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**REVIEW**

# Endogenous Antinociceptive System and Potential Ways to Influence It

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**Summary**

The biological significance of pain is to protect the organism from possible injury. However, there exists a situation, where, in the interest of survival, it is more important not to perceive pain. Spontaneous suppression of pain or weakening of nociception is mediated by an endogenous antinociceptive (analgesic) system. Its anatomical substrate ranges from the periaqueductal gray matter of the midbrain, through the noradrenergic and serotonergic nuclei of the brain stem to the spinal neurons, which receive "pain" information from nociceptors. Moreover, the activity of this system is under significant control of emotional and cognitive circuits. Pain can be moderated primarily through stimulation of positive emotions, while negative emotions increase pain. Paradoxically, one pain can also suppress another pain. Analgesia can be induced by stress, physical exercise, orosensory stimulation *via* a sweet taste, listening to music, and after placebo, i.e. when relief from pain is expected. Since pain has sensory, affective, and cognitive components, it turns out that activation of these entire systems can, in specific ways, contribute to pain suppression.

**Key words**

Antinociceptive system • Analgesia • Stress • Diffuse noxious inhibitory control

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## Introduction

Pain is a complex process that has sensory, affective, and cognitive components. It also affects the activity of the autonomic nervous system, neuroendocrine system, and behavior. While acute pain has a mostly positive function when warning the body against potential injury or tissue damage, chronic pain is a condition without any biological significance that worsens the quality of life of those affected and is frequently accompanied by depressive states. Pain mechanisms have much in common with stress mechanisms, i.e. acute pain represents acute stress and chronic pain chronic stress. In both cases, various homeostatic mechanisms are activated to ensure that the organism manages these situations optimally. Therefore, pain is now seen as a homeostatic emotion (Craig 2003). However, unlike other sensory modalities, pain is unpleasant at threshold intensities. Moreover, acute pain induces negative emotions and is uncomfortable, all while serving a significant biological function, i.e. it activates patterns of behavior that protect the body from further injury.

In pain, unlike other perceptions, the relationship between the intensity of the nociceptive stimulus and the intensity of subjectively felt pain is not necessarily linear. For example, it is not uncommon for even serious injuries to cause little or no pain. The question is, what causes pain to be spontaneously inhibited in certain cases, and where does the suppression occur?

There are several regions of the central nervous system (CNS) associated with pain control. Pain can be reduced at the peripheral level, the spinal cord, and supraspinal structures, however, since its function is to warn of potential injury, the ratio of pronociceptive and antinociceptive processes is set to limit and constrain

antinociception under normal conditions. However, there are conditions in which the ability to not feel pain becomes a necessity, i.e. when the organism must activate mechanisms that are important for adaptation and in extreme survival situations.

## Stress-induced analgesia

The trigger region for each stress response is activation of paraventricular (PVN) and supraoptic nuclei of the hypothalamus, which produce corticotropin-releasing hormone (CRH), vasopressin, and oxytocin. While the afferentation of supraoptic oxytocin neurons is relatively poor and includes mainly painless somatosensory and visceral afferentation from the periphery and central afferentation from the structures of the limbic system, neurons that convert all sensory modalities including pain transmission participate in the activation of PVN with subsequent CRH production (Sawchenko *et al.* 1996).

When processing the stress stimulus, a cascade of events is initiated consisting of the gradual activation of the hypothalamic-pituitary-adrenal axis. In reality, it involves the coactivation of two different interacting systems, the hypothalamo-pituitary-adrenal/cortisol system, and the sympatho-adreno-medullar system. There is positive feedback between the PVN, which releases CRH, and the noradrenergic locus coeruleus. CRH stimulates the production of noradrenalin, which further stimulates the formation of CRH; additionally, both dampen their production (Stanford 1995). CRH release can also be enhanced by acetylcholine and serotonin, while GABA and opioids inhibit CRH secretion. The intensity of the stress response is largely dependent on feedback control mechanisms. Classic glucocorticoid feedback consists of inhibiting the formation of ACTH and CRH; however, it was found that cortisol can also inhibit noradrenergic neurons and thus weaken their stimulatory effect on CRH production (Pacak *et al.* 1995). In some types of stress, the stress response is potentiated by vasopressin, which, like CRH, stimulates ACTH production (Kjaer 1993). The intensity of the stress response can be selectively modulated by the opioid system *via* stimulation of metenkephalin and dynorphin on sympathoadrenergic activity and the inhibitory effect of β-endorphin (Fontana *et al.* 1997).

Opioid neurons in the brain are distributed in three functional circuits: the nigrostriatal and mesolimbic dopaminergic system, the hypothalamo-pituitary axis, and the descending antinociceptive system (Simon and Hiller 1994). All three areas are activated under stress, but the latter plays a major role in pain modulation. The antinociceptive descending system includes the midbrain, the medulla, and the spinal cord. Hierarchically, the highest center is the periaqueductal gray (PAG) in the mesencephalon. Very strong analgesia can be induced through electrical stimulation, morphine application, or glutamate microinjections into this region (Carstens *et al.* 1990).

## The role of periaqueductal gray

PAG neurons receive numerous inputs directly from the cortex, hypothalamus, and amygdala (Bandler and Keay 1999, Vianna and Brandão 2003). Also, it receives afferentation from lower brain regions such as nucleus tractus solitarius (NTS) and parabrachial nuclei (Roeder *et al*. 2016). PAG neurons do not transmit projections to the spinal cord directly. They do so *via* the brain stem where it affects the activity of serotonergic and noradrenergic neurons located in the rostroventromedial medulla (Lau and Vaughan 2014, Chen *et al*. 2017, Tobaldini *et al*. 2019).

Additionally, there are cells in this area referred to as pronociceptive “on” and antinociceptive “off” cells. These neurons were first discovered during painful stimulation of rats with electrodes implanted to register unit activity. Pronociceptive “on” cells were always activated, while antinociceptive “off” cells were inhibited before a painful defense response (Neubert *et al*. 2004, Carlson *et al*. 2005, Heinricher *et al*. 2008).

The internal functional organization of the PAG is divided into ventrolateral and lateral regions, which are activated by different types of pain. The ventrolateral PAG is activated by deep somatic and visceral pain, while the lateral PAG receives nociceptive information from the body surface, such as nerve endings in the skin. The afferentation of the ventrolateral PAG comes mainly from the spinal cord and NTS, but it lacks somatotopic organization, which is also consistent with the fact that visceral pain is not precisely localized. The lateral PAG receives afferents from the spinal cord, as well as from the trigeminal nuclei, although, these follow clear somatotopic projections. Electrical stimulation of different parts of the PAG induces different autonomic reactions and behavior. These responses can manifest as hypotension, bradycardia, and passive defense reactions (freezing) during stimulation of the ventrolateral PAG

and as hypertension, tachycardia, and active stress coping ("fight or flight" reaction) during stimulation of the lateral PAG (Bodnar *et al.* 1980, Bodnar 2000, Vianna and Brandão 2003, George *et al.* 2019).

Both types of behavior are associated with analgesia, but their mechanisms are different. The analgesia induced by ventrolateral PAG stimulation can be described as opioid, whereas stimulation of the lateral PAG induces non-opioid analgesia. These different mechanisms of analgesia have been extensively studied in rats using swim stress. The involvement of the opioid or non-opioid system depended on swimming time and water temperature. Swimming in cold water (about 2 °C) or long-term swimming, independent of water temperature (more than 5 min), caused analgesia that was blocked by MK-801 (a non-competitive antagonist of glutamate NMDA receptors), which suggested a non-opioid type of analgesia. Conversely, swimming in warmer water (20-32 °C) or short-term swimming, induced analgesia that was blocked by naloxone (an opioid receptor antagonist) and thus suggesting an opioid-type of analgesia (Terman *et al.* 1984). Although it is difficult to unambiguously establish a sharp boundary between opioid and non-opioid analgesia, numerous animal experiments indicate that most weak stressors cause opioid analgesia, whereas very strong stressors cause non-opioid analgesia.

What is the biological significance of different analgesia systems? These mechanisms were studied by Bodnar *et al.* (1980), who developed the so-called *collateral inhibition model* for pain control systems. It assumes that there is a specific hierarchy in the antinociception system that prevents both types of analgesia from being activated simultaneously. If one system is more active, it will dampen the other system, i.e. the opioid system inhibits the non-opioid system *via* collateral inhibition and vice versa. A similar mechanism is at work in sensory systems to enhance "signal-to-noise" contrast in which the most activated neurons inhibit their less active neighbors. Bodnar also suggests that this arrangement might have some adaptive purpose, since the pattern of behavior that is more significant at the same time, not only in terms of pain suppression but also in terms of better coping with the situation under which the pain arose, will be most activated.

In men, deep brain stimulation of the periaqueductal gray is used in the treatment of intractable phantom limb pain or anesthesia dolorosa which are refractory to pharmacotherapy. PET scan showed that stimulation of the PAG reduced radioligand binding through the release of endogenous opioids but this did not correlate significantly with pain reduction (Sims-Williams *et al.* 2017).

Measurement of heart rate variability during stimulation of ventral PAG in patients with chronic neuropathic pain showed changes in LF/HF ratio (increase in parasympathetic activity) which correlated significantly with reported analgesia (Pereira *et al.* 2010). Analgesic or antinociceptive effects are similar to vagal stimulation, which also attenuates pain (Bohotin *et al*. 2003).

## Physical exercise as a stressor

When something hurts, movement in the affected part of the body is reduced, thereby protecting the body from further injury. In the case of non-adaptive chronic pain, the behavior is generally affected, and physical activity is significantly reduced. In contrast, active athletes and ballet dancers have been repeatedly shown to be less sensitive to pain (Guieu *et al*. 1992, Tajet-Foxell and Rose 1995, Farasyn and Meeusen 2003). However, even in untrained individuals, aerobic and isometric exercise has been shown to weaken the perception of pain stimuli from various modalities (Janal 1996, Gajsar *et al*. 2017). Physical exercise is also a stressor (Koltyn 2000, Gerber *et al.* 2017) and the analgesic system most activated will depend on, among others, the intensity, type, and length of exercise.

*Opioid system*

The response of the opioid system changes after exercise. A study conducted in rats with sciatic nerve ligation, which induces hyperalgesia, showed that if these animals were allowed to run in running wheels, their pain threshold did not differ from that of the control rats (Stagg *et al*. 2011). In addition, in rats allowed to run, the level of beta-endorphin and met-enkephalin, in rostroventromedial medulla (RVM), increased significantly compared to the restricted from running group. After intense physical activity, the release of endogenous opioid peptides increases and signal transduction, through G protein activation of μ-, δ- and κ-opioid receptors, increases, particularly in the sensorimotor cortex and hippocampus (Arida *et al.* 2015).

Simultaneous involvement of the opioid system in the modulation of both pain and locomotor activity was demonstrated in an experiment conducted on female

mice selected according to the amount of running wheel activity. After blocking opioid receptors with naltrexone in parallel with a reduced thermal threshold, the amount of locomotor activity was reduced in both selected lines (Li *et al*. 2004).

People who regularly run describe a feeling of euphoria "runner's high" that is associated with the activity. In a volunteer group, a PET study using [$^{18}$F] FDPN, which is a radioligand with approximately the same affinity for all types of opioid receptors, was performed before and after a half marathon (Boecker *et al*. 2008). At the finish, they were asked to evaluate the intensity of the euphoria induced by running using a visual analog scale. The more intense the euphoria experienced after the run, the greater the difference in opioid receptor occupancy with radioligand compared to their baseline. This difference was especially obvious in the anterior cingulate cortex, orbitofrontal cortex, and insula, where opioid receptor occupancy by the radioligand was negatively correlated with euphoria. The more receptors occupied by endogenous opioid peptides, the more intense the euphoria they experienced.

*Non-opioid systems*

Since it has been shown that exercise alters noradrenaline, dopamine, and serotonin levels, it appears that the monoaminergic system may also contribute to analgesia (Meeusen and De Meirleir 1995). The descendent antinociceptive system includes the noradrenergic pathways from the locus coeruleus that project to the dorsal horns of the spinal cord and synapse with second-order neurons of the pain pathway. The analgesic effect is mediated by alpha-2 adrenergic receptors. During exercise, the locus coeruleus is activated from proprio- and baroreceptors *via* NTS as well as CRH. The effect leads to impaired detection and discrimination of sensory stimuli. LC neurons send their axons to the ventral tegmental area (VTA), where, through activation of alpha-1 receptors, they stimulate glutamate release, which in turn increases the activity of dopaminergic neurons (Clark *et al*. 1986, Devilbiss *et al*. 2012, McMorris 2016).

*Endocannabinoid system*

Modulation of pain by stimulating cannabinoid receptors can be done peripherally or centrally. Endogenous cannabinoids in the CNS bind to cannabinoid CB1 receptors, which are mostly found in the dorsal root ganglia, superficial layers of the Rexed zones in the spinal cord, the RVM, and PAG (Maione *et al*. 2006). At the level of the spinal cord, the transmission of pain is reduced due to decreased release of glutamate from nociceptive neurons. In the PAG, endocannabinoids inhibit GABAergic neurons, and therefore, the disinhibited PAG neurons activate the descending antinociceptive system (Aubrey *et al*. 2017). Binding of endocannabinoids to receptors can lead to (1) the opening of potassium channels along the cell membrane causing hyperpolarization or (2) blockade of calcium channels at the presynaptic terminal. Both mechanisms reduce the release of mediator from presynaptic terminals (Maione *et al*. 2006).

In 2003, the first work that recorded increased levels of anandamide in the blood after intense exercise was published (Sparling *et al*. 2003). Since then, many parallel animal and human studies have been performed to elucidate the cannabinoid mechanism in analgesia. In rats, aerobic exercise increases cannabinoid receptor expression and arachidonoylglycerol (2-AG) and anandamide (AEA) levels in the PAG. In contrast, CB1 or CB2 receptor blockade before exercise does not induce analgesia (Galdino *et al*. 2014). In humans who had to perform submaximal isometric exercises, the mechanical pain threshold was significantly increased after exercise, the subjectively experienced pain intensity decreased, and the level of endogenous cannabinoids (AEA, 2-AG and others) increased, regardless of whether the opioid system was blocked, using naltrexone, before exercise (Koltyn *et al.* 2014).

## Pain relief by other pain

Diffuse noxious inhibitory control (DNIC) is a pain-modulatory mechanism that reflects the activity of the descending endogenous analgesia system. It represents an attempt to objectify performance of the endogenous pain control system, i.e. to test the balance between facilitatory and inhibitory processes and thus to estimate the size of the individual analgesic potency (Pud *et al*. 2009, Yarnitsky *et al*. 2010). Currently, the term has been replaced by the expression, conditioned pain modulation (CPM). The method is based on the observation that one pain can suppress another pain and involves the measurement of thermal or mechanical pain thresholds (test stimuli) at rest and then during simultaneous conditioned cold or mechanical pain stimulation (i.e. the cold pressor test and the tourniquet method) on the contralateral limb. If the integrity of the

endogenous analgesic system is maintained, then the pain threshold during and after tonic pain stimulation is increased. In healthy people, DNIC has been shown to be stronger in men than in women and was not dependent on personality characteristics or degree of distraction. In contrast, DNIC is attenuated in patients with chronic pain of various etiologies (Nijs *et al.* 2012, Wilder-Smith *et al*. 2010). It is believed that an attenuated DNIC may also be one of the causes of chronic pain (Pud *et al*. 2009, Sprenger *et al.* 2011) and the clinical implications of testing for DNIC efficiency might identified patients with higher risk for development of post-operative chronic pain (Yarnitsky *et al.* 2008).

Active athletes have, in addition to increased resting pain thresholds, greater hypoalgesia after CPM compared to non-sporting individuals (Ellingson *et al*. 2014, Lemley *et al.* 2015, Flood *et al*. 2017). It should be noted, however, that increased inhibitory capacity can also play a negative role since weakened negative signals sent out from the body or signals arriving late can cause overestimation of their strength and lead to injury.

## Pain, pleasure, and expectation

The study of the role of dopamine in analgesia suggests that both types of analgesia, i.e. opioid and non-opioid, seem to represent only the extreme poles of a continuum. In many cases, the two systems overlap each other. There are areas of reward and punishment within the limbic system in which dopamine plays a pivotal role and in which it also plays an important role in suppressing tonic pain (Borsook *et al*. 2007, Leknes and Tracey 2008, Meyer *et al.* 2009). Mesolimbic dopaminergic neurons of the VTA project into various areas of the forebrain, including the nucleus accumbens (Altier and Stewart 1999). This pain control system is activated under stress by releasing endogenous opioids which cause the indirect release of dopamine from these neurons through inhibition of GABAergic neurons (Johnson and North 1992, Koob 1992).

The first evidence that pain stimulation may induce analgesia under specific circumstances was reported by Gear *et al.* (1999). Their observation led them to the idea that under certain conditions, even painful stimuli can be "rewarding", i.e. the stimuli can activate the reward system. They found that intense pain caused by subcutaneous administration of capsaicin or by immersing a limb in hot water can weaken some nociceptive reflexes for an extended period or can increase the mechanical pain threshold. The antinociceptive effect can be blocked by prior administration of either the dopaminergic antagonist, flupentixol or by the opioid antagonist, naloxone. Other experiments in anesthetized animals have shown that the antinociceptive effect was correlated with the intensity of the painful stimulus; more intense stimuli induce stronger subsequent analgesia (Gear *et al.* 1999). This form of analgesia can be weakened by the administration of the GABA A receptor agonist, muscimol to the rostral ventromedial medulla, but not by naloxone (Killian *et al.* 1995).

In our previous study we have shown that individuals with body modifications as well as without body modifications had higher thermal pain thresholds during public demonstration of painful techniques compared to thresholds measured at control neutral conditions. These observations lead us to conclude that in emotionally charged environment, pain threshold in our participants was top-down modulated *via* affective and cognitive processes (Yamamotová *et al.* 2017).

Relief from pain can be achieved even without any manipulation, using a placebo. Thus, activation of descending controls is associated with a more complex psychological phenomena and is dependent on expectation (Benedetti *et al*. 2005, Benedetti and Amanzio 2013). Placebo analgesia is a condition in which pain is eliminated or reduced after administration of a substance without any pharmacological effect. The placebo effect can be both analgesic and algesic, i.e. if a chemically inactive substance is claimed to cause pain, a specific group of people will experience pain. A negative effect of a placebo is referred to as a nocebo. Endogenous opioids have been implicated in the mechanism of action of placebo analgesia, whereas opioid receptor antagonists, e.g. naloxone, have been shown to weaken the analgesic placebo effect. On the other hand, the CCK receptor antagonist, proglumide, enhances both the effect of opioids and the analgesic placebo effect, but only in placebo responders; in non-responders, proglumide has no effect (Benedetti 1996, Benedetti and Amanzio 1997).

More recent studies have shown that the dopaminergic system is activated simultaneously with the opioid system. Placebo-induced activation of opioid neurotransmission was detected in the anterior cingulate, orbitofrontal and insular cortices, nucleus accumbens, amygdala, and PAG. Dopaminergic activation has been observed in the ventral basal ganglia, including the

nucleus accumbens. A PET study showed that dopaminergic D2/D3 mediated receptor activity and μ-opioid activity correlated positively in the nucleus accumbens (Scott *et al.* 2008)

## Pain as a route to escape from reality

The body should be a source of satisfaction and pleasure for man, with feelings that allow us to enjoy life and make it pleasant. On the other hand, dissatisfaction with one's body may increase suffering and increase self-destructive tendencies. Negative life events accompanied by physical and mental trauma can change the perception of one's body and attitude towards it, such that the body will be rejected, hated, damaged, and destroyed. Such individuals are less susceptible to physical pain but also other bodily processes (Fishbain *et al*. 2001). Avoiding and escaping physical and mental reality is a way to cope with the unmanageable emotional consequences of trauma, this condition is referred to as dissociation. Dissociation is also defined as an inability to normally interpret information and experiences, a condition manifested by amnesia, depersonalization, and derealization.

The same three principal components that characterized different aspects of pain can be observed in dissociative states. If we regard dissociation as a defense mechanism that is activated in marginal situations, then the sensory component of dissociation will protect against pain (analgesia), the affective component of dissociation will protect against negative emotions, and the cognitive component of dissociation (amnesia) will prevent memories of traumatic events accompanied by pain.

Similar insensitivity to pain has been reported in young people who have survived suicide attempts compared to individuals of equal age with similar types of injuries that were unrelated to suicide, e.g. an accidental fall from height (Orbach *et al*. 1997). Their pain threshold was positively correlated with depression, anxiety, dissociation, and a negative relationship to one's body.

## The role of the sensory systems

The most natural analgesic, although not as effective in adults, is an intake of food or drink with a sweet taste. A review on the effect of sucrose on pain in young children showed that the heart rate and negative emotional manifestations, including crying, were reduced in addition to a reduction in pain (Stevens and Ohlsson 2000, Harrison *et al*. 2010). The "sweet-induced" analgesia is mediated by the opioid system, and carbohydrate intake has been shown to increase morphine-induced analgesia in rats. Testing this effect by administering sucrose and saccharin showed that morphine-induced analgesia was significantly greater in sucrose-fed rats than in rats consuming a standard-diet (Kanarek and Homoleski 2000, Eikemo *et al.* 2016).

In addition to orosensory stimulation, olfactory stimulation can also participate in pain suppression. The increased thermal pain threshold in the lemon essential oil odor exposed rats indicated the ability of olfactory stimulation to affect pain pathways and brain areas related to pain modulation (Ceccarelli *et al.* 2004). In mice exposed to linalool (odorous components of lavender extract), immunohistochemical analysis revealed that odor-induced analgesia is probably mediated by hypothalamic orexin neurons (Tashiro *et al.* 2016).

The importance of visual perception in evaluating pain was shown by experiments conducted in people who were blind from birth (Slimani *et al*. 2013). In addition to reduced sensory pain thresholds, these individuals subjectively experienced more intense pain during stimulation than healthy subjects. However, thresholds for non-painful mechanical or thermal stimuli were the same as in healthy controls. Similar results can be observed in healthy people after prolonged visual deprivation (Zubek *et al*. 1964). These findings show how vision is critical in detecting threatening stimuli, especially painful stimuli. New anatomical studies provide evidence of the existence of a pathway connecting the anterior cingulate cortex with a key area (Brodmann area 19) involved in the processing of painful stimuli in the visual cortex (Vogt and Pandya 1987).

Patients with low back pain often have difficulty in precisely defining the part of the back that hurts because they perceive the painful area as being dimensionally altered. Common mechanisms of pain perception relative to the body do not lie at the periphery but in the CNS, and hence, pain becomes an integral part of the multimodal representation of our body. Currently, methodological procedures are developed to study both the perception of pain and the body's organization.

Diers *et al.* (2016) published a study showing that visual feedback can reduce pain. They focused on patients with chronic back pain, and because we do not see our backs, they used a camera to photograph the

patient from behind and transmit the image of their back to a monitor while producing a painful stimulus. Patients with chronic pain evaluated the stimuli as more painful than healthy persons, but when using visual feedback, they perceived the stimuli as being significantly less painful. This experiment implies that looking at a painful area may weaken the aversive experience of the stimulus and may result in the stimulus being considered as less threatening. The authors believe that this method could be used to train and diminish pain perception in patients with chronic pain.

Moseley *et al.* (2008) showed how pain could be managed in patients with chronic upper limb pain. Patients were tasked with exercising the affected arm and recording the perceived pain intensity. They looked at the exercising hand either with magnifying glasses or with minimizing glasses. Looking at the twice enlarged hand not only caused stronger pain, but the hand swelled more after exercise, on the other hand, the pain was perceived as much weaker when the painful hand was seen as being diminished in size.

## Body perception and pain suppression

An interesting finding was described in a study Gallace *et al.* (2011) which focused on pain perception in the hands, depending on their position relative to the body, i.e. whether they are side by side or crossed. In this context, a new concept of "cross-hand analgesia" is being introduced. The theoretical basis of this experiment was based on the fact that pain experience depends on a complex interplay between anatomical and spatial representation. They showed that merely crossing the arms across the centerline of the body weakens pain perception and increases pain thresholds when stimulated. The likely explanation for this phenomenon is a mismatch between the two reference frameworks of body perception that help localize external stimuli. One reference frame is anatomical (where on the body) and the other is spatial (where in space). Normally, these two systems provide similar information; however, when the hands are crossed across the center axis of the body the information processed by both systems is confusing. Experiments using evoked potential analysis showed that there is a delay in stimulus processing when arms are crossed. This hypothesis was confirmed by findings from fMRI studies (Torta *et al*. 2013). During painful stimulation of crossed arms, the posterior parietal cortex was activated less than during stimulation of uncrossed arms.

In contrast, areas that were responsible for attention, homeostasis, and physical representation, i.e. the frontal and cingulate cortex and insula, were more active when the hands were crossed. Thus, how intensely something will hurt us depends not only on the arm stimulated but also where, in space, the arm is located relative to the central axis. Moreover, crossed arms are part of a defensive posture, which is sometimes used to face a threat that could be injurious. Therefore, the increased pain threshold in this posture may also signal the onset of activation of the endogenous antinociceptive system.

Perceptual distortion can also include phantom pain, where patients after amputation experience severe pain in a non-existent limb. Because *to see* means to feel less pain, the mirror technique, or "Mirror Therapy" (MT) is often a helpful technique for rehabilitation purposes, especially for patients with this type of problem. Mirror therapies are based on the principle that the patient has an amputated limb hidden behind a mirror and then tries to make synchronized movements of both limbs while observing the healthy limb in the mirror. In this situation, there is a conflict between visual feedback from the supposed movement of a non-existing limb and proprioceptive feedback from the healthy limb. Information about the apparent movement of the amputated limb can significantly reduce the activity of the pain management system (Foell *et al*. 2014). The activity in primary motor areas contralaterally increases to the affected side, and subsequently, the pain intensity in the affected limb is reduced; it is better to prevent phantom pain than heal it. Several studies have also been performed in this context to show that the use of MT before a planned amputation can reduce the risk of phantom pain after the procedure (Hanling *et al*. 2010). The illusion induced by the reflection of the movement of the healthy limb in the mirror can activate the system of mirror neurons in the brain. This system represents a basic brain mechanism that transforms sensory representations of others' behavior into one's own motor representations concerning that behavior (Rizzolatti and Sinigaglia 2016).

In conclusion, our understanding of antinociception or endogenous analgesia is now undergoing an evolution that is similar to the one that transformed our understanding of stress. Stress has long been considered a nonspecific adaptive response to stressors. Only in recent years have we seen more and more evidence of its specificity, which is manifested in

different degrees of different stressors with different functions. Regarding antinociception, which was originally considered a nonspecific defense response to pain, it now appears that there is some specificity depending on how intense the pain is, how it is induced, in what context it is evaluated, and the optimal way to face it. Although the "common final path" might be similar, consisting primarily of the activation of the opioid and dopaminergic systems, the routes that activate them can be different.

## Conflict of Interest

There is no conflict of interest.

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