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Review

Facing the experience of pain: A neuropsychological perspective

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Abstract

Pain is an experience that none of us would like to have but that each one of us is destined to experience in our lives. Despite its pervasiveness, the experience of pain remains problematic and complex in its depth. Pain is a multidimensional experience that involves nociception as well as emotional and cognitive aspects that can modulate its perception. Following a brief discussion of the neurobiological mechanisms underlying pain, the purpose of this review is to discuss the main psychological, neuropsychological, cultural, and existential aspects which are the basis of diverse forms of pain, like the pain of separation from caregivers or from ourselves (e.g., connected to the thought of our death), the suffering that we experience observing other people's pain, the pain of change and the existential pain connected to the temporal dimension of the mind. Finally, after a discussion of how the mind is able to not only create but also alleviate the pain, through mechanisms such as the expectation of the treatment and the hope of healing, we conclude by discussing neuropsychological research data and the attitude promoted by mindfulness meditation in relation to the pain. An attitude in which, instead to avoid and reject the pain, one learns to face mindfully the experience of pain.

Keywords: Pain; Neuropsychology; Mindfulness; Self; Time; Mind

1. Introduction

Every human being is destined to meet pain in his life. Aeschylus (525–456 BC), the great Greek playwright, majestically expressed this concept: "No mortal ever spend their lives completely unscathed from pain, everyone pays the price of pain to life" (Aeschylus, *Coefore*, lines 1018–19). Pain is a strong, burning experience. When pain is present the whole mind is involved, when it is absent the thought recalls the threat. The experience of pain, although strong and compelling, remains in its depth problematic and complex.

The ancient Greeks called the pain "*algos*" and referred to physical pain on one side (I feel pain, I am sick, I suffer, etc.), while at the same time recognizing to pain an inner component, which we call psychic (I am distressed, afflicted, troubled, etc.) [1,2]. Humans, like many other living beings, do not feel pain only in the presence of an injury or

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during an illness but also due to a separation from, for instance, the caregiver. When one removes the mother hen, chicks begin to chirp for the pain of separation from the mother, the same way as the kittens or small human beings [3–6].

Along with the pain of separation humans can feel the pain of others. When a child is sick and suffering, the mother generally identifies herself in the pain of her baby and she suffers as well. Psychology calls "empathy" the capacity to suffer next to another. In everyday life, the ability to share the sorrows of others is called compassion [7,8]. Humans can experience pain in many forms: physical pain, the grief of separation, and the pain of others; however, the most terrible form with which we must confront all our life is probably the anxiety and anguish of pain that can happen to us in the future [9].

Probably humans are the only living beings capable of imagining the future. They live with a neuropsychological device that is able to reconstruct the past (episodic memory) and to imagine the future. This device allows humans to travel mentally in time [10,11]. The possibility of living and travelling mentally in time is the basis of many cognitive abilities typical of human beings, such as the construction of instruments and the ability to develop stories. However, the sense of time has placed humans in front of their most certain possibility, namely that of being sure to die. For this reason the ancient Greeks called human beings "the mortals" [2,12]. Hence, human beings have thought of their own death [13].

The anguish of the death of our loved ones and the thought of our death are probably the basis of the fundamental questions of existence: why I came to the world, what I am called to do in this life, what will happen to me after death? Generally, those who think of their death do not smile. Many prefer to avoid the concern of death not thinking about it, while others are caught by fear or dread. In the more balanced conditions, the thought of our own death is associated with melancholy, a pain experience difficult to define: mild, deep and poignant. In this regard it should be noted that the Greek word "*algos*" is also connected to the word "*alego*" which means: "I care", "I am prompt", from which the Latin word "*religio*" derives [9,14,15]. The experience of pain is therefore not only the basis of neuropsychological and philosophical reflection but also a royal road that leads to the existential dimension.

2. The neuroscience of pain

The human body has numerous receptors for pain arranged on the surface of the body (skin), into the deeper tissues (muscles, tendons, bones) and in the internal organs. These receptors signal to the central nervous system the presence of a lesion, a fracture or of an inflammatory reaction. The information of pain receptors (nociceptors) reach the spinal cord (or the nuclei of the cranial nerves for pain sensations of the head) using fibers coated or not with myelin (Aδ myelinated fibers and unmyelinated C-fibers). In the spinal cord these fibers are connected with the neurons of the first lamina of the posterior gray horns. This is a neural structure that has evolved from the sympathetic nervous system, a system involved in the alert reactions (e.g., preparation for fight or flight) and stress [16,17]. This allows us to understand why a painful stimulus generally causes a reaction of alert, waking up, or anxiety.

The neurons in lamina I of the posterior horns give rise to a bundle of fibers that pass into the anterolateral white column in the spinal cord: the spinothalamic bundle. There are several pathways and systems that process painful information in the brain [18]. For reasons of simplicity we mention the three major components of what has been called the "pain matrix": the lateral system, the medial system, and the descending system implicated in the control of pain [19] (Fig. 1). The lateral system involves the lateral spinothalamic ascending pathways that project to the lateral thalamic nuclei and hence to the primary somatosensory areas of the parietal cortex. This system is able to discriminate the intensity, duration, and location of the painful stimulus. The medial system also originates from the spinothalamic bundle but involves the medial thalamic nuclei. These nuclei project their information to the structures of the limbic system, namely to the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), (anterior) insula, and the parietal operculum. The medial system is thus responsible for the emotional processing of pain, namely the feelings of suffering and distress [20,21].

As we mentioned, in humans there also exists a descending system responsible for the regulation of pain (Fig. 1B). Many brain structures, if stimulated electrically during neurosurgery, are able to inhibit pain. Of these structures, the most important are the ACC, OFC, the primary and secondary somatosensory cortex and some subcortical structures, such as the hypothalamus, thalamus, and amygdala [22]. However, the structure that can produce the most important analgesic effects is located in the brain stem and is the periaqueductal gray (PAG). From the PAG other fibers originate

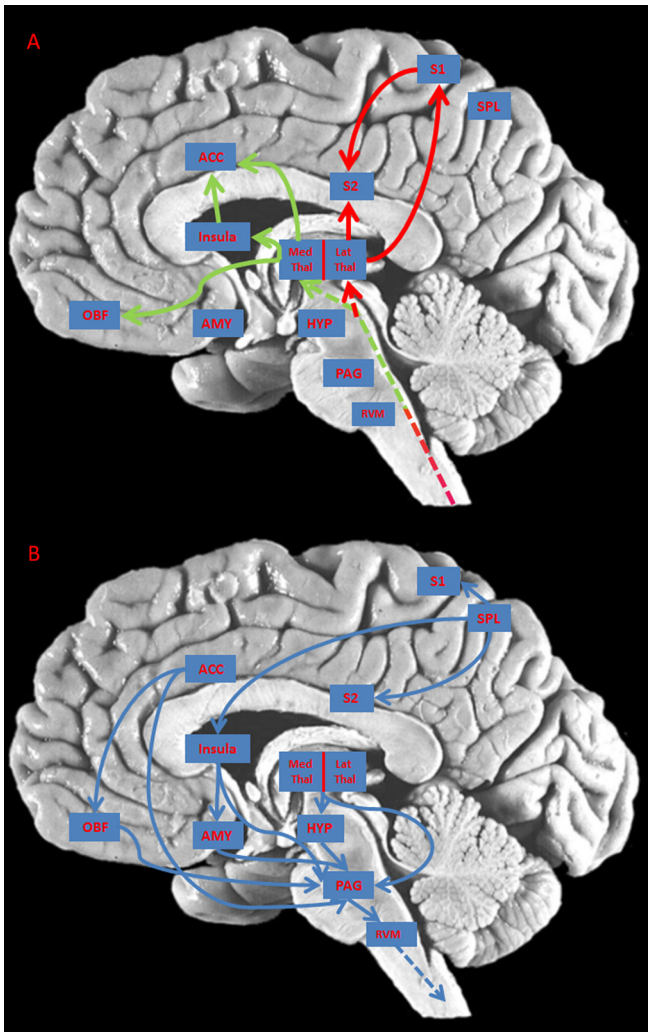

Fig. 1. A) Main afferent pain pathways. Nociceptive information enters the brain from the spinal cord. Two main afferent pain pathways are depicted both involving multiple brain regions. In red is shown the lateral system. It involves spinothalamic ascending pathways that project to the lateral thalamic nuclei (Lat Thal) and hence to the primary and secondary somatosensory areas of the parietal cortex (S1 and S2, respectively). This system is able to discriminate the intensity, duration, and location of the painful stimulus. In green the medial system is reported. It originates from the spinothalamic bundle and involves the medial thalamic nuclei (Med Thal). These nuclei project their nociceptive information to the structures of the limbic system, namely to the anterior cingulate cortex (ACC), the orbitofrontal cortex (OFC), and (anterior) insula. The medial system is responsible for the emotional processing of pain. B) Pain perception is modulated via different descending pathways. Limbic brain areas such as the anterior cingulate cortex (ACC) and the insula, and other brain regions including the orbitofrontal cortex (OBC), the amygdala (AMY), the Thalamus (Thal), and the hypothalamus (HYP) project to the periaqueductal grey (PAG). The PAG indirectly controls pain transmission through the rostroventral medulla (RVM). Other descending circuits involved in pain modulation include projections from the superior parietal lobe (SPL) to the primary and secondary somatosensory cortex and insula. See the main text for further details concerning the different neuropeptides and neurotransmitters involved in pain regulation (see also [141]). The sagittal view of the brain was modified from the original version taken from the Anatomy atlas of the central nervous system by Pietro Gobbi and Daniele Di Motta (http://atlassnc.uniurb.it/Default.htm). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

that inhibit pain reaching the posterior horn of the spinal cord, either directly or through paths that originate from the *raphe nuclei* (serotonergic system) and from the *locus coeruleus* (noradrenergic system) [23].

Numerous neurotransmitters are involved, at both the peripheral and central levels, in the control of pain. For example, at the level of the skin lesion numerous substances that increase pain are released, such as the substance P, histamine, serotonin, and the prostaglandins. Painkillers and nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, are able to limit the pain by reducing the synthesis of prostaglandins. The anandamide, which is an endogenous

cannabinoid neurotransmitter, reduces pain by preventing the release of histamine [24]. Moreover, the oxytocin, a neuropeptide released in the paraventricular and supraoptic nuclei of the hypothalamus, exerts a significant analgesic action through the activation of inhibitory neurons of layers I and II of the dorsal horn [25,26]. In addition, at the peripheral level (C-fibers and neurons of the dorsal horn) there exists a form of memory for pain. The repeated activation of pain fibers produces sensitization, mediated by the N-methyl-D-aspartate (NMDA), which tends to greatly reduce the pain sensibility threshold thus increasing the sensation of pain [18].

The most important neurotransmitters that regulate pain at the central level are endogenous opioids, endocannabinoids and oxytocin. The resin extracted from the *Papaver somniferum*, has been used for centuries to reduce pain because it contains substances (opium and its derivatives) that bind to receptors of neurotransmitters involved in the regulation of pain called endogenous opioids (endorphins, enkephalins, dynorphins) [27]. The endogenous opioids are mainly produced in the hypothalamus and the PAG, but exert their effects both at the level of the spinal cord and at the central level, and particularly in the medial system. Morphine, a potent analgesic drug, is the most abundant opiate found in opium and its analgesic action is limited by an endogenous neurotransmitter (cholecystokinin) and by a drug (*naloxone*). Even the endocannabinoids (both endogenous and exogenous, such as the *marijuana*) play an analgesic action both at the level of the spinal cord and in the brain. Such actions can be blocked by administration of a specific drug, the *rimonabant* [28,29]. Finally, oxytocin has a significant analgesic action not only at the level of the spinal cord but also at the central level [30,31].

3. The pain of separation

For Sigmund Freud (1856–1939), the most important aspect of the mother–child relationship consisted in nutrition. The child approaches the mother to feed and breast milk constituted, in his opinion, the most important source of gratification. For the development of personality, Freud has therefore focused mainly on the digestive tract, considering the mouth and anus as essential structures for psychic development [32,33]. In the second half of the last century, the psychiatrist John Bowlby (1907–1990) has, however, pointed out that the primary need for a child is not nutrition, but rather the need to be protected. In this new vision of the relationship between mother and child, the body surface and the contact become priority over feeding. In the first years of life the child is motivated to maintain contact with his caregiver, because this relationship allows him to survive. In this period, the mother's ability to tune to the child's physical, mental and communicative needs, together with the ability to relieve the sense of despair, determine in the child's brain and mind the development of a secure bond of attachment, which will be the basis for all subsequent relationships that the individual will develop with other human beings [34,35].

The link between the pain system and the attachment system is represented at the neurobiological level mainly by the endorphins and oxytocin [36,37]. These neurotransmitters seem to play a role, in fact, both in the regulation of pain and in the relationship that binds the child with their parents. The role of attachment in mammals has been studied by analyzing the physiological responses to separation distress. If baby mammals are removed from caregivers, they show immediate behaviors (panic attacks) and long-term changes characterized by decreased body temperature and sleep, release of stress hormones (corticosteroids) and activation of alert systems. At the central level, they face a decrease in the secretion of endogenous opioids [6].

The reaction to separation (or panic reaction) is inhibited or mitigated by the administration of opioids and oxytocin. The circuit of the panic reaction allows the construction of social bonds and is the basis of the attachment behavior. This circuit provides the neurophysiological and neurochemical basis for feelings of security and social acceptance. Brain structures involved in the reaction of panic are the PAG, the nucleus of the *stria terminalis*, the ventral septal area, preoptic area, dorsomedial thalamus and the anterior portions of the cingulate gyrus. All these structures are involved in the production and release of endogenous opioids and have receptors for the hormones that regulate stress [38,39].

In animals, the reaction to separation is also typically measured by the separation-induced distress vocalizations. If a small chick is removed from the mother he will begin to peep. As soon as he is put next to the hen he will stop doing it. If he is alone and contained in the hands and gently caressed he will present a reaction of comfort stopping to peep and closing his eyes. It was discovered that these behaviors are mediated by the release of oxytocin and endogenous opioids, because the reactions of separation in small chicks can also be neutralized by the administration of morphine [6,40]. Numerous species of birds and mammals need contact and social interactions, which are regulated by the release of endorphins and oxytocin [41,42]. Experimental studies have shown that reactions to separation are

potentiated by the administration of the chemical mediators of stress (corticotropin-releasing factor, CRF, and agonists of glutamate receptors), while music tends to reduce the stress of separation (probably by increasing the secretion of endogenous opioids) [43,44].

Panic attacks seem distinct from the reactions of fear, because the neural circuits that underlie these two emotions are probably different [6,45]. Panic attacks are characterized by a sudden feeling of severe illness and near-death, and by a constant search for the comfort of other people and possibly health care professionals. In the history of people suffering from panic attacks there are often memories of episodes of early separations and separation anxiety (insecure attachment) [46,47]. Pharmacological treatment of these disorders are not anxiolytics (e.g., benzodiazepine) but antidepressants, such as tricyclics, or the selective serotonin reuptake inhibitors (SSRI) [48]. Panic attacks thus seem related with separation anxiety and depression rather than with fear [49,50].

The nature of depression seems to be more related to the primary experience of the loss of relationships and with the desperation of a child who has been permanently separated from the figure of reference. The separation from the parents of a baby at first causes intense vocalizations and crying that can help parents finding the baby. If the child is not found, it may be more advantageous, from an evolutionary point of view, that the baby regresses into a state of behavioral inhibition. This "depressive state" can help the baby to save the available energies, limiting exposure to possible external threats. The silence also makes the baby less localizable by possible predators [51,52]. At the neurochemical level, the first stage of separation is characterized by the release of stress hormones (CRF → adrenocorticotropic hormone, ACTH → corticosteroids) followed by the release, until the exhaustion of the cerebral reserves, of brain biogenic amines (norepinephrine, serotonin, and dopamine). For this reason, depression improves after intranasal administration of oxytocin and after the intake of antidepressant drugs that increase the brain level of biogenic amines, although probably the most effective cure should be to restore as much as possible significant social and emotional relationships [53,54].

4. Feeling the pain of others

The pain is first of all an individual experience. A wound is, in fact, an injury that could threaten the integrity of an organism. In this sense, the experience of pain is a key factor in the process of individuation [2,9]. However, living beings and in particular human beings, have a high degree of socialization. The mind of human beings develops and functions only in relation with others. This is underlined, for instance, both by the neural systems showing the so-called mirror functions and by the mental devices that help us to read the minds of others [55,56]. So we can feel our pain, but we are also able to feel the pain of others (empathy) and to feel pain for the conditions of misery of our neighbors (compassion) [57].

Empathy and compassion, like all human feelings, have a neurological substrate. A few years ago, a group of researchers studied the brain structures that were activated in a group of girls when they suffered a painful stimulus and when they saw that the same stimulus was applied to their boyfriends [58] (for further studies on empathy for pain see [59,60]). When the girls were receiving the painful stimulus both the structures for sensory discrimination of pain and those involved in the emotional components of pain got activated (e.g., the ACC, the anterior insula and the brainstem). Of importance, when they saw that the same stimulus was applied to their boyfriends only the structures important for the emotional components of pain were activated [58]. This means that empathy for the pain of others produces an activation of the emotional components of pain similar to those activated when we feel the same stimulus.

These results confirm a neurophysiological study in awake patients during neurosurgery [61]. To decide which structures need to be removed, in the case of a tumor or drug-resistant epilepsy, the neurosurgeon may decide to introduce fine electrodes in the brain to record electrical activity. It was thus found that the electrical activity of some neurons in the ACC was correlated with both the recording of the emotional response to pain stimuli suffered by the patient, and with the same pain stimuli that the patient saw applied to others. Such neurons in the ACC were thus mirror neurons for pain.

Not only physical pain is able to activate the emotional components of pain but this happens also with numerous other conditions of a social nature. Neuroimaging studies have highlighted that social exclusion also activates the typical areas of pain. If an individual is excluded from some social activities, such as a game, the typical areas of emotional pain tend to activate (ACC and the ventral prefrontal cortex) [62]. Not only social exclusion activates the emotional areas of pain but the same areas are activated when we experience or witness an injustice [63]. In addition, the ACC (along with the caudate nucleus and the dorsal nucleus of the thalamus) are activated when a subject thinks

of his death [64]. This means that the emotional pain, the pain of social exclusion and injustice share the same neural structures with the pain of separation from oneself. With these studies it was possible to understand in more depth some of the neuropsychological aspects which are at the basis of social life and ethics [7,8].

5. The pain and the experience of time

Time, one of the most mysterious phenomena in the universe, is connected in many ways to pain. It is indeed well-known that the expectation plays a fundamental role in the perception of pain. During the Second World War soldiers on the front line, who had horrific injuries, such as amputation of a limb, did not complain because they knew that for them the war was over [65]. On the other hand, the expectation of danger, that is the imagination of something dangerous that comes close, is the basis of feelings of anxiety and distress. As already mentioned, it is known that humans can extend their imagination to a future and absolutely certain episode that is a major source of anguish and emotional pain: their own death [66]. According to the philosopher Martin Heidegger (1889–1976), the human being is able to live an authentic life only when he is aware of his death [13]. Death is an event that humans can know only through the death of others, or through self-reflection. It is probably the most extreme form of separation. The death of our dear separates us from them. In addition, our death separates us from life and in a sense from ourselves.

In spite of the great discoveries of modern physics, the concept of time remains largely unknown [67–69]. By contrast, over the past two decades we have begun to understand what time is from a neuropsychological perspective. This has been possible thanks to the study of some patients with memory disorders. The most important contributions have been brought by the psychologist Endel Tulving. In the early eighties he had the opportunity to study a patient – KC – who, as a result of a serious head injury with bilateral lesion to the hippocampus, had developed complete amnesia [70]. More specifically, the patient was no longer able to set any new memory of the events of his life (episodic amnesia), but his memory of the meaning of words and knowledge of the world was preserved. Tulving realized that KC not only was no longer able to "reconstruct" the memories of his past, but he was also no longer able to imagine the future. In other words, he had lost the ability to travel mentally in time.

The investigation of the patient KC has allowed Tulving and colleagues to hypothesize the existence in the human mind of a device that allows humans to travel mentally through time (*mental time travel system*). The operation of this device, both in the tasks of reconstruction of the past and in the imagination of the future, is associated with bilateral activation of specific brain regions: the hippocampus, the medial parietal cortex (e.g., precuneus), and the medial frontal cortex [71]. These same brain structures are also involved in self-referential thought [72]. This confirms the close relations that exist between the temporal dimension of the mind, the autobiographical memory, and the concept of Self. Thus, the psychic components of pain and anxiety in humans are closely connected with the dimensions of time, memory, and the deeper structure of personality [73–75].

6. Alleviating pain through the mind

In the last decades, investigations in the fields of psychology and neurobiology of pain have allowed to document the importance of the interactions between the mind, the brain, and the body. One of the best known methods for studying these interactions is the *placebo effect* [76,77]. This term refers to the ability of substances considered to be inert (like distilled water) to produce therapeutic effects. The placebo effect represents a change that occurs at the level of the body and the mind; it is activated by a therapeutic ritual, or ingestion of a substance, and is determined mainly by the "expectations" of the patient. According to Western medical science, almost all the therapeutic effects of traditional medicines, which have used thousands of substances and preparations, have to be related to the placebo effect. In a similar manner, the therapeutic rituals and the miraculous healing phenomena described in numerous works in the anthropological literature were probably based on the neurobiological systems underpinning the placebo effect [78].

One of the most notorious cases of the placebo effect is the story of Mr. Wright [79,80]. This was the case of a patient with a malignant lymphosarcoma in a very advanced stage involving numerous lymph nodes. Mr. Wright had huge tumor masses in the neck, armpits, groin, chest, and abdomen. Despite this desperate situation, the patient had read in the papers that a new cancer drug had been discovered, the *Krebiozen*. He thus asked doctors to be included in clinical trials involving this drug, but because his life expectancy was less than two weeks he was initially excluded from the program. Mr. Wright did not lose heart; he begged the doctors to be inserted into the program and

was eventually referred to the first injection of Krebiozen, a Friday afternoon. At follow-up, on Monday, the doctor thought to find the patient dying while he had instead risen from his deathbed going around the hospital joking and talking with the nurses and other patients. His tumor masses, long insensitive to radiation treatment, were reduced by half in only two days. In the space of ten days, Mr. Wright was discharged from the hospital and pronounced clinically cured. The patient resumed his normal life while the other patients who had taken Krebiozen showed no significant improvement.

Nonetheless, after two months Mr. Wright's health began to deteriorate and he was again hospitalized after that he had heard in the press negative news about the efficacy of the new drug in the treatment of cancer. At this point, the doctors realized that the healing had to do with emotional and psychological factors. They recommended to Mr. Wright to no longer follow the news of the newspapers because they referred to a lot of the drug deteriorated. They proposed to start a new treatment with a more refined and powerful version of Krebiozen, which consisted of injection, without the knowledge of the patient, of distilled water. The recovery was even more spectacular than the first time. Tumor masses melted, the patient returned to normal life for another two months, until a news appeared in the press by the American Medical Association in which it was argued that the Krebiozen was an ineffective drug in treating cancer. A few days after the publication of this announcement Mr. Wright was hospitalized in terminal conditions and died in two days.

The mind thus has the ability to heal and possibly sicken people (*nocebo effect*). These effects are connected with the temporal dimension of the human mind, as the ability to heal or soothe the pain are related to complex neuropsychological events concerned with the expectation, trust and hope. The imagination of a future better than the present situation activates the hope; on the contrary, the imagination of a worsening activates anxiety and depression. The mind is able to cancel or reduce the perception of pain because the expectation can modulate anxiety; in addition, the intake of a drug considered effective can activate reward mechanisms which are able to release dopamine, an important "euphoric" neurotransmitter, in the ventral striatum [81]. Moreover, there exist implicit learning phenomena (e.g., conditioning) linking intake of a drug to the cessation of pain. The individual may learn that taking one tablet of a certain size and color can result in a reduction of pain. For these reasons, sometimes oral intake of a painkiller contributes to reduce pain (e.g., migraine) before the drug can be entered into the circulation [82,83].

The pain is the condition in which the placebo effect has been most studied, because the psychological component plays a certain role in its regulation. Currently, researchers do not study only the clinical effects (i.e., pain reduction) which either follow the intake of placebo substances or particular therapeutic rituals (e.g., hypnosis, shamanism, etc.), but they also evaluate the possible changes that occur at the physiological and neuropsychological levels. These investigations have revealed that the placebo effect is linked to the release of endogenous opioids, endocannabinoids, and dopamine in the brain. Moreover, the administration of a placebo is able to activate the descending system implicated in the control (inhibition) of pain. If brain activation patterns of patients with pain are studied after the administration of an opioid (morphine), a placebo, or during a session of hypnosis in which the patient is asked not to experience pain, in all these cases there will be an activation of the neural systems involved in the control of pain (dorsolateral prefrontal cortex, ACC, OFC, insula, nucleus accumbens, brainstem). Furthermore, all of these conditions reduce the activation of the sympathetic nervous system [84–88].

As we mentioned, the mind is not only able to heal or soothe the pain, it may also be able to determine disease and increase the pain (*nocebo effect*). In some societies, where people believe in voodoo magic, the *nocebo effect* can lead to situations of extreme stress, which may extend to cause cardiac arrest and death of the person subjected to the magical procedure. In the case of pain, anticipatory anxiety causes in the brain the release of cholecystokinin (which inhibits the release of endogenous opioids) and a decrease of the release of dopamine with a consequent reduction in pain threshold [89]. Also the structure of personality seems to influence the expectations, hopes and trust of the individual. These psychological aspects influence the perception of well-being, pain control, and the regulation of stress. As known, the latter system is involved in the physiological regulation of several vital functions, including the sleep–wake rhythms and the regulation of the immune system [76,77].

7. The pain of change

One of the most significant achievements of contemporary neuroscience has been the clarification of what consciousness and mind are. Achieving this knowledge has been a very difficult and complex process since it is through the mind that we are able to know. In a sense, the conscious mind was so close to the object investigated that the latter

was obscured. Now things seem to be a little clearer. Many authors believe that consciousness is the world that appears every morning when we wake up after a, more or less unconscious, sleep. When the world appears, two "entities" are manifested to consciousness: on the one hand the objects that populate the world and on the other the subject (the self) who observes and interacts with them. Both the objects in the world and the self are arranged in space and, as we have seen for humans, also in time [90–92].

Now we begin to think that the objects, the self, the space and the time may not be real, but only "mental constructs". Out there, probably there is neither space nor objects, nor the self or the time, as we understand them, but perhaps something different that for the moment we cannot know [93–95]. As mentioned above, these basic dimensions that allow us to orient with efficiency in the world are, maybe, constructions of the mind. However, they are not arbitrary constructions, as they have developed through millions of years of evolutionary history of the species in interaction with their environments [96–99]. The discovery that the concepts of space, time, object, and self are probably constructions of the mind, has slowly attracted attention within neuropsychological research of numerous clinical cases in which, as a result of lesions in the brain, the patients have partial disturbances of consciousness. Thus, there have been described many syndromes in which patients have lost some aspects of spatial cognition (e.g., neglect, blind vision, visual impairments in patients blind from birth after a cataract operation) or some components of the knowledge of the self (e.g., emisomatoagnosia, Capgras syndrome, Fregoli syndrome, alien hand syndrome, the out-of-body experiences, experiences of depersonalization); there have also been reported syndromes in which patients have deficits in object and motion recognition (apperceptive agnosia, associative agnosia, color blindness, akinetopsia, simultanagnosia) or have lost track of time (deficit in the mental time travel system) [74,75,100].

In the various species of vertebrates there are, obviously, qualitative and quantitative differences in the organization of the mind; however, it seems that the most basic forms of the mind are also present in vertebrate species considered to be more simple, such as the fish [101,102]. The organization of the brain in all vertebrates, indeed, has a layered structure. All vertebrates possess what has been called the "basal block" consisting of a spinal cord, the brain stem (with a well-developed and layered optic tectum), the hypothalamus, the oldest portions of the cerebellum, and some telencephalic structures (e.g., diencephalon, olfactory lobe) [103,104]. This set of structures is able to provide a first representation of the world and of the self, which unfortunately has long been underestimated. Above the structures of the "basal block", in reptiles, birds, and mammals have developed the structures of the so-called "second block" (basal ganglia, structures of the medial cortex such as the insula and limbic lobe, and structures of the lateral cortex) [99,105].

In mammals, the "second block" has presented a considerable development of both the medial cerebral cortex (hippocampus, limbic lobe) and the lateral cortex (temporal lobe and parietal lobe). As pointed out by the paleoneurobiologist Harry J. Jerison, mammals have evolved from a group of small reptiles that have adapted to the nightlife, developing thermoregulation (to move in cold environments) and a representation of the world no longer based on the sense of sight but mainly on the senses of smell and hearing [106–108]. Therefore, in mammals the mind has reached what can be defined as "second level of development"; from the first level of visual representation of the world (present in fish and reptiles) it passed to a second type of imaginative representation of the world. The world perceived in the dark through the senses of hearing and smell has been re-represented in mammals through visual imagination. This second level of representation of the world has enabled the development of imaginative memory and probably of dreams with high visual content. Finally, the development of language provided a "third level" of representation of reality. Through the words, sentences, and texts it is possible to represent the world in an even more abstract way than with visual imagery that, however, still seems to be at the basis of language [109,110].

At this point it is questionable whether in the outside world there are space, time, and objects. Albert Einstein believed that the concept of "object" was probably a creation of the human mind and of some other animal [111]. The idea that there are stable objects is operationally useful for moving through the world. If I refer to a particular book or a particular car it is not difficult to understand each other at the practical level. However, it is necessary to distinguish the practical level from the ontological level. For the Greek philosopher Heraclitus (535–475 BC) and for the Indian philosophical and psychological genius known as the Buddha (485–405 BC) objects do not really exist but there exist only processes. In this sense, a book, a car, a house originate (are built), show (last for a certain period of time), and then disappear. For Heraclitus and the Buddha all things behave like fire: originate, burn up, and then are extinguished [112,113]. Now we know that all entities known in the universe are, in effect, processes.

Moving from a worldview formed by "stable objects" to a worldview formed by processes is not easy. The confusion between a representation of the existing world composed of space, time, objects, and self and the ontological

dimension has generated in humans what has been called the "pain of change", or the pain of existence [114]. To consider the world as ontologically consisting of objects has encouraged humans to desire to possess and accumulate. Not only humans have been affected by the fear of change, which probably has its neurobiological origin in the pain of separation. Moreover, in current scientific and philosophical thinking, the idea has prevailed that the equilibrium is the ideal condition, while it is obvious that the biological and cultural life are based only on changes, or the progressive succession of one crisis after another. In thermodynamic, in fact, equilibrium corresponds to the "Heat Death" [115]. Humans have learned through culture and education to consider the processes as objects and, at a deeper level, to consider the self as an object of indefinite or eternal duration. Thus, the idea of separation from the self and the thought of one's own death have become the primary sources of anguish [13]. Instead of changing the perspective, many cultures, especially the West, have developed a series of myths and stories to avoid the pain of change [116]. Starting with some typical human neuropsychological experiences (e.g., out of body experiences, OBEs), supernatural realities have probably been conceived in which the change is no longer present and the self (often referred to as soul) is eternal [117]. Instead of dealing with the pain with awareness, trying to stay with dignity in front of it, it was decided to adopt the strategy of avoidance and escape [118]. Unfortunately, the escape from a psychological problem does not extinguish the problem, but probably nourishes it [73,119].

8. Facing pain in a "mindful" way

Mindfulness meditation is one of the oldest ways of facing pain. Meditation has originated in the spiritual sphere [120]. This happened in ancient India, first within the Hindu tradition as the search for a state of bliss and union with the whole (*samadhi*), and then within the Buddhist tradition that emphasized how the *samadhi* and the final extinction (*nibbana*) were to be achieved through a state of mindfulness (*sati*) [121,122]. The attitude of being mindful in front of pain has been taught over two thousand years ago by the Buddha. In his psychological approach, the Buddha put the discomfort and pain (*dukka*) at the center of the path (*dharma*) that leads to liberation (*nibbana*). It is only through awareness of physical and/or psychological pain (e.g., anxiety, dissatisfaction) that one can start the path to liberation that the Buddha didactically divided into eight steps (eightfold path) [113]. In general, in a more or less automatic fashion, physical and psychic defense mechanisms take place when we are called to deal with the pain. On the psychic and emotional level, the response to pain depends on many variables, including, for example, the styles of attachment and the personality traits [3–5,123].

According to numerous schools of clinical psychology, the major components of personality (defined in clinical psychology as "ego"), which are mainly represented in implicit memory systems, consist of a series of automatic response schemas to conditions of danger and pain [73,119,124–126]. Thus, every automatic response to a condition of danger or pain strengthens the ego. Faced with a threat or a pain it is spontaneous to first defend ourselves, stand up, and stiffen. The most common attitude in the face of pain is that of escape, or, if this is not possible, the protest or angry resignation. Similarly, in the face of physical pain the natural reaction is to reject it and muster the strength to get rid of it. The pain appears as an external agent that disturbs our equilibrium. In this way, something that is often within ourselves (psychological, existential pain) is projected to the outside. Our ego no longer recognizes and welcomes the pain that is a part of his being.

The attitude of mindfulness meditation in the treatment of pain is completely different from the so-called natural reactions. First of all, the universality of the conditions of illness, suffering and pain are recognized. As we mentioned, do not feel the pain when present may depend on automatic avoidance mechanisms. Through mindfulness one learns to become aware of physical and/or psychological pain when it is present; moreover one also learns, slowly and with a lot of difficulties, to become aware of the impulses that arise in response to pain. Thus, instead of reacting, we learn to stand still and look carefully at all the sensations of pain and at what is happening in our minds. Not only we try not to run away from pain, but we also try to cultivate an attitude of kind reception of it, maintaining at the same time a slight smile on the lips and an attitude of non-attachment (*letting go*) [127–129].

Several clinical studies have investigated the effects of mindfulness meditation on the reduction of chronic pain [130–132]. In general, these works suggest that the practice of meditation leads to a reduction of perceived pain, improved mood, and reduced anxiety and psychiatric symptoms associated with chronic pain syndromes. Moreover, through the techniques of brain imaging, the researchers have tried to study the modalities through which mindfulness meditation is able to reduce the pain [133–135]. For example, in the latter study, the participants who were meditating during painful stimulation showed a significant reduction in pain unpleasantness and pain intensity; this reduction was

globally associated with increased activation in regions involved in pain regulation (rostral ACC and right anterior insula) and with deactivations in regions related to affective pain perception (reticular nucleus of the thalamus and the OFC). The modulation of pain obtained through mindfulness meditation has, therefore, some similarity with other cognitive techniques for reducing pain, such as hypnosis and placebo; all of these techniques are able to modify the activation of the rostral ACC. However, according to Zeidan et al. [136], mindfulness meditation does not lead to activation of the dorsolateral prefrontal cortex as in the reduction of pain by a placebo effect; rather, it leads to a reduced activation of the areas involved in the emotional response to painful stimuli (OFC) and to a deactivation of some components of the *mental time travel system* (e.g., hippocampus), with a likely reduction in anticipatory anxiety [136].

Stand mindfully in the face of pain, without falling in, without complaining, and without running away is not an easy task and it is a result never reached in a definitive manner. Even for those who practice mindfulness meditation on a regular basis for many years, every encounter with physical and psychological pain is a challenge between the psychological habit of avoiding the pain and the ability to stand in front of it with a slight smile on the lips. The courses of eight weeks of mindfulness meditation that are organized in a number of hospitals to cope with the pain are definitely a good starting point; however, the understanding of what mindfulness really is, is achieved only through a series of insights that come from a long and steady meditation practice [137–139]. In fact, according to Grant and Rainville, they are required at least 2000 h of practice (about eight years with a meditative practice of 1 h per day) to be able to develop some analgesic effects through meditation [140]. To mindfully face the experience of pain is therefore not at all easy, but it is possible.

Conflict of interest

The authors declare no competing financial interests.

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