Review

PHYSICAL, EMOTIONAL, AND SOCIAL PAIN DURING COVID-19 PANDEMIC-RELATED SOCIAL ISOLATION

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Abstract

Background: The recognition and management of the socio-emotional pain facing the COVID-19 pandemic refer to different, but interdependent, clues regarding cognitive and emotional aspects of the pandemic threat, considering the need of social distancing as a prophylactic procedure to avoid spreading the pathogen. The socio-emotional condition at the time of outbreak subsidizes the (re)modulation of interactive neural circuits underlying the risk assessment behaviour at physical, emotional, and social levels. Experiences of social isolation, exclusion or affective loss are generally considered to be some of the most “painful” things that people face. The threats of social disconnection are processed by some of the same neural structures that process basic threats to survival. **Discussion:** The lack of social connection can be "painful" due to an overlap in the neural circuitry responsible for both physical and emotional pain related to feelings of social rejection. Indeed, many of us go to great lengths to avoid situations that may engender these experiences. Because of this, this work focusses on times of pandemic, the somatization mentioned above seeks the interconnection and/or interdependence between neural systems related to emotional and cognitive processes, to a point in which the person involved in that aversive social environment becomes aware of himself, the others, and the threatening situation experienced to avoid daily psychological and neuropsychiatric effects. **Conclusion:** Social distancing during the isolation evokes the formation of social distress, raising the intensity of learned fear that people acquire, consequently enhancing the emotional and social pain.

Key words: social distancing, social pain, emotional pain, neurosciences, COVID-19.

Key Points: The COVID-19 pandemic has impacted the lives and health of persons worldwide. Associated with the new context of social isolation we invited reader community is invited to consider the impact a long-term of isolation impact on health. Then, the social distancing during the isolation can evoke painful physical, emotional and social experiences.

1. Introduction

1.1 Victims of The Alienist

The discussion regarding the consequences of the social isolation on human being health is not a novelty, considering that these factors have been studied since 1987 in Brazil, that characterize the beginning of the Psychiatric Reform Movement (Brazilian Health Ministry, 2018). Since the times of the Brazil Empire, under the reign of Dom Pedro II, there were asylum hospitals, in which people were submitted to long-lasting social isolation due to mental diseases.

These psychiatric hospitals were known for separate mental illness patients from the rest of healthy people putting together patients considered non-suitable for the social relationship. According to Saraceno (1999), the asylum is a variable independent of the socioeconomic conditions of the country in which it is situated, consisting of a place for resetting the exchange of social skills”.

In the Asylums, people were hospitalized during several years, sometimes until their decrease, as reported by Maurício Lougon’s experiences (Lougon M 2006) during the de-institutionalization of Juliano Moreira Colony, from 1982 to 1985, highlighting the hospitalization of 2600 patients, in their majority elderly, who lived years of their lives suffering several kinds of abandon, violence and social isolation.

The psychologic consequences coming from that long-lasting hospitalization in Asylums such as Juliano Moreira Colony are the following: (a) a lack of autonomy of patients regarding the choice of medical treatment and forced familiar exclusion; (b) the limitation of the physical spaces and social experiences in the society, highlighting that the psychiatric hospital becomes the residence of the patient with mental disease. In this case,

the life of the patient is limited to the psychiatric hospital activities, searching a meaning for their lives and daily routine, but facing the emotional pain caused by the absence of their parents and actual home (Salles and Barros 2013).

The Psychiatric Reform Movement accomplished in the last decades could offer better medical care and more attention to the mental health of these patients who have lived for years under bad sanitary conditions, socially isolated. New approaches were established, such as Therapeutical Houses, Psychosocial Care Centers; Homecoming Program, Acquaintanceship and Cultural Centers, and Mental Health Clinic, that allowed the development of the autonomy feeling regarding the own life of the patient, healthy social relationship and mental health, the opportunity of working, and better living conditions (Salles and Barros 2013).

Interestingly, like illustrated in *The Alienist* (Assis 1998), the new world context of the COVID-19 pandemic, people considered healthy were suddenly obligated to socially isolate themselves inside their homes, or even in places far from their familiar homes, due to their work beside potentially infected people. The social isolation caused by COVID-19 pandemic threatening also caused a forced poor affective behaviour during absences in traditional social events, such as funeral, weddings, and anniversaries, in addition to isolation from parents infected by COVID-19 pathogen (Danzmann et al. 2020).

The social isolation caused by COVID-19-related quarantine may cause severe post-traumatic stress disorder, not only by pandemic fear, but also by unemployment, loss of parents without mourning, and by the risks of traumatic familiar experience, such as those regarding the isolation with a potential aggressor in the same environment, coexisting

daily with a non-escapable threatening situation, similarly to the patients with mental diseases forgotten inside the Asylums in the past.

Health professionals aiming at avoiding additional psychological damages must carefully manage possible stigmatization of both infected and healed people, in addition to people submitted to aggressive social interactions inside their homes, chronic stress, fear, sadness, helplessness, and jitters, causing increased serum levels of cortisol and consequently immunological system impairment and susceptibility to other diseases and also COVID-19 re-infection.

1.2 Impact on health caused by social isolation

The COVID 19 pandemic is a global public health risk that has a profound consequence on every aspect of human life. Due to high transmissibility and the lack of a vaccine capable of immunizing the population, restrictive measures such as social isolation are implemented and encouraged (Zhai et al., 2020). The question is based on the perspective that while the social impacts of isolation meet public health benefits, psychological and neuropsychiatric problems can be triggered (Wang et al. 2017). As a result, social isolation may be reflected as a risk factor equivalent to the harmful effects caused by smoking and obesity (Holt-Lunstad et al. 2010) as reduced well-being, depression (Heikkinen and Kauppinen 2004), cognitive decline (Wilson et al. 2007), pain (Aslund et al. 2010; Karayannis et al. 2019) and mortality (Patterson and Veenstra 2010; Steptoe et al. 2013). This trigger may be more problematic in older people, due to decreasing economic and social resources, functional limitations, the death of relatives and spouses, and changes in family structures and mobility (Administration on Aging, 2013).

Research shows that social isolation and loneliness have an impact on health. However, it is interesting to mention that different dimensions (objective or subjective) are investigated in this construct of social isolation (Cornwell and Waite 2009; Valtorta et al. 2016). Objective social isolation is the physical separation, the absence, or inability to interact with other people. Tools that address participation in groups, social activities and events, frequency of interaction, and the social network are investigated (Cornwell and Waite 2009; Coyle and Dugan 2012; Valtorta et al. 2016). On the other hand, subjective social isolation is characterized by self-perceptions and quality of the relationships between a given person with members of his/her social networks, as well as perceived integration and involvement in social networks (Valtorta et al. 2016).

Coyle and Dugan (2012) also showed that both loneliness and objective social isolation were significantly related to the presence of a mental health problem. Then, both objective and subjective isolations are correlated but are not the same constructor (Shankar et al. 2013). That phenomenon is possible to show when people have experienced objective social isolation but they can feel subjectively isolated or not (Coyle and Dugan 2012).

1.3 Social isolation and pain

Studies suggest that social relationships have an important role in pain. Individuals with larger self-reported social group size showed higher pain tolerance (Johnson and Dunbar 2016). Experimentally-induced social exclusion and perceived social support respectively increase and reduce the severity of acute experimental pain (Brown et al. 2003; Eisenberger et al. 2006; Master et al. 2009). Inversely, poor relationships and self-imposed

isolation over time have been correlated with chronic pain (Smith and Osborn 2007; Snelling 1994).

Hormonal stress responses and anxiety are evoked by social isolation when happening in the early life of adult rodents and social support can play a role as a buffer against stress (DeVries et al. 2003). Moreover, there is evidence that social distress potentiated the sensitivity to physical pain (Aslund et al. 2010). Eisenberger and collaborators (2006) also showed that socially excluded individuals displayed lower pain thresholds to unpleasant heat stimuli. In addition, pain coping and social support during early rheumatoid arthritis (AR) can beneficially influence long-term outcomes in AR. (Evers et al. 2003). In addition, chronic musculoskeletal pain has an association with perceived social support and pain interference (Ferreira-Valente et al. 2014).

Biopsychosocial factors are also frequently regarded as significant factors that can increase the risk of poor prognosis of low back pain, but the “social” component in the biopsychosocial model has received little attention. Perceived social isolation is prevalent in patients with low back pain of any duration (Hawthorne et al. 2013) and this can be a crucial but under-investigated prognostic factor for that condition. The point prevalence of patients who perceive at least some social isolation is 43% when they have low back pain, being 24% higher than in the general population (Hawthorne et al. 2013).

The recurrent pain episodes have also been associated with a lack of understanding about endometriosis symptoms and with the resignation of women during social isolation (Mellado et al. 2016). Considering that, inflammatory and immunologic factors are modified during endometriosis, and social isolation may also change it. The social isolation can interfere on endometriosis via these factors (Cacioppo et al. 2011).

The sequelae of perceived social isolation associated with chronic pain include maladaptive responses, work loss and financial security, being anxious with others, experiencing loss of traditional family roles, losing care and concern for others, sexual dysfunction, depression, anxiety and realizing that others do not understand the life lived with low back pain (Bowman 1994; Schwartz and Slater 1991).

Depressive symptoms are an important factor to consider when interpreting the link between social and physical health. Individuals with low back pain and higher levels of baseline depression experienced a slower recovery process (Melloh, Elfering, Stanton, et al. 2013). Individuals with depressive symptoms and acute and subacute episodes of low back pain (LBP) were more likely to have persistent pain in a 6-month follow-up (Melloh, Elfering, Käser, et al. 2013).

In animals, the social isolation altered the neurochemical systems such as enhanced presynaptic dopaminergic function in the nucleus accumbens and the prefrontal cortex, a decrease in presynaptic serotonergic function, and an imbalance in dopamine and 5-hydroxytryptamine (5-HT) in the frontal cortex (Crespi et al. 1992; Fone et al. 1996; Jones et al. 1992). Animals that were isolated during the infancy display a long-lasting effect on acute heat pain sensitivity, disturbing primarily the C-fiber-related pain pathways, suggesting a selective disruption in the ascending antero-lateral spinal-thalamic pathways (Tuboly et al. 2009). Moreover, the housing conditions are an important factor evoking modifications in pain perception in animals, and it was also showed that isolation of juvenile animals caused significant changes in pain sensitivity, which might be due to changes mainly in the number and activity of μ -opioid receptors (Defeudis et al. 1976; Van Den Berg et al. 1999).

1.4 Multiple faces of pain pathways: from nociception to pain perception

According to the International Association for the Study of Pain (*IASP*), nociception is referred as “activity that occurs in the nervous system in response to a noxious stimulus,” whereas pain is “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (Raja et al., 2020). Nociception thus includes the mechanisms by which noxious stimuli are detected by the peripheral nervous system, encoded, transferred, and unconsciously treated by the central nervous system structures.

Sensitization of sensitive fibers, including nociceptive fibers, is the common denominator after injury or inflammation, which results in the release of chemical mediators from different cells. The released chemical mediators act by directly activating the nociceptors or even sensitizing them (Julius 2001; Kandel 2014).

Chemical mediators can activate or sensitize nociceptors, which are free nerve endings of pseudo-unipolar neurons dendrites, whose cell bodies are found in the ganglia of the dorsal root of the spinal nerve and trigeminal nerve sensory ganglion that process these traumatic or inflammatory stimuli (Kandel 2014; Millan 1999) Messlinger, 1997. The axons of these pseudo-unipolar neurons, called primary afferent fibers, carry nociceptive information to the central nervous system.

Three types of receptors for free nerve endings are associated with two types of primary afferent nerve fibers. Considering a functional criterion, they are: (a) mechanosensitive nociceptors with A δ low myelinated and medium diameter fibers, with conduction speeds of 5 to 30 m/s; (b) mechanothermal nociceptors with A δ fibers, and (c)

polymodal nociceptors with not myelinated C fibers of small diameter with a conduction speed of about 1 m/s, which respond to thermal, mechanical and chemical stimuli (Julius 2001; Millan 1999).

Figure 1: Pain pathways from nociception to sensory discriminative perception and emotion pain (Source authorship).

The nociceptive stimulus recruits peripheral nociceptors that carry the nociceptive signal to the first somatosensory neuron located in the dorsal root ganglion of the spinal nerve, which connects with the second-order neuron located in the dorsal horn of the spinal cord. It is precisely situated on II, III, and V Rexed's laminae, of the dorsal horn of the spinal cord, in which the primary afferent neuron makes the first synapse with the second neuron (Figure 1). The second neuron sends axons that will form the neoespinothalamic and paleoespinothalamic tracts, after crossing the median plane of the spinal cord and sends afferent ascending projections to the great supraspinal centres, such as the reticular

formation, the limbic system, the posterolateral ventral nuclei (neo-spinal-tract nucleus) and intralaminar (paleoespinotalamic tract) of the dorsal thalamus (Marshand, 2012) (Figure 1).

The trigeminal component of the anterolateral system has its first neuron in Gasser's semilunar ganglion, which establishes synapses in the spinal nucleus of the trigeminal nerve, where the second-order neurons of the pathway are located, whose axons cross the midline and comprise the trigeminal lemniscus, which goes to the posteromedial ventral nucleus of the dorsal thalamus. From the dorsal thalamus, through the corona radiata, the third-order neurons connect with the somesthetic cortex, where they spread somatotopically (Marshand, 2012).

It is important to emphasize that the second neuron can connect with different nuclei of the brain stem, including the periaqueductal gray matter (PAG) and the nucleus raphe magnum (NRMg), which are areas involved in the endogenous downward modulation of pain system. The primary (S₁) and secondary (S₂) somatosensory cortexes, which receive afferents from the dorsal thalamus, are involved in the quality of the sensory perception of pain, which includes location, duration, and intensity of pain. Tertiary neurons also project to limbic structures, including the anterior region of the cingulate gyrus cortex (Cg₁) and the insula, which are involved with the affective and emotional components of pain (Marshand, 2012), as well as the hypothalamic nuclei, parabrachial area and amygdaloid complex (Hammond 1989). These connections emphasize that the pain is more than the activation of sensory components. The anterior cingulate cortex also sends glutamatergic inputs to the posterior hypothalamic nucleus, modulating the perception of painful stimuli in a threatening situation (Falconi-Sobrinho et al. 2017).

Additionally, how pain is felt is mediated by perceptual processes, and depending on how the stimulus is perceived, the pain sensation may vary (Lucchelli, Cattaneo and Zattoni, 1978; Shapira, McClelland, Griffiths and Newell, 1970). In addition to the above, several studies have been shown, that the physical form of drugs and their appearance can alter their effect in cases for the treatment of pain (Sallis and Buckalew, 1984; Bar and Neta, 2006, 2007; Silvia and Barona, 2009; Westerman et al., 2012.), also, it has even been shown that stimuli that are associated with pleasure, liking and disgust are also related to how the effect of medications is perceived (Wan et al, 2015).

1.5 Emotional aspects of pain

According to IASP, about one in five people suffer from chronic pain worldwide. The effects on quality of life are devastating. A study published in 2006, analyzed 126 patients with chronic pain and found that the group had several affective and cognitive impairments, such as insomnia (60%), difficulty to concentrate (36%), depression (33%), and anxiety (27%). Even the professional life of the affected people seems to be affected: 52% of the participants had losses at work due to pain (Breivik et al. 2006).

Over the past few decades, the influence of anxiety on pain perception has been extensively investigated. Anxiety is accepted as one of the determining psychological factors in the subjective experience of pain (Tang and Gibson 2005). Asmundson and collaborators (1996) pointed out the existence of a link between anxiety disorder and pain, demonstrating that the prevalence of anxiety is higher in people who suffer from chronic pain. Furthermore, chronic pain and anxiety disorders coexist in 45% of chronic pain patients screening positive for an anxiety disorder (Asmundson and Katz, 2009).

Knaster and collaborators (2012) showed that the diagnosis of anxiety disorder precedes the onset of pain in more than 75% of individuals. Similarly, Shaw and collaborators (2010) identified that patients who suffered from low back pain were 2.45 times more likely to develop chronic low back pain when they were diagnosed with a generalized anxiety disorder.

There is a high association of comorbidity between anxiety and chronic pain, and some researchers postulate that this type of pain may be an expression of chronic post-traumatic stress disorder (Grande et al., 2004; Otis et al. 2003). There are functional and metabolic similarities between NP and post-traumatic stress disorder, with mPFC playing a key role in the integration between that comorbid (Feldman 2004, Liberizon and Phan, 2003). There are reports in the literature showing in both human patients and laboratory animals, that the presence of chronic pain causes changes in functional reorganizations in cortical and subcortical structures, including mPFC (Apkarian et al. 2009; Baliki et al. 2006; Medeiros et al. 2019a,b, 2020a,b; Metz et al. 2009), dorsal thalamus (Apkarian et al. 2004), amygdaloid complex (Han et al. 2005; Ji et al. 2010), and anterior cingulate cortex (ACC) (Li et al. 2010).

Considering the pain pathways. The nociceptive stimuli cause action potentials that get through of the anterolateral system and the neospinothalamic tract in the most important spinal-thalamic tract reaching the primary somatosensory cortex, through the specific thalamus-cortical system and is involved in the physical sensation of pain (Lumley et al. 2011). The affective experiences of pain-related connexions reach supraspinal brain structures through the paleospinothalamic tract, which recruits the periaqueductal gray

matter, amygdaloid complex, parabrachial area, hypothalamus and insula (Lumley et al. 2011; Vogt et al. 1993, Hammond, 1989)

Information from these both pathways comes together in the ACC and insular cortexes. Thus, it is the combination of nociceptive and affective inputs to these areas—elicited by the same stimulus—that influences interoceptive homeostasis (Craig 2003) and response prioritization (Lumley et al. 2011; Price 2000a). Hence, both types of information about pain contribute to our subjective experience and, ultimately, our response to it. It is from this theory that we seek to establish the anatomical links between emotions and pain (Figure 1).

Several areas are consistently activated in PET and fMRI studies when pain is involved. The second somatosensory (S₂) and insular cerebral regions, as well as the ACC, are the cortical areas most consistently activated during the experience of pain (Cauda et al. 2012; Peyron et al. 2000). The thalamus is often activated as well, as an intermediate diencephalic relay regarding the somatosensory ascending neural pathways. These areas reflect activation of the anterolateral system, especially where the spinal –thalamic tracts converge on the insula and ACC. Meta-analytic connectivity modelling was utilized to identify areas that were active across multiple types of stimuli, as well as attentional, emotional, and reward tasks (Cauda et al. 2012) (Figure 1).

The insula, dorsal ACC, and thalamus were again consistently activated. The neural activity in these structures reflects both external inputs of pain and internal reflection on pain, much in line with Melzack and Casey's two-stage theory of pain described previously in brief (Melzack and Casey 1968). The ACC appears to be particularly important in the affective interpretation of pain. Some investigation dissociated the circuitry involved in

emotional and attentional modulation of pain and showed that the ACC was the largest modulator of mood and influenced pain unpleasantness, but not pain intensity. Attentional modulation associated with pain intensity was not as robust but activated the anterior insular cortex (Villemure and Bushnell 2009).

The ACC likely acts as a mediator between cognition and emotion, with connections to the limbic system structures (Falconi-Sobrinho et al. 2017) and prefrontal cortex (PFC), as well as to somatosensory areas (Stevens et al. 2011). Because the ACC is so closely linked with affective processing and it is consistently activated during the experience of pain, the ACC likely plays a role in affective regulation during the experience of pain (Zugaib et al. 2014; Zugaib and Menescal-de-Oliveira 2017). Both emotional and physical pain elicit activity in these common areas, and conditions that affect one system (e.g., drugs, neural plasticity) may affect the function of the other-ultimately altering the experience of pain.

1.6 Neurobiological aspects of social pain

Due to this close link, emotional pain appears to mimic certain aspects of physical pain in terms of brain activity and pain perception. For example, social rejection elicits similar activation in the same areas as physical pain, and greater sensitivity to physical or social pain is associated with greater sensitivity to physical pain. Social organization is not an exclusive characteristic of human beings; social ties are essential for the well-being and survival of mammals (Baumeister and Leary 1995).

The impossibility of self-care after birth and during a postnatal period, mammals need the support of a caregiver. Then, this long period could have organized a "system of

social ties". This system, in turn, could use parts of the physical pain system to "alert" us when we have lost a social bond. Considering that the distance from a caregiver is a threat to survival. Feeling "hurt, anguished" with this separation leads the threatened person to develop adaptive strategies to avoid distance (Panksepp 1998).

Social ties are important for survival. Thus, using a social attachment system together with the physical pain system will capture attention and alert us to real or potential damage in social relationships (Panksepp 1998). In this sense, social isolation, like what we are living in, can cause unpleasant experiences, described as pain and recruits at least part of the same neurobiological substrates that underlie experiences of physical pain. Multiple ascending pathways carry physical pain information to supraspinal structures, adding aspects of autonomic system activation, escape, motor orientation, arousal, and fear (Price 2000b). The integration between somatosensory inputs and cognitive aspects also seems to happen in posterior parietal cortical areas (Friedman et al. 1986).

Nociceptive information pathways that integrate structures such as insular cortex and amygdaloid complex converge at the level of the ACC, a mechanism by which somatic perceptual and cognitive characteristics of pain would be integrated with rudimentary and attentional emotional mechanisms (Price 2000b) (Figure 2). Thus, the ACC coordinates the association of somatosensory characteristics of pain with pre-frontal brain mechanisms involved in the association of significance and long-term implications for pain (Figure 2).

Studies show the involvement of these areas not only in the processing of physical pain but also in social pain. Social pain is defined as the unpleasant experience that is associated with actual or potential damage to one's sense of social connection or social value; such as showing to social rejection, exclusion, negative social evaluation, or loss

(MacDonald and Leary 2005). The analysis of neuroimaging has shown the activation of structures like the dorsal (d) part of the ACC and insular cortex anterior in individuals who have experienced social exclusion (Eisenberger 2012a). These regions are known to play a role in the distressing experience of physical pain. Moreover, the dACC and AI may have a modulatory role in the links between social rejection and both inflammatory activity and depression. Considering the components of pain, sensory-discriminative, and affective-motivational, the last one is related to aspects of emotion, arousal, and behavioural programming (Treede et al. 1999) (Figure 2).

Figure 2: Neural areas that have been shown to be related to physical pain, affective (emotive) pain, social pain (Source authorship).

In this way, the processing of social suffering is dependent on the activity of brain regions associated with the affective component of pain, involving the prevention of social damage hazards and serves as a punishment-based reinforcement to teach organisms to avoid threatening stimuli in the future.

In investigations performed in laboratory animals, the ACC injury (dorsal and/or ventral divisions) reduces anguish-related vocalizations, behaviours related to social separation in non-human mammals. In experiments of isolation and maternal separation another encephalic area involved in the processing of suffering is the PAG (Hadland et al. 2003).

In human beings, cingulotomy induces in decreased self-awareness, together with a reduced concern for other people's opinions or social judgments (Tow and Whitty, 1953). Associated with that, patients can still feel and localize pain sensation (sensory component intact) but the pain no longer “bothers” them (Foltz and White 1968). In addition, individuals with more social support or who spend more time with friends show reduced activity in the dACC and insula in response to social exclusion (Eisenberger, Taylor, et al. 2007). In contrast, greater self-reported social disconnection during real-world social interactions is associated with greater activity in the dACC and PAG in response to social exclusion (Eisenberger, Gable, et al. 2007). In this sense, there is support in the literature for the critical role played by ACC in the processing the distress associated with social separation or disconnection.

Another aspect that can be changed due to social isolation is the inflammatory process in addition to changes in the transcriptional activity of the human genome. The increased activity of the pro-inflammatory transcription controls neural pathways with

glucocorticoids responsible for the high risk of inflammatory disease in individuals who experience chronically high levels of subjective social isolation (Wager et al. 2009). Furthermore, the increased activity of dACC and AI in a stressful situation and/or social isolation can contribute to the increase in inflammatory activity (Wager et al. 2009). The increased circulation of pro-inflammatory cytokines, such as IL-6, mediates the relationship between social exclusion and depression and is related to the intensity of pain in some populations (Sturgeon and Zautra 2016).

In a neurochemical perspective, opioids have already been shown to affect not only analgesic but also to reduce the distress associated with separation (Eisenberger 2012a). The endogenous opioid system is associated with regulation of the distress caused by physical pain-inducing a neurochemical regulation of the distress associated with social separation. In animals, low doses of exogenous opiates reduced distress-induced vocalizations of socially isolated puppies as well as the pleasure associated with the social connection (Panksepp et al. 1978). According to Way and collaborators (2009), individuals with the G allele showed greater reactivity to social rejection in encephalic structures (dACC and AI) previously demonstrated to be involved in the processing of social and physical pain. Thus, dACC is considered a critical place for the influence of opioids on social pain. The authors suggest that the A118G polymorphism, specifically related to the μ -opioid receptor is generally involved in both social pain and physical pain (Way et al. 2009).

In rodents, social isolation is associated with a decrease of neurogenesis in the hippocampus, an increase in cortisol levels (indicative of stress), and with anxiety-like behaviour (Cinini et al. 2014). Among puppies, it has been shown that early life stress can

permanently impair hippocampus-dependent learning and memory in addition to increasing susceptibility to depression by reducing adult neurogenesis in the hippocampus (Karten et al. 2005).

The social isolation causes neurological changes that can induce social pain. Although neuroimaging studies show the activation of dorsal anterior cingulate cortex and anterior insula in situations of physical and social pain, there is evidence that these same areas are activated in other stressful situations (Eisenberger 2012b; Sturgeon and Zautra 2016). Thus, the role of anterior cingulate cortex and the anterior insula, can be broader as a neural alarm system for survival (Eisenberger 2012c). Almeida-Santos et al. (Almeida-Santos et al. 2019) demonstrated that animals in social isolation had alterations in the glutamatergic neurotransmission in the olfactory bulb and the dorsal hippocampus, a neurochemical phenomenon that the authors associate with the deficit of social memory in addition to compromising communication between areas.

Interestingly, daily administration of acetaminophen compared to placebo in two studies showed reduced self-reports of social pain, as well as reduced activity in both dACC and AI, when experiencing social exclusion (DeWall et al. 2010).

1.7 The treatment of pain in the post-pandemic COVID-19

The return to clinical pain management will have to deal with the biopsychosocial requirements of the post-Pandemic period of COVID-19. The resumption of clinical pain management will have to cope with the biopsychosocial requirements of the post-pandemic period of COVID-19. The health care professionals will have to face the challenge of

dealing with the overlap of physical and emotional pain and the possible process of catastrophic pain triggered or aggravated by the COVID-19 pandemic.

Beyond the typical challenges of self-managing a chronic disease, disease management has become significantly more complex with the implementation of social distancing, including limiting nonessential health care visits. This has led to confusion about how patients with chronic diseases should balance managing their disease and reducing their risk of infection. That adaptative process directly impacts clinical symptoms, especially pain (Michaud et al. 2020).

The exposure of the population to traumas, such as witnessing and caring for seriously ill people, perceived life threat, mortality and mourning, deaths of health professionals, can impair the mental health of the population, and consequently, increase the risks of developing psychological distress and progression to psychopathology, including post-traumatic stress disorder (Neria and Sullivan 2011; Schultz and Engelhardt 2014).

Concerning the comprehension or eliminating the epidemic-associated stigma, it is necessary to create strategies to deal with the psychological stress of the post-pandemic period (C. Wang et al. 2020) and to identify its possible implications for the rehabilitation process and management of pain. In fact, there is evidence that shows increased levels of distress to suffering in people living in countries significantly affected by COVID-19 (C. Wang et al. 2020; Xiang et al. 2020).

Moreover, it is suggested that patients with suspected or confirmed infection with SARS-CoV2 may experience fear and anxiety about the consequences of COVID-19, including death and severe physical disability. Besides, the boredom, loneliness and anger

can be experienced by quarantined individuals. It is also suggested that the symptoms of anxiety and distress can be aggravated in these people, symptoms that can also occur in those who are in social isolation (Jahanshahi et al. 2020).

Studies show that individuals with severe illness or multiple comorbidities have higher levels of psychological symptoms in the face of that crisis. The impact of the COVID-19 pandemic in Spain was assessed and it was demonstrated that individuals who reported chronic illnesses had higher average levels of stress, anxiety and depression in comparison with participants who did not report such illnesses (Ozamiz-Etxebarria et al. 2020). In this sense, post-pandemic patients may become more vulnerable to the frustrations and disabilities resulting from the disease and its physical symptoms, particularly pain. People with chronic pain such as those with orthopedic or rheumatic pathology often tend to manifest emotions of revolt, anger, anxiety or even depressive symptoms, which are not only reflected in the interaction with others, but can also influence negative, symptomatology and disease progression (Ozamiz-Etxebarria et al. 2020).

In a study that evaluated experiences of patients with rheumatic diseases in the United States of America during the COVID-19 (Michaud et al. 2020), the most commonly reported emotions were anxiety, nervousness, worry, and fear. Some observed that anxiety/stress seemed to worsen their arthritis symptoms.

Approximately half of the patients in a North American cohort described significant disruption to their rheumatology care, including disrupted or postponed appointments and self-imposed or physician-directed changes to medications (Sirotych et al. 2020). The change or interruption of treatment can cause worse chronic pain, both due to treatment failure and to the psychic symptoms of the post-pandemic period.

The perceived intensity of the painful symptoms is thus exacerbated by the symptoms of disability, anxiety, depression, sleep disorders, poor quality of life and health costs. Likewise, psychological distress has been identified as a potential way in which an episode of pain influences the development of persistent disabling symptoms (Park and Park 2020). Thus, health professionals may encounter the challenge of dealing with the increase in painful symptoms and the difficulty of reducing the levels of physical disability of patients. A good way to assess this intensity of pain perception is to adopt assessment instruments that assess broader aspects of pain.

Increasing evidence has shown that pain science education positively affects pain, disability, pain catastrophization, movement limitations and general health costs. For this, it is necessary that both subjective and objective physical assessment, embrace a biopsychosocial approach instead of just a biomedical procedure. Patients with chronic pain suffer from severe fear, which should allow us to develop a treatment strategy that directly reduces that aversive-stimulus-related emotion, thus improving the physical and psychosocial well-being of these patients (Hall et al, 2020).

In a biopsychosocial view, psychological factors are believed to play an important role in the onset and progression of chronic pain. The cognitive-behavioural model of avoiding fear of chronic pain suggests that pain-related fear contributes to the development and maintenance of pain-related disability (Dinner et al, 2016). Therefore, addressing the beliefs, cognitions and behaviours associated with patients' pain symptoms has become an important issue for consideration during the treatment, particularly of chronic pain. These overlapping strategies impact pain surveillance, which in turn can also lead to increases in the perception of pain severity.

Another point to be taken into account by the physician and physiotherapist in the post-pandemic is that the process of catastrophizing pain, which worsens in the face of psychological suffering linked or not to pain, may be present or even increased. According to Severeijns and collaborators (2001), patients with chronic pain who catastrophize reported greater pain intensity felt more incapacitated by their pain problem and experienced more psychological suffering. Catastrophization was a powerful predictor of pain intensity, disability and psychological distress, even when controlled by physical impairment. Thus, we can conclude that catastrophization plays a crucial role in the experience of chronic pain, contributing significantly to the variation in pain intensity, pain-related disability and psychological suffering.

There is growing evidence that, when pain neuroscience education is provided to patients with chronic musculoskeletal pain, it can result in decreased pain, pain catastrophization and disability and improved physical performance (Puentedura and Flynn 2016; Wijma et al. 2016). Pain neuroscience education is increasingly used as part of a physiotherapeutic treatment in patients with chronic pain. A thorough clinical biopsychosocial assessment is recommended before pain neuroscience education to allow an adequate explanation of pain neurophysiology and biopsychosocial interactions in an interactive and patient-centred manner.

A more broadly analysis of pain, evaluating the somatic, cognitive, emotional, behavioural and social factors trying to establish what is the most dominant mechanism of pain, as well as assessing the provocative and disturbing biopsychosocial factors in patients with chronic pain. The use of that approach allows the clinician to specifically classify patients and adapt the treatment plan (Wijma et al. 2016). Concerning that approach, the

physiotherapist will be able to understand the processes of pain in the post-pandemic period, observe its clinical implications, evaluate and outline the most assertive behaviours.

Inpatient consults require new approaches too. For example, many consultations could occur in a nonpresential way, without the need to see the patient in person, with most of the historic gathering occurring via telephone or videoconference with the primary team members. The primary approach would be to assemble the patient's history, review the data, write the note, discuss the case, formulate a differential diagnosis, and recommend a treatment plan (Koumpouras and Helfgott 2020). That procedure, initiated on an emergency basis for a pandemic period, can be implemented in the clinical monitoring of the patient between consultations, as well as being a tool for interaction between the different health professionals involved in the treatment of pain (Koumpouras and Helfgott 2020). Examples of interventions that can effectively be delivered over the internet for patients with chronic pain include: managing stress, addressing sleep disturbances, teaching mindfulness practices, cognitive strategies, pacing activities, social support programs, simple physical exercises, and observing a healthy lifestyle (Shanthanna et al. 2020).

It will be necessary to assess the impacts of COVID-19 on patients with chronic pain, based on multidimensional and multi-professional information for better decision-making and conducting the rehabilitation processes. The acceleration of ongoing processes caused by pandemics can also improve medical procedures and protocols, as well as the understanding of the need for more suitable conduct based on the individual as a human being and not only focused on the clinical symptoms of his/her health conditions, including pain.

2 Neurosciences related to emotional and social pain during the Covid-19 pandemic

Emotion comes from the Latin "*ex + movere*" which means "to move out". In the stressor event, as COVID-19 pandemic, this movement can be related to neuroplasticity (Orrù et al. 2020). Neuroplasticity-associated emotions are inherent to the social process of sensitization (Garland et al. 2010). Regarding that point of view, it is noticeable that the pandemic outbreak experienced by people in several regions of the world has as a crucial aspect for the activity of neural pathways, capable of decreasing the consciousness and decision-making behaviours (O'Callaghan et al. 2017). The stressors processes, therefore, promotes brain changes, coming from scientific education, which happens to produce and preserve factors that have a social and emotional burden (Lupien et al. 2018).

In fact, the encephalon is impacted by the external environment to be sensitized (Agorastos et al. 2018). Awareness comes from a critical and reflective process that results in the formation of experienced subjects beyond being merely informed. This perspective enables a broader understanding of human behaviour in the face of synaptic strengthening and weakening in emotional situations (Padilla et al. 2016), such as the Covid-19 pandemic.

The pain arising from this phenomenon involves neural networks that affect memory, attention, self-regulation (risk assessment behaviours), and executive functions (decision making, planning, logical reasoning, etc.) (Chedid 2007; Cosenza 2008; Guerra et al. 2004; Houzel 2012; Ribeiro 2013). Emotional and social pain can trigger adaptative responses during the organism-environment interaction, and exert influence on limbic neural systems underlying the behaviour, modifying neural connectivity, neuroplasticity,

coding and modulation of behavioural responses related to perception, attention, memory, reasoning and problem solving (Tyng et al. 2017).

The COVID-19 pandemic threatening may also cause influence in human brain development, influencing the cerebral neuroplasticity, with different peaks of synaptic density coming from environmental stimuli that occur during life (Blakemore and Choudhury 2006). The emotional pain comes from the possible cognitive "shake" that the Covid-19 pandemic can cause, reflecting on the neuroplastic capacity of the individual and, consequently, his/her social behaviour. In this follow-up, the relationship between neuroplasticity and emotional pain, in Covid-19 pandemic time, can be characterized by the involvement of health in its broad sense: physical, social and mental health.

The generation of the negative or positive impact of Covid-19 on behaviour and development of the central nervous system involves the need for adaptive strategies of improved socioemotional and cognitive control capacity during life, in order to avoid consequences such as pain (Compare et al. 2014). Thus, the neuroplasticity of emotion-related structures is currently under the threat stimuli represented by Covid-19 pandemic. More specifically, the integrated activity of neural networks modulates autonomic responses as well as somatosensitivity (Christensen et al. 2020).

In this context, the limbic system, which according to recent advances in neuroimaging, acts as the neuroanatomical basis of emotional behaviour, is highlighted as one of the regions to be possibly affected by the SARS-Cov2 virus. Moreover, it fits the thought that most of the ascending reticular activating Sistem (ARAS) neurons situated in the brainstem will critically influence the activation of the cerebral cortex during pain

suffering, elaboration of emotions and during social threatening situations (Venkatraman et al. 2017).

At a socio-emotional consideration and the consequent emotional pain in face of the Covid-19 pandemic, it is possible to think about the direct influence on the movement of people in face of the prophylactic measure of social isolation, probably due to the importance of the modulation of the connection between the ventral *striatum* and the motor cortex, through the nigro-thalamic pathway (Aoki et al. 2019).

The Covid-19 pandemic, therefore, involves synaptic changes and the formation of new patterns of neural activity. The approach on neuroplasticity has been constant in the scientific environment, especially investigations that seek a multisensorial understanding (Oby et al. 2019).

Notably, the number of publications involving emotional and social pain is growing; however, significant contributions are still small. Associated with the new context of life that the Covid-19 pandemic has imposed with direct influences on emotional and cognitive aspects of human behaviour, and on the interaction with the social environment in which they are living, it is suitable the improvement of our skills for the understanding the human behaviour and the emotional pain arising from the process of adaptation in a threatening situation. The neuroscientific approach of the human brain activity in the time of coronavirus will contribute to the opening of paths for a broader understanding of human behaviour, during the social isolation, highlighting the physical, emotional and social pain during the covid-19 pandemic.

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Legend of Figures

Figure 1: Pain pathways from nociception to sensory discriminative perception and emotion pain.

Figure 2: Neural areas that have been shown to related physical pain, affective (emotive) pain, social pain.