptors for opioid, cannabinoid, GABA and glutamate. These are part of a reward feedback system: tegmental neurons become more active when predicting reward, as with drugs of abuse. GABA receptor positive cells are primarily in the caudal region of the VTA and regulate the firing of their dopaminergic counterparts, providing a 'master brake' for reward feedback loops. Cocaine reward seeking behavior is mediated through theta band oscillations between hippocampal CA3 and GABAergic interneuron inhibition of VTA dopaminergic cortical output.

Pons (locus ceruleus)

Locus ceruleus (LC) neurons in the floor of the fourth ventricle at the level of the pons provide the majority of norepinephrine innervation to the rest of the brain via ascending and descending projections. Afferents to the LC come from the hypothalamus, cingulate and amygdala which permit generalized arousal in the presence of fear or threat. Medial prefrontal cortex projects excitatory efferents to the LC in proportion to the overall level of arousal of the subject. Stimulation of the LC activates descending inhibition of spinal pain projections.

Red nucleus

The RN is situated at the level of the pons and dorsal to the substantia nigra. As part of the

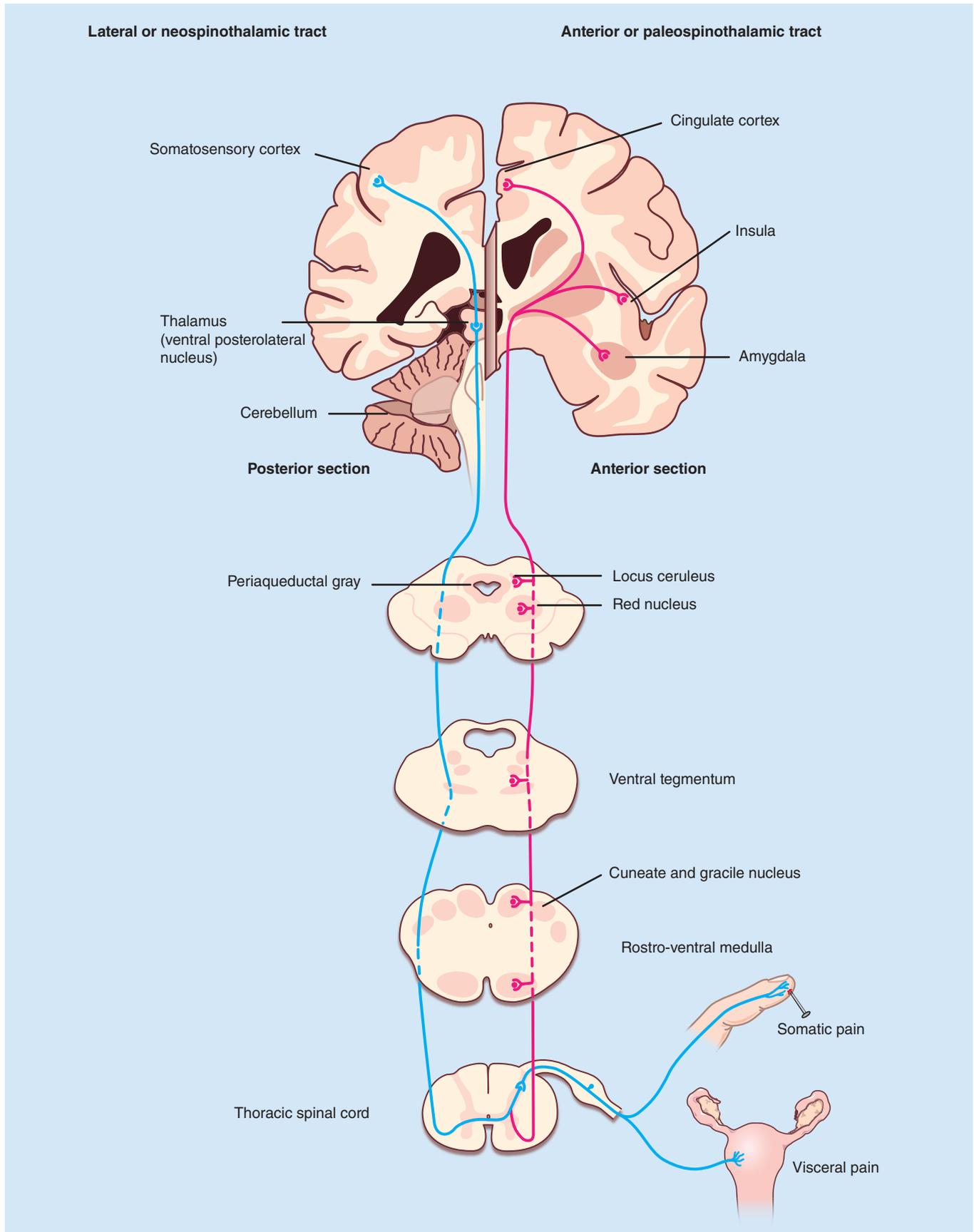


Figure 1. The neurobiology of pain perception: peripheral, midbrain and cortical tracts (see facing page). Nociception begins in the periphery and ascends through hindbrain, midbrain and thalamus. Different nuclei along this path have the potential to downregulate (suppress, or produce analgesia) ascending signals. Similarly each of these locations can become dysregulated, allowing the development of neuropathic pain, either from a peripheral or central source.

descending motor system, the RN is not typically considered to have an important role in pain processing, but a number of studies suggest otherwise [9]. RN stimulation leads to increases in the pain threshold (an antinociceptive effect) and this seems to be under upstream control by the nucleus raphe magnus. The targets of the RN analgesic effect are the somatic pain receptive neurons of the thalamic ventralis posterolateralis. Visceral pain analgesic targets of the RN are also in the thalamus.

Periaqueductal gray

Situated around the cerebral aqueduct deep in the tegmentum of the midbrain, the PAG is a well-known target for pain modulation. Electrical stimulation typically produces analgesia, targeting dorsal horn neurons in the distal spinal cord. The ventral PAG has opioid receptors, and stimulation of these produces analgesia through descending mechanisms. Similarly, endogenous cannabinoid receptors in the PAG act to suppress hyperalgesia and allodynia [10]. Stimulation of CCK receptors within the PAG produces the opposite effect: a facilitation of nociception and suppression of opioid driven analgesia. This occurs through a feedback loop involving a spinal–PAG–medulla–spinal circuit [11]. This loop is sensitive to ovarian hormones and may underlie a mechanism related to pain responsiveness in the menstrual cycle and postpartum.

One of the best studied nociceptive systems is the connection between the PAG, rostro-ventral medulla and dorsal horn of the spinal cord. This is primarily based on the presence of MOR in the PAG, which are activated by morphine and inhibited by naloxone. This produces analgesia or analgesia reversal based on descending excitatory projections to the RVM [12]. The PAG has a high concentration of MOR and up to 50% of PAG neurons projecting to the RVM have these receptors. Ascending nociception is blocked at the spinal cord level through inhibition of the spinal dorsal horn neurons. Activation of this pathway by higher centers is the basis for stress induced analgesia through the activation of MOR and cannabinoid receptors [13].

Prevailing evidence indicates that tonically active GABAergic interneurons are suppressed by opioids and cannabinoids, thus disinhibiting the antinociceptive activity of the PAG projections. One potential underlying mechanism is that the Ca(v)3.2 T-channel-dependent activation of ERK in PAG is required for the development of hyperalgesia [14].

• Diencephalon

Habenula

The habenula is a small group of nerve cells on the floor of the third ventricle near the pineal. It has an impact on multiple behaviors and its role in pain has recently been reviewed [15]. The habenula is positioned to have an evaluative role as part of the descending pain system. Specifically the lateral portion receives afferents from the frontal cortex and spinal cord lamina I via the lateral hypothalamus, while the medial portion receives afferents from nucleus accumbens and the septum. Efferent projections descend to other important pain modulating regions, such as the PAG, ventral tegmentum and raphe nuclei. Electrical stimulation of the habenula can produce naloxone reversible analgesia. There is a high density of opioid receptors in the habenula, and it connects to the limbic forebrain with hindbrain pain modulation centers. In this position, it is not surprising that the habenula has a role in both chronic pain and addiction.

Hypothalamus

The hypothalamus is a heterogeneous region composed of several different nuclei and it has a role both in pain facilitation and inhibition. Descending suppression of dorsal horn nociception occurs via GABA receptors in the hypothalamus acting on descending noradrenergic and dopaminergic spinal receptors [16]. Oxytocin is produced in the hypothalamus and produces analgesia in both inflammatory and neuropathic pain models. This mechanism results from oxytocin based stimulation of GABAergic interneurons in spinal cord lamina II, producing a local inhibition in the dorsal horn. In some animal models of neuropathic pain, the hypothalamus is involved in pronociception via increased levels

of central substance P [17]. This occurs through NMDA receptors, which when blocked prevent the substance P-dependent hyperalgesia.

The thalamus

The thalamus is an important target of ascending spinal activity and its role in pain perception and pain pathology has been reviewed [18]. The thalamus can be divided based on its embryology into three primary areas: the dorsal, ventral and epithalamus. The dorsal thalamus contains the most cortical projections while the ventral thalamus projects directly to the dorsal thalamus via GABA containing neurons. Activated peripheral A-delta and C-fibers terminate in lamina I, II and deep lamina V of the appropriate spinal cord level, then project directly to the dorsal thalamus via the spinothalamic tract. Alternatively, indirect projection to the dorsal thalamus can occur from pain sensing nerve fibers by way of spinoreticular, spinomesencephalic and mediolemniscal pathways.

Connections of the spinal cord with the thalamus can be grouped into a medial and lateral division. The lateral division contains ventral posterior (VP) nuclei and posterior nuclei while the medial pathway connects to intralaminar nuclei, medial dorsal (MD) nucleus and the midline nuclei. Somatotopically organized tactile input from the mediolemniscal pathway project to VP. This nucleus represents a convergence of both tactile and nociceptive input from different spinothalamic tracts. Thalamic nuclei in turn can be further subdivided based on their connectivity, with amygdala connections to the medial MD [19]. The dorsal thalamic nuclei have independent, reciprocal connections to the cortex. Connections of S1 and S2 to the VP create a somatosensory thalamocortical loop. Nociceptive specific (posterior/triangular) posterior neurons project to S2, while non-nociceptive projections do not. Pain specific cortical connections of the thalamus also include topographic medial MD projections to orbitofrontal cortex (OFC) and insula projections from the ventromedial MD [20]. The lateral MD has reciprocal connections to the anterior cingulate.

• Striatum

Made up of the caudate and putamen and lying lateral to the thalamus, the striatum is typically thought of as part of the dopaminergic motor system. However, the striatum has important ascending and descending pain modulation

effects. Excitatory afferents from pyramidal cortical neurons and thalamus project to the striatum, as well as ascending dopaminergic afferents from substantia nigra. GABAergic neurons from the globus pallidus also project to the striatum. Efferents project cortically to the supplementary motor area (SMA) and caudally to the substantia nigra, thalamus and superior colliculus.

• Amygdala

The amygdala is a bilateral cluster of cells in the temporal poles known to be involved in emotional processing and memory. It can be subdivided into several nuclei including the central (CeA) nucleus involved in sensory and pain processing and its lateral capsular subdivision (CeLC). Afferents to the nociceptive amygdala arise from the dorsal horn neurons and relay in the nucleus parvasalis. The role of the amygdala in persistent pain is discussed below.

• Cerebellum

Although typically considered to be part of the motor control system, the cerebellum clearly has a role in pain perception [21]. The role of the cerebellum in pain perception has been consistently demonstrated and its connections to the descending pain inhibitory pathways make this a reasonable conclusion. However, the precise role in pain facilitation or inhibition has yet to be described. Activation based on psychological pain and suffering consistently activated mid-brain regions such as the cerebellum and cerebellar vermis [22]. The cerebellum is the target of ascending pain afferents. These cerebellar connections occur in feedback loops with other brain regions, the most pertinent to pain being the frontal loop [23]. Efferents from the dorsolateral prefrontal cortex (DLPFC) project directly to pontine nuclei, which in turn project excitatory mossy fiber connections to the cerebellum via the middle cerebellar peduncle. Efferents from the cerebellum are from the inhibitory Purkinje layer back to the DLPFC. The second cerebellar loop includes efferents from premotor (M1, SMA) and somatosensory (S1, superior parietal lobule) cortex via the RN to the inferior olive, which then projects through the inferior cerebellar peduncle to the cerebellar cortex. The inferior olive also receives projections from nociceptive centers in the brainstem such as the PAG and zona incerta, which then also project to the cerebellum. Both the spino-ponto-cerebellar and spino-olivo-cerebellar pathways are electrically

coupled to peripheral A-delta and C-fiber nociceptive stimulation. Electrical or pharmacological (opiate microinjection) stimulation of the cerebellar lobes and nuclei can produce analgesia and raise nociceptive thresholds. Microinjection of a glutamate agonist into the cerebellar fastigial nucleus decreased response to visceral nociception.

• Cortex pain processing

One of the challenges in the neurobiology of pain is that there is no single cortical structure or pathway responsible for all aspects of the pain experience. For example, the visual system begins with perception of an external stimuli by the peripheral organ (retina), decussates and then synapses in the thalamus (lateral geniculate), and then spreads out in the optic radiations to reach visual cortex, which is itself organized into primary (V1) through higher order processing regions (V2–V6). Although more complex than described, such a neatly organized, linear processing of peripherally detected stimuli does not occur for nociception. Instead, there have been multiple theories (models) proposed to account for the complexity of the pain experiences. Each of these models has its own merits and can be described generally as the medial/lateral pain systems model, the pain matrix model (updated to reflect several overlapping but sequential pain matrices) [24] and the dynamic pain connectome [25]. These models must all account for the multimodal nature of pain. There is an intrinsic, somatotopic, mechanical aspect to nociception, but also a cognitive component, and an emotional or evaluative one [26]. This is known as the nociception-perception-suffering model [27].

Although lesion and stimulation studies provide the illusion that each nucleus is firmly connected to the next through synapses and receptors, in reality the brain is an electrochemical dynamo, constantly in oscillatory motion with different frequencies connecting different regions that come in and out of coherence [28]. The brain at rest is not actually at rest, it is in what has become known as the default mode. The network of areas that are active is known as the default mode network [29]. This network is susceptible to disruption in chronic pain states [30,31].

• Insula & operculum

Deep in the Sylvian fissure between the frontal and temporal lobes lays the insular cortex. This is a roughly triangular region, with an agranular

anterior (rostral) and granular posterior division, separated by a sulcus. The lateral-most region of the frontal lobe covers the insula like an eyelid, giving this region the Latin name ‘operculum’. Although subdivisions exist, these areas of cortex are often discussed together as the operculo-insular complex (OIC). The insular cortex is implicated in a wide range of diverse functions including pain perception, motor control, emotional regulation and self-awareness. Activation in the OIC has been found in proportion to the degree of painful somatosensory stimulation. Additionally, the OIC has reciprocal connections with the ACC, PFC, amygdala and S1 which together create the conscious pain experience. External stimulation of the insular cortex can replicate pain while insular ablations decrease pain perception and pain related behaviors.

In current models of the pain perception matrix, posterior insula (PI) activity represents one of the earliest events in conscious nociception. After activity in the primary network, the secondary network which includes anterior insular cortex becomes activated, along with other regions to determine the amount of attention resources that will be allocated to the pain stimulus.

• Cingulate cortex

Lying between the corpus callosum and the cingulate sulcus on the medial aspect of both cerebral hemispheres, the cingulate cortex is a major contributor to nociception, along with modulating fear, memory and other thought processes. It has several subdivisions based on cytoarchitecture, function and connectivity: the anterior cingulate cortex (ACC), the middle cingulate cortex (MCC), the posterior cingulate cortex (PCC) and the retrosplenial cortex (RSC). The ACC has long been considered to be required for the affective, emotional component of both acute and chronic pain and is part of the first order of cortical neurons to respond to painful stimulation. Affective value for different experiences seems to be encoded in the ACC, with negative memories and values encoded in the subgenual ACC and positive memories in the posterior ACC. The cingulate sulcus and midcingulate are the ‘motor’ division of the cingulate, driving behavioral responses to emotional stimuli. The posterior cingulate is related to somatosensory cortex and resolves body orientation and spatial orientation in relation to personal relevance of sensory information [32].

The ACC is activated in pain perception and the attendant emotional response to pain seems to at least partially originate in this region [33]. The role of the cingulate cortex in cognition has been linked to the negative emotional aspects of pain perception, but its role may be more complex. The cingulate gyrus appears to have three general subregions: an anterior division with close connections to the orbitofrontal cortex, the amygdala involved in valuation (including reward and negative affect) and a midportion involved in the generation of action based on stimulus valuation [34]. The posterior cingulate is involved in memory encoding, but there may be up to eight identifiable cingulate subregions, each with its own connections and subtleties of cognitive experience processing.

Different subregions of the cingulate are responsible for different aspects of emotional perception. The aMCC is activated by negative stimuli, such as punishment or nonreward. This is distinguished from the pACC which activates with positive reward [35]. Importantly, both of these areas require coactivation of the OFC to encode their negative (or positive) affective response; activation of these cingulate areas alone is not sufficient to produce perception of emotion. Descending projections from the ACC to the thalamus (lateral thalamus), PAG, amygdala, hypothalamus and parabrachial nucleus provide a mechanism for control of autonomic response to stimuli, potentially permitting the development of dysautonomias in chronic pain syndromes [32]. Pleasantness or unpleasantness of presented stimuli is dichotomized in the pACC, particularly when reflecting on an internal emotional state. The aMCC is involved in decision making regarding reward/approach or fear/avoidance behaviors. The aMCC can be thought of as the motor area of the cingulate gyrus, where many different emotional aspects of stimuli (including error, anticipation and response selection along with fear and reward) are brought together to form a go or stop response [36].

Acute experimental pain generally activates the MCC, while the posterior ACC has demonstrated decreases in fMRI signal. Some of this decrease may be associated with pain anticipation or fear, which leads to decreased ACC functioning. Motor cortex stimulation has helped to map out the connections of the cingulate cortex, demonstrating synchronous activity between the subgenual ACC and PAG,

MCC and pons, and the posterior ACC with the pons and PAG. Subregion analysis suggests that the pACC/aMCC is associated with processing the affective component of pain. The role of the pMCC is to select the correct motor responses to aversive stimuli and control attention. Attention to unpleasantness activates a theoretical medial pain circuit comprised of the pACC, PI and amygdala, in addition to the OFC. Neurosurgical cingulotomy and ACC ablation has been used to treat a number of human chronic pain syndromes with variable efficacy [37].

• Prefrontal cortex

The OFC sits at the front of the brain, with several subdivisions spread across the medial aspect of the hemispheres wrapping around to the roof of the orbit. This region has extensive connections with other regions of the pain matrix, including ACC, OIC and S1. Additional connections to deeper structures such as the thalamus, medial temporal lobe, hypothalamus, amygdala and brainstem make this a polymodal association and motor region. Affective pain perception is proportional to OFC activation in complex regional pain syndrome [38]. Tight connections with the thalamus have led to the theory that certain chronic pain states arise from abnormalities of the electrical frequency between the thalamus and cortex, which has been termed thalamocortical dysrhythmia [39].

The concept of the pain matrix is required to adequately explain many of the experimental observations in pain perception. The most important is that activation (stimulation) of any one individual region does not produce the subjective experience of pain [40]. VBM analysis showed significant decreases in gray matter density in areas associated with pain processing and modulation, in other words the DLPFC, the thalamus and the middle cingulate cortex [41]. Pain processing within the PFC seems to follow a posterior to anterior gradient, with more anterior representing more abstract perceptions and actions [42]. This is perpendicular to a ventromedial gradient that encodes the emotional salience of stimuli, along with producing affective states and regulating emotional or behavioral responses [43]. The ventromedial PFC (orbitofrontal and perigenual) regulates the voluntary control of noxious stimuli and is active in states where the subject still complains of pain in the absence of peripheral stimulation [44].

Descending control of midbrain pain modulating regions such as the PAG seem to be under control of the PFC, where these regions form part of a loop where PAG projects back to principal pain matrix regions such as the OIC [45]. Other areas of the pain neuromatrix change based on condition with some increasing and some decreasing activation in response to the task. These included midline structures such as the ACC, PCC, thalamus, caudate and putamen; along with left and right cortical regions of the PFC (BA47 and BA10, BA9), insula and cuneus [22].

- **SMA/motor cortex**

The SMA is often found to be involved in studies of experimental pain perception (table 1 of [24]). Increases and decreases in activation have been found, which may be due to both the heterogeneity of the underlying pain production method, as well as the differences in modalities (e.g., fMRI, PET, EEG) used to determine the changes in activity. Although variably involved, increases in SMA activity have been consistently found in multiple studies of neuropathic allodynia (*ibid* table 2). This is not surprising since pain perception according to the current three-phase model ends with activity in the motor area of the cingulate cortex, where the emotional valence of a pain signal is turned into a behavioral action (typically to move away from the pain stimulus).

- **Somatosensory cortex**

Lying just posterior to the central sulcus, the somatosensory cortex receives information from body regions according to a map with more medial cortex connected to rostral regions (face, hand) while more lateral cortex is related to caudal regions (feet). A-delta nociceptors project to a spatially organized somatotopic map in primary sensory cortex, providing a method for the body to localize pain onto its own surface [46]. This somatotopic organization is limited to S1 cortex, mimicking the non-nociceptive homunculus; but this organization does not continue in secondary somatosensory or posterior parietal cortex [47].

Using a nociceptive evoked potential recording, the somatotopic representation of the body in the S1 postcentral gyrus was demonstrated [47]. In parallel with the evoked potential in S1, somatotopic nociceptive potentials were also demonstrated in the operculum, with the foot represented in deeper areas and the hand

and face in more lateral areas. Somatotopic organization has also been demonstrated for tactile response in the anterior and PI and S2 in the operculum. Simultaneous potentials were also demonstrated in secondary sensory posterior parietal cortex, but without the same somatotopic organization. Latencies of evoked potentials in the operculum and S1 were similar, indicating that somatotopically organized nociceptive information is processed in parallel by different cortical areas simultaneously. Nociception produced evoked potentials in parallel in M1, S1 and the operculum, all at the same latencies [48]. This suggests that these regions are part of a first-order processing network that is activated directly by peripheral nociception. S1 responses to mechanical stimulation produced more activation than in those with nociception.

- **The cortical pain matrix**

The concept that the interaction of several diverse brain regions (a matrix) permit nociception to come to consciousness originated with Melzac's neuromatrix [49]. Unlike the visual system, the perception of pain activates multiple cortical areas simultaneously. Each of these areas subserves a different aspect of the pain experience. Only when all areas are integrated in the frontal cortex does the complaint of pain and pain related behaviors begin to emerge (Figure 2). Regions of the cortical pain matrix each provide a different but requisite aspect of the pain experience beginning with nociception and mapping of pain, and including the emotional and cognitive behavioral aspects of pain.

The concept of the pain matrix in normal and abnormal pain states can be organized into a set of sequentially activated, overlapping matrices [24]. Historically, pain pathways were divided into a medial pathway leading to the ACC as an emotional aspect of pain and a lateral system leading to somatosensory cortex as the physical aspect of pain. There is still support for this approach since in a neuropathic pain model using PET, where a clear medial thalamic pathway projecting to limbic forebrain structures (anterior insula, pACC, striatum and PFC) was demonstrated [50].

Although the concept of a pain neuromatrix provides an attractive approach to a complex problem and permits translation from research findings to clinical relevance, several caveats must be acknowledged. Individual variability in pain perception to noxious stimuli is significant,

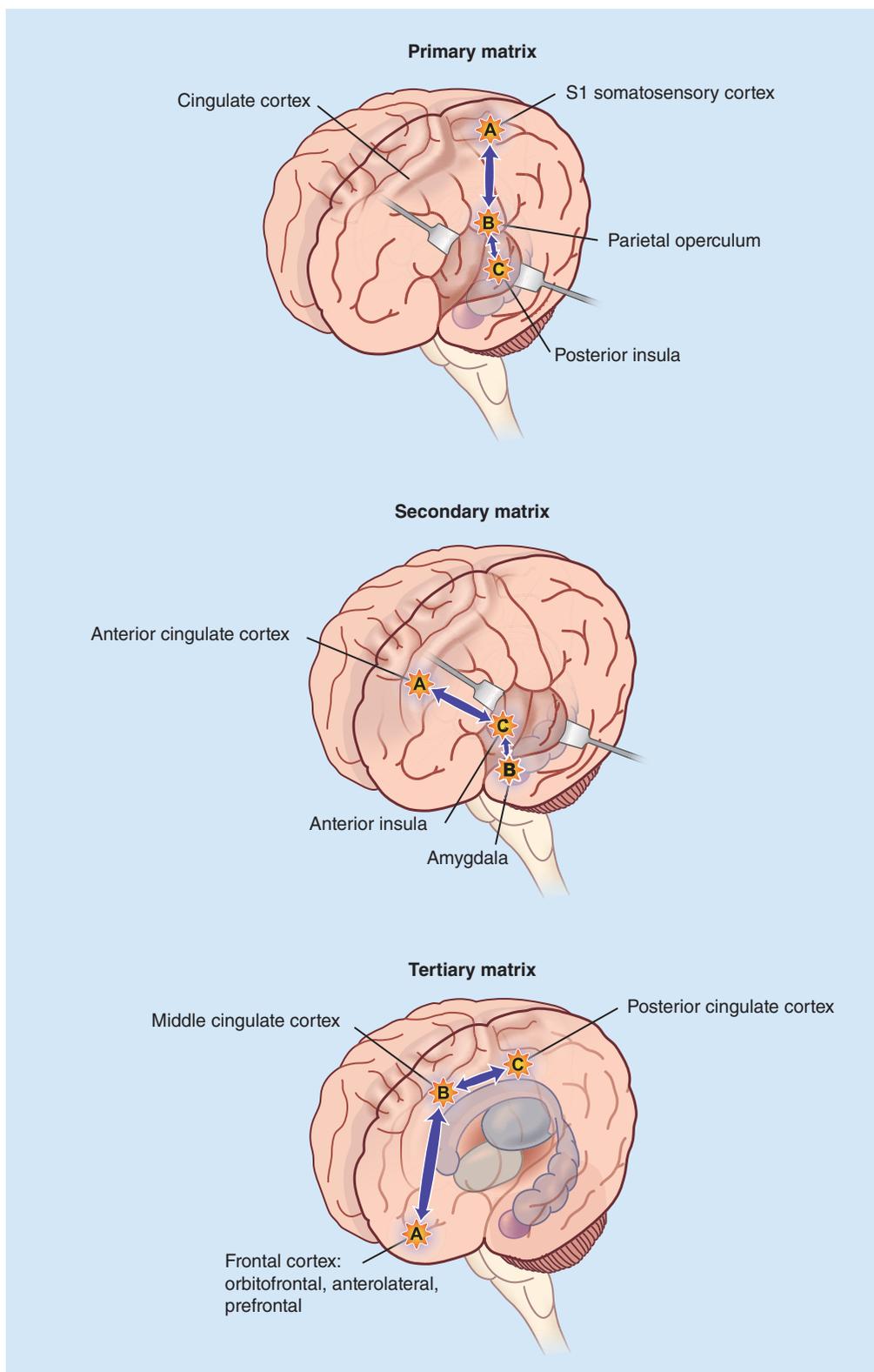


Figure 2. The cortical pain matrix as a series of overlapping systems. The primary matrix provides the location information to the pain stimulus, while the secondary matrix focuses attention (or not) on the pain. These operate in parallel, simultaneously. The third matrix integrates the signal from the first two, and then begins to generate a behavioral response.

and some of this is due to genetic variation, even at the level of the peripheral receptor [51]. At the cortical and subcortical level, epigenetic phenomena introduce individual variation in behavioral responses even among genetically identical subjects [52]. In addition to individual variation, several aspects of the pain neuromatrix are also activated by nonpainful stimulation and may be part of a salience or cognitive processing network that may be called upon to provide behaviorally appropriate reactions to a wide range of events [53]. Even with the understanding that current methodology may not be able to precisely define pain-related cortical activation in a universal manner, the contributions of different regions of the cortical neuromatrix are becoming clear [24].

- **Primary cortical pain matrix: pain & location**

Peripheral nociceptive signals ascend in the spinothalamic tract, relay in several thalamic nuclei, and then project to the cortex (Figure 2, top panel). First-order projections of this system to the cortex include the PI and the medial parietal operculum [54]. Stimulation of this posterior OIC produces pain [55], and ablation of this area extinguishes pain producing seizures [56]. Although the PI appears to be a necessary first step in the perception of pain, it is not sufficient to produce the full pain experience, which includes attention, emotional and cognitive simultaneous components to produce pain behaviors and a complaint of pain.

First-order projections to the cortex seem to occur in parallel to both operculo-insular and somatosensory/motor cortex [48]. Using intracortical evoked potentials the receptive field for the non-noxious stimuli was found to be much broader, with specific subregions in somatosensory and motor cortex responding in a similar time frame as operculo-insular cortex. These were in the top of the postcentral gyrus (S1 and S2, but not 3a or 3b) and M1.

- **Secondary cortical pain matrix: attention & affect**

The posterior OIC projects forward to the mid- and anterior insula and up to the mid- and anterior cingulate cortex (Figure 2, middle panel). At this level of signal processing other aspects of cognition are called upon and these regions are not specific for pain perception. Processing of nociceptive stimulation in the insular cortex

seems to have a specific spatial and temporal distinction. Based on fMRI responses, initial pain stimulation moves through the PI to the mid and anterior insula to encode spatial and temporal elements of the pain experience [57]. These areas are suggested to add the ‘where’ and ‘when’ components to perception of the pain stimulus. Consistent increased activation of the OIC on the ipsilateral side is related to persistent pain [24].

Although these second-order areas may have other roles in cognition, they can change the nature of pain perception by increasing or decreasing nociception induced activity through descending inhibition of thalamic, brainstem and spinal cord [58], and through ascending inhibition of other cortical areas involved in pain perception [59]. Activation of the ACC and AI occurs in a number of other behavioral situations. This activation may provide a cortical signature for attending to a stimulus and its negative emotional valence, such as mirroring suffering, guilt, or empathic pain [60]. Second-order processing areas are required for ascending nociception to reach consciousness. The capacity to declare that pain is occurring requires conscious perception, resulting from activation of a diffuse network connecting frontal and parietal association cortex [61]. These areas are separate from third-order nociceptive processing regions but are required for conscious perception of pain.

- **Tertiary cortical pain matrix: cognitive meaning**

A number of cognitive states can impose significant changes on pain perception, including placebo, nocebo, religious beliefs and self-control. These effects are related to activity changes in OFC, pACC and anterolateral PFC (Figure 2, bottom panel). These areas are activated in cognitive tasks that change the nature of pain perception [45] and meditation related analgesia [62]. Higher glutamate levels in the PCC of fibromyalgia patients correlates with catastrophizing [63]. Just as there appears to be a posterior to anterior gradient of nociception processing in the insula, the PFC also seems to have a hierarchy of perception and action abstraction. Ventromedial areas, such as the pACC and OFC, identify emotional stimuli and regulate affective state, especially in control of negative valence situations [64]. This order of nociception processing relies on memory to put the stimulus in context, and thus includes medial and lateral PFC,

following temporally after activation of first- and second-order matrices [43].

Adding cognitive meaning to a pain stimulus is contextual; the ethnicity of the subject changes the cortical response to pain expressions [65]. Pain related behaviors such as catastrophization can be linked to anterior activity, particularly in the alpha band [66]. These studies demonstrate asymmetry in alpha power in catastrophizing patients, indicating that laterality will need further investigation to better understand pain behaviors. Currently most studies indicate pain matrix activation in the left and primary pain matrix [67].

• **Cortical matrix processing summary**

The higher order matrix is closely connected to subcortical regions involved in modulation of the ascending nociceptive signal such as the PAG. Through this mechanism reappraisal of pain has the potential to both increase and decrease ascending nociception to the first-order cortical matrix. Other results of chronic back pain accompanied by brain atrophy suggest that the pathophysiology of chronic pain includes thalamocortical processes [68].

Support for the three matrix approach also comes from electrophysiological studies of evoked pain [69]. Source localization showed three main brain networks: an early network at 8.3 and 3.5 Hz involving brainstem, operculum and prefrontal cortex peaking at 77 ms, a middle network of operculum, amygdala and midcingulate, and a third network of anterior-cingulate at 4.5 Hz. Finally, there was an operculum and midcingulate network that persisted over the entire time interval, peaking at 245 ms at 2.1 Hz. Based on the MCC relationship to motor cortex, this last portion of the matrix would be related to pain behaviors.

• **Visceral pain**

The mechanism underlying visceral pain perception is expected to be slightly different from somatosensory pain if only because the body map for viscera must be referred onto the surface for localization purposes. Using esophageal pain stimulation with EEG recording, a set of pain perception networks were found to be sequentially involved over time. This finding was substantially related to the first through third-order pain perception network described by fMRI [69]. At each order of processing, several areas correlate at a specific frequency and time.

The first-order occurs at a latency of 77ms with a frequency of 8.3 Hz in the brainstem, bilateral operculum and prefrontal cortex. These same areas are part of a second-order network occurring at 90 ms with a slower frequency of 3.5 Hz. The third network includes the MCC, ACC, bilateral operculum and amygdala at 247 ms latency and 4.5 Hz. A fourth network becomes active at 245 ms in the 2.1 Hz range and includes the MCC and bilateral operculum. In a more focused study, right anterior insula activated in chronic pelvic pain patients, and this correlated with pain intensity [70].

Interestingly, sexual arousal and orgasm in women increase activity in many regions of the pain matrix: hypothalamic paraventricular nucleus, amygdala, accumbens-bed nucleus of the stria terminalis-preoptic area, hippocampus, basal ganglia (especially putamen), cerebellum, and anterior cingulate, insular, parietal and frontal cortices, and lower brainstem (central gray, mesencephalic reticular formation and NTS) [71]. Much of this is probably due to the nature of second- and third-order pain matrices having an involvement with attention and affective processing.

• **Pain control**

One of the most important aspects of the nociceptive system is the capacity to suppress pain related behaviors in the correct context (as in combat with predators, fleeing, among others). This is required to permit contextually appropriate behaviors (fight or flight) to occur without being overwhelmed by pain signals (also known as stress induced analgesia). Similarly, there must be a mechanism in place to reset the system. The failure to properly suppress non-threatening pain or to reset nociception after the initial stimulus has resolved are critical elements to the development of neuropathic pain.

Also known as the endogenous analgesic system, pain inhibition at the spinal level results from descending efferents originating in the RVM, and stimulated by PAG neurons [72]. Both the PAG and RVM express MOR, and these are the targets for most narcotic pain medications. Projections to the spinal cord from the RVM are both serotonergic and noradrenergic, which function to suppress pain perception before it can rise to the level of consciousness in the cortex. The diffuse noxious inhibitory control (DNIC) system [73] refers to the phenomenon of pain suppression through application of a

counterirritating pain stimulus. These originate in a spino-bulbal-spinal loop involving neurons with whole body receptive fields to produce a caudal to rostral suppression, rather than a top down cortical nociception suppression. In clinical and psychophysical testing, the system that allows a subject to consciously regulate pain perception has been termed the heterotopic noxious conditioning stimulation. In general, these are cold pressor tasks with a conditioning and a test stimulus designed to evaluate cold pain tolerance. Although sometimes used to refer to any central mechanism that induces analgesia, the DNIC is technically only active in the presence of a second pain stimulus.

Voluntary activation of the DNIC is thought to underlie psychological control of pain response, exemplified by experienced meditation practitioners. This concept is supported by recent evidence demonstrating that several aspects of the pain perception matrix (OIC, S2, ACC, thalamus) can be activated voluntarily to produce analgesia [74]. Activation of the secondary and tertiary matrix (OFC and amygdala) was shown in other pain suppression tasks [75]. Dysfunction of higher order pain matrices has been demonstrated in somatoform pain disorders, with changes in the default mode in pain matrix regions [67].

Placebo analgesia

The control of pain through placebo mechanisms has long been identified, but recently the underlying neurobiology has become better appreciated [76]. From a neuroscience perspective, the placebo response is the psychobiological component of symptom change, independent of spontaneous fluctuations or methodological bias. Typically this represents the study of expectation and learning. The most well studied system includes the opioids, since naloxone (an opioid antagonist) blocks most types of placebo analgesia. This is the same effect as that produced by CCK type 2 agonists, indicating that the opioid and CCK type 2 receptors balance each other in the placebo response to pain. Placebo effects can include other systems, such as cannabinoid receptors, and the dopaminergic system. The locations for placebo effects in the cortex include the DLPFC, ACC, insula and nucleus accumbens.

Nocebo effects (increased pain in response to an inert stimulus) are mediated by the pronociceptive CCK receptors, particularly type 2.

Portions of this response are also mediated by anxiety, since in anxiety provoked social defeat situations, CCK antagonists can block the hyperalgesic response. The amygdala and amygdalo-frontal serotonergic projections also mediate anxiety responsive hyperalgesia. An anticipatory nocebo effect spread through a social network increases salivary prostaglandins and thromboxane, indicating that in some instances the central nocebo expectation can be translated into a systemic immune-endocrine disruption. This effect likely has a genetic predisposition, protecting some but not others in a population.

• Persistent pain mechanisms

Classically chronic pain with an unclear origin was often called 'neuropathic pain'. The current International Association for the Study of Pain guidelines now reserve 'neuropathic' for pain that has a demonstrable neurologic lesion [77]. This approach however leaves many patients who have unexplained pain in a particular region with only a descriptive and not a mechanistic understanding of their pain. In a clinical setting most of these patients will complain of chronic pain. More current terminology would describe these as having a persistent pain syndrome [78]. Typically some injury (infection, event) has occurred and the normal mechanisms that would allow pain resolution have failed, leaving these patients with a perception that their pain is continuing, even though the original stimulus has been eliminated. A number of risk factors for persistent pain syndromes are being investigated, all of which upon the neural processing of pain perception.

Peripheral mechanisms & persistent pain

Peripheral sensitization of these end terminals can occur through a number of mechanisms that are present in states such as inflammation and cancer. Supporting mast cells, platelets, neutrophils and macrophages release chemical mediators such as ATP, prostaglandins, NGF and glutamate which regulate end terminal protein activation and translation [79]. Transcriptional up regulation results in more peripheral nociceptors, but also induction of phosphorylating enzymes such as phospholipase C. This changes the peripheral nociceptors to become more active by lowering their threshold for firing. G-protein-coupled receptors also mediate amplification or suppression of peripheral signal transduction, which are the targets for antinociceptive ligands

such as cannabinoids and opioids. Peripheral sensitization facilitates sodium channel depolarization and prodromal activation of the nerve soma in the dorsal root ganglion.

Other inflammatory mediators and biomarkers have been identified in the periphery. In an effort to better describe the biologic component of chronic pain conditions, researchers have used microdialysis methods to identify the presence of biochemical substances in the interstitium surrounding peripheral tissues. These studies suggest that in patients with chronic myalgia, increased levels of 5-HT, glutamate, pyruvate and lactate are observed. 5-HT is an inflammatory mediator with different roles in central and peripheral pain processing [80]. In the periphery, 5-HT acts as an inflammatory mediator and is released after tissue injury. Glutamate also acts in the periphery as a nociceptive mediator and is released by the primary afferents. Lactate and pyruvate are increased in the interstitium likely resulting from increased anaerobic conditions in the periphery. NGF is implicated in initiating and sustaining chronic pain. Skin injected experimentally with NGF has shown to increase the proportion of mechanically sensitive C-fibers sevenfold. Additionally, 3 weeks after NGF injection, the mechanical thresholds were decreased, receptive fields increased, and the conduction velocity increased for these silent nociceptors when measured. These findings were present despite lack of significant change in intraepidermal nerve fiber density, reinforcing the mechanism of sensitization of silent nociceptors [81].

Persistent activity activates transcription of intercellular signaling mechanisms, which produce changes in protein translation and modulate the sensitivity of the peripheral nerve terminus [82]. These changes can also alter cell body sensitivity and produce ectopic discharges and oscillations. Changes in activity can spread through gap junctions to the surrounding nerve soma, which become secondarily sensitized. Within the dorsal root ganglion inflammatory cells such as T cells and neutrophils may infiltrate in chronic pain states, which can also lead to persistent pain [83]. In chronic pain states, such as with various bone pain disorders, extensive sprouting of peripheral nociceptor nerve endings can occur, leading to hyperalgesia and allodynia based on peripheral mechanisms [84]. This is mediated by growth-associated protein expression in the setting of chronic inflammation

and calcitonin gene-related peptide expression in sarcomas and other painful tumors.

Silent nociceptors exhibited a delayed activation to low pH stimuli when compared with the mechano-sensitive fibers. Furthermore, silent nociceptors responded to a second stimulus with longer lasting and more intense discharge. This prolonged discharge may be responsible for the persistent and sustained pain following an initial noxious stimulus. If the low pH was combined with the inflammatory mediator PGE-2, the silent nociceptors exhibited sensitization after repeated stimuli and responded with greater than twofold increase in duration and intensity [85]. This suggests that under inflammatory conditions, the silent nociceptors remain active with sustained discharge, contributing to the development of chronic pain. In the setting of chronic pelvic pain, these silent afferents awaken from quiescence and simultaneously transmit signals to the dorsal horn. Once the conditions for activation of these silent afferents are met, the dorsal horn receives multiple pain signals all at once [86].

Spinal cord

In the spinal cord level, presynaptic release of glutamate is bound on the postsynaptic terminal to provide prodromal conduction. A number of presynaptic mechanisms lead to decreased primary afferent depolarization, such as enkephalins and GABA B receptors [87]. Presynaptic modulation of cGMP and myosin light chain kinase increase activation at the synapse. Postsynaptic glutamate receptors can be modulated, producing increased sensitivity and heightened prodromal conduction. Persistent nociceptive activity modulates NMDA receptors, leading to long-term potentiation (LTP) of spinal signaling and the development of unregulated persistent pain [88]. LTP is a mechanism underlying the deregulation of a number of neuron types in pain perception pathways which can lead to chronic pain at any level. Retrograde signaling from the constitutively activated spinal cord neuron back to the peripheral nerve can occur through cyclo-oxygenase and nitric oxide intermediaries. Other postsynaptic signal facilitation can occur through phosphorylation of potassium channels. In the spinal nerve nucleus, persistent activation leads to calcium and cAMP binding to a number of unknown genes. This produces increased transcription of pain-related genes.

The rostra ventromedial medulla

Persistent pain occurs with activation of the RVM by CCK injection, which can be blocked by a 5-HT₃ antagonist, ondansetron. The RVM contains both the neurokinin 1 receptor and its ligand, Substance P. Neurokinin 1 agonists can modulate hyperalgesia dependent on 5HT-3, GABA_A and NMDA receptors. Alteration of the interplay between these receptors can also prevent the development of hyperalgesia and allodynia. This is mediated by RVM control of FOS expression in the superficial and deep dorsal horn of the spinal cord. Stimulation of the primary motor cortex can activate the DNIC and block persistent pain; this mechanism is mediated through activation of serotonergic receptors in the RVM [89].

Cuneate nucleus & nucleus gracilis

In persistent pain models this region demonstrated increased neuropeptide Y and c-fos expression [90]. This is thought to be due to an increase in the magnitude of cuneate afferents. This type of central sensitization can be attenuated by pretreatment with lidocaine. Other spinal models of pain demonstrate up regulation of several receptors [91]. These included GABA transporter 1, in addition to an increase in microglia and increased GABA uptake. Other animal models have described increased phosphorylated NR1 neurons, ipsilateral phosphorylated p38 neurons, galanin and neuropeptide Y in the gracile nucleus in response to the development of persistent pain.

Pons (LC)

Stimulation of the LC activates descending inhibition of spinal pain projections. Lesions produce increased hyperalgesia through increased responsiveness of dorsal horn neurons [92]. LC neuron terminals are the target for treatment of persistent pain with norepinephrine reuptake inhibitors. Similarly gabapentin, another approved treatment for chronic pain, is thought to act via activation of norepinephrine LC neurons or attenuation of inhibitory postsynaptic potentials with the LC. Other studies have demonstrated decreased persistent pain with decreased LC function [93]. These conflicting results may be the result of heterogeneous neuron populations, as in the RVM.

Red nucleus

By contrast, persistent pain models demonstrate upregulation of cytokines such as TNF- α , IL- β

and NGF in the RN. These changes occur in proportion to the development of allodynia. As part of the DNIC, the RN receives efferents from sensory and motor cortex, indicating that the motor based rubrospinal tract can be used to produce analgesia at the level of the hindbrain or spinal cord.

Habenula

Increased activity is found in drug seeking behaviors and electrical stimulation produces a decrease in reward directed behaviors in the habenula. Altered activity in the habenula may underlie opioid induced hyperalgesia [94] and the addictive behaviors related to chronic stress and fear avoidance. Due to its position controlling the descending pain centers of the rostroventral medulla (RVM), the habenula has been postulated as a target for modulation in chronic pain disorders [72].

The thalamus

The importance of the thalamus as a relay station between ascending spinal nociception and the cortical activation in chronic pain lies in the theory that peripheral nerve injury produces chronic pain through a central rather than a peripheral mechanism (centralization) [95]. Although some studies conflict and not all have a similar spatial resolution, decreases in thalamocortical connectivity seem to be important in diabetic and fibromyalgia patients. The decreases were in the VP and MD nuclei of the thalamus and a reciprocal decrease in the insula. Animal studies confirm that in chronic pain states there is a decrease in volume of S1, anterior cingulate and insula [96]. Although there is volume and functional loss in these areas, electrophysiology studies indicate that the VP nucleus becomes disinhibited in chronic pain states, developing lower baseline thresholds and spontaneous hyperexcitability with expanded receptive fields [97].

Striatum

Activation of striatal D2 receptors decreases persistent pain via RVM nociceptor inhibition [98]. In addition, striatal D2 activation produces an increase in descending pain inhibition via spinal serotonergic and dopaminergic receptors. These effects can be reversed by activating alpha-2 adrenoceptors or inhibiting striatal NMDA receptors. Serotonergic and dopaminergic descending pain suppression works in parallel, while striatal NMDA induced hypersensitivity

occurs through suppression of spinal GABAergic inhibition.

Amygdala

Amygdala connections are up regulated rapidly (within a few hours) after the onset of tonic nociceptive stimulation, creating a mechanism behind the development of negative affect with chronic pain. Increased connectivity is proportionally related to the degree of allodynia that develops, which occurs through an NMDA independent pathway [99]. Efferents from the amygdala to the LC are glutamate dependent and inhibit the noradrenergic LC outflow. Activation of Erk, as in the ACC, occurs following persistent pain. Increased Erk activity is proportionally related to sensitization behavior [100]. Neurons in the CeLC increase their responsiveness during persistent pain states [101]. The volume of the amygdala increases in response to chronic pain stimulation due to the generation of new neurons. The amygdala is thought to be important for the emotional and behavioral consequences of persistent pain particularly the development of depression symptoms.

Insula & operculum

Functional connectivity was shown to be increased in chronic pain patients between several regions in the pain matrix in default mode testing [31]. This included enhanced mPFC connections to PCC/precuneus (PCu) and RSC. Individual differences in pain rumination in the chronic pain patients (but not in healthy controls) positively correlated to mPFC functional connectivity with the PCC/PCu, RSC, medial thalamus and periaqueductal/periventricular gray as compared with the default mode.

Chronic pain patients exhibited less deactivation in response to a task than healthy controls in several areas: mPFC, amygdala, PCC. The decrease in deactivation in the mPFC was related to the duration of chronic pain. These findings suggest that tertiary pain matrix sites may become atrophic with long-term pain stimulation. In chronic back pain patients using a simple visual attention task, despite performing the task equally well as controls, displayed reduced deactivation in several key default mode network regions [30]. Mesolimbic dopaminergic projections to the anterior insula modulate nociception. Activation of D2 receptors in the insula or blockade of D1 receptors decreases nociception in a persistent pain model [102].

Cingulate cortex

Fluctuation of activity in the ACC in chronic pain patients is related to spontaneous fluctuations in chronic pain intensity [103]. ACC neuron activation occurs during pain aversive behavior and inhibition of ACC excitatory transmission attenuates nociception based learning. ACC based learning requires connection with other nociception regions, since PAG ablation prevents the effects of ACC stimulation. Cingulate pyramidal neurons undergo (LTP) in response to peripheral nerve injury. These changes occur through both presynaptic glutamate and postsynaptic AMPA alterations, mediated by adenylyl cyclase [104]. Increased expression of the c-Fos gene (a marker for noxious stimuli activated neurons) has been correlated with persistent pain, which is blocked by SNRI medications [105]. Persistent pain models also demonstrate a decrease in ACC cannabinoid 1 receptor sensitivity rather than a decrease in number of receptors [106].

Prefrontal cortex

Tight connections with the thalamus have led to the theory that certain chronic pain states arise from abnormalities of the electrical frequency between the thalamus and cortex, which has been termed thalamocortical dysrhythmia [39]. Decreases in chronic pain related behaviors can be achieved by OFC ablation, dopaminergic blockade, or infusion of morphine [107]. Development of allodynia and hyperalgesia has been linked to the over expression in OFC of IL1- β inflammatory genes, as well as apoptosis genes caspase-1, 8 and 12 [108]. Interestingly, both the behavioral and gene expression changes could be blocked by ozone injection. In persistent pain, there is a highly reproducible pattern of decreased activation in the ventromedial (along with the dorsolateral and anterolateral) prefrontal cortex [24].

Somatosensory cortex

Postcentral S1 cortical areas lose their normal somatotopic organization in chronic regional pain syndrome. This is restored to normal when a spinal neurostimulator successfully produces pain relief [109]. In multiple studies of chronic pain models, S1 activation occurs contralateral to the applied pain stimulus [24].

Persistent pain assessment

The best methodology for assessing chronic or persistent pain is currently under study. Most

importantly, it is becoming clear that using a battery of tests of biopsychosocial function can be used to identify individual subgroupings within a pain population, some of which are more likely to respond to particular treatments more than others [110]. A similar approach has been used to mathematically identify patients with high and low pain states in the pelvic floor [111], and in chronic pelvic pain in general [112]. Biomarkers of muscle metabolism suggest that in some persistent pain patients' serotonin, lactate and pyruvate can be used as an adjuvant assessment tool [80].

Conclusion

Pain perception occurs through a complex cascade of events beginning in the periphery, ascending through the spinal cord and brainstem, and then spreading out from the thalamus to a complex matrix of simultaneously activated cortical areas. Each of these steps in the cascade of pain perception can become dysfunctionally activated, leading to persistent pain. This dysfunctional activation can be quite persistent, producing long-term pain in patients without obvious evidence of disease. Understanding the neurobiology of pain perception can help to improve empathy among caregivers, and provides a rich environment of targets for researchers in chronic pain syndromes.

Future perspective

The complexity of the pain perception system provides many different individual areas, loops and matrices where neuropathic pain can arise. Similarly, it presents many opportunities for intervention in chronic pain states. Many of these will be targeted at the different levels of pain perception detailed here. In the periphery, novel agents targeting nociceptor receptors, second messengers and signaling will continue to be developed. The TRPV1 and 2 receptors and other channel blocking agents are under investigation as potential targets for modulating the perception of pain in the periphery [113]. Similarly, gene mutation and gene therapy trials modifying pain receptor related genes such as Nav1.7 are under investigation [114]. Peripheral cannabinoids agonists are also being investigated [115].

Central pain signaling mechanisms in the brainstem and cortex include a range of potential signaling pathways, many of which are already

being used for pain control therapies, such as serotonin selective reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Based on the many different locations detailed above, there is a wide range of possibilities for novel agents to have an impact. Modulating pre- and postsynaptic signaling in spinal cord at the receptor level is under investigation [116]. As the genetics underlying the changes that drive LTP in peripheral and central sites become better understood, ERK1, ERK2 and MeCP2 genes will become targets for individualized pain therapy [117]. The interaction between neurons and supporting glial cells can contribute to neuropathic pain and new methods approaching this aspect of chronic pain are being investigated [118]. Using antibodies to NGF is a novel approach to central sensitization, which is currently under development [119].

New tools to address neuropathic pain in the cortex, such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation, not only provide novel approaches to studying the function of the nervous system [120] but also provide new approaches to treat chronic pain through noninvasive stimulation [121]. Invasive neurostimulation therapies have been proposed to patients with neuropathic pain refractory to conventional medical management in order to improve pain relief, functional capacity and quality of life [122].

With the recent advances in neuroimaging technology and computing power, a better understanding of the nervous system is becoming possible. With this will come an improved understanding of the mechanisms underlying chronic pain. As this knowledge progresses, novel treatment opportunities will present themselves, which will transform the management of chronic pain patients.

Acknowledgements

The authors wish to acknowledge Steve Getch for producing the illustration artwork.

Financial & competing interests disclosure

Portions of this work were supported by the Summa Foundation. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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