Review article

The anatomy of pain and suffering in the brain and its clinical implications

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A B S T R A C T

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Chronic pain, with a prevalence of 20–30 % is the major cause of human suffering worldwide, because effective, specific and safe therapies have yet to be developed. It is unevenly distributed among sexes, with women experiencing more pain and suffering. Chronic pain can be anatomically and phenomenologically dissected into three separable but interacting pathways, a lateral 'painfulness' pathway, a medial 'suffering' pathway and a descending pain inhibitory pathway. One may have pain(fullness) without suffering and suffering without pain (fullness). Pain sensation leads to suffering via a cognitive, emotional and autonomic processing, and is expressed as anger, fear, frustration, anxiety and depression. The medial pathway overlaps with the salience and stress networks, explaining that behavioural relevance or meaning determines the suffering associated with painful-ness. Genetic and epigenetic influences trigger chronic neuroinflammatory changes which are involved in transitioning from acute to chronic pain. Based on the concept of the Bayesian brain, pain (and suffering) can be regarded as the consequence of an imbalance between the two ascending and the descending pain inhibitory pathways under control of the reward system. The therapeutic clinical implications of this simple pain model are obvious. After categorizing the working mechanisms of each of the available treatments (pain killers, psycho-pharmacology, psychotherapy, neuromodulation, psychosurgery, spinal cord stimulation) to 1 or more of the 3 pathways, a rational combination can be proposed of activating the descending pain inhibitory pathway in combination with inhibition of the medial and lateral pathway, so as to rebalance the pain (and suffering) pathways.

1. Introduction

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (Bonica, 1979). Chronic pain, i.e. that extends beyond the period of healing of the original insult or injury, and hence lacks the acute warning function of physiological nociception (Treede et al., 2019) is not simply a temporal extension of acute pain but involves distinct mechanisms (Kuner and Flor, 2016). Whereas acute pain can be considered a symptom of an underlying problem, chronic pain is now defined by the international Association for the Study of Pain and International Classification of Diseases (ICD)11 as pain that extends

beyond 3 months, irrespective of the cause, and chronic pain can thus pain be recognized as a health condition in its own right (Treede et al., 2019; Scholz et al., 2019), and not a mere symptom of another disease. Chronic pain is further subdivided in (1) chronic primary pain; (2) chronic cancer-related pain; (3) chronic postsurgical or posttraumatic pain; (4) chronic neuropathic pain; (5) chronic secondary headache or orofacial pain; (6) chronic secondary visceral pain; and (7) chronic secondary musculoskeletal pain (Treede et al., 2019).

The prevalence of chronic pain, lasting more than six months, i.e. before the ICD11 code, is 20 %, both in the USA (Dahlhamer et al., 2018) and Europe (Breivik et al., 2006), and about 30 % in China (Yongjun et al., 2020), which is similar to the prevalence in low-income and middle-income countries (Jackson et al., 2015). Chronic pain is the

Table of definitions

Sensitization   change in the strength of response to a single stimulus due to repeated exposure to that stimulus

Peripheral sensitization   sensitization at the level of the nociceptor or dorsal root ganglion

Central sensitization   sensitization at the level of the spinal cord or brain

Suffering   an unpleasant experience associated with negative cognitive, emotional, and autonomic response to a stimulus

Chronic pain   pain lasting for more than three months.

Chronification   transition from acute to chronic pain

Salience   behavioural relevance

Central pain   pain resulting from a lesion in the central nervous system.

Centralized pain   pain syndromes characterized by widespread or diffuse pain, fatigue, mood and sleep disturbances, and poor quality of life, often comorbid with other centralized pain syndromes and irritable bowel syndrome.

Sex   the anatomy of an individual's reproductive system and secondary sex characteristics

Gender   social roles based on the sex of a person or personal identification of one's own gender based on an internal awareness

major cause of human suffering worldwide, because effective, specific and safe therapies have yet to be developed (Disease et al., 2018). High impact chronic pain, i.e., chronic pain that frequently limits life or work activities occurs in 8 % of the population (Dahlhamer et al., 2018). Chronic pain is associated with multiple other symptoms in about 1/3 of the patients, including a combination of irritability, depression, anxiety, and sleep problems (Breivik et al., 2006; Yongjun et al., 2020; Mills et al., 2019). But chronic pain is also associated with cognitive dysfunction, such as problems of attention, learning, memory, and decision making (Moriarty et al., 2011), as well as cardiovascular disease (Mills et al., 2019). Chronic pain and its co-morbidities lead to increased disability (Mutubuki et al., 2020), carrying globally the highest

disability associated burden (Disease et al., 2018). The correlation between chronic pain and disability creates a huge cost to society ($560-635 billion per year) that is double that of the annual costs of heart disease ($309 billion), cancer ($243 billion), and diabetes ($188 billion) (Gaskin and Richard, 2012), and back pain alone amounts to 1.7 % of the global national product on a yearly basis (van Tulder et al., 1995).

Many of the currently available pain therapies are either inadequate or cause uncomfortable to deleterious side effects (Jensen et al., 2014; Stucky et al., 2001). The key to more successful pain treatment is a better understanding of the mechanisms that generate and maintain chronic pain.

2. Pain and pleasure as a phylogenetically old motivation system

Epicurus (341-270 BCE), based on the philosophy of Plato and Aristotle, proposed that the pursuit of pleasure and absence of pain is the purpose of life. This was further developed by Jeremy Bentham (1748–1832), who in his philosophy of Utilitarianism stated that "Nature has placed mankind under the governance of two sovereign masters, pain and pleasure." Utilitarianism states that one has to maximize pleasure and minimize pain. Yet, a more fundamental question is whether pain and pleasure are not only determining the purpose of life, but also the mechanism of life, and form the basis of natural and sexual selection.

To survive as an individual and a species, even our oldest ocean-dwelling ancestors must have been able to react to the environment to feed, evade predators, defend territory, and reproduce (Loonen and Ivanova, 2015). During the Cambrian explosion 540 million years ago practically all major multicellular animal phyla started appearing (in the fossil record). The phylogenetically oldest chordata, the lancelet fish (amphioxus) has no true brain, if a 'brain' is defined as subserving the entire body, being bilobar, consisting of specialized parts, and multisynaptic (Sarnat and Netsky, 2002). The honour of having the first brain arises in hagfish and the vertebrate lamprey (Loonen and Ivanova, 2015). These hagfish and lamprey have a basic motivational circuitry, consisting of the habenula and ventral striatum (nucleus accumbens) (Loonen and Ivanova, 2015). This motivation to seek reward (ventral striatum) and flee from misery/punishment (habenula) permits an organism to learn what is beneficial and harmful for survival and procreation (Loonen and Ivanova, 2015). The phylogenetically old
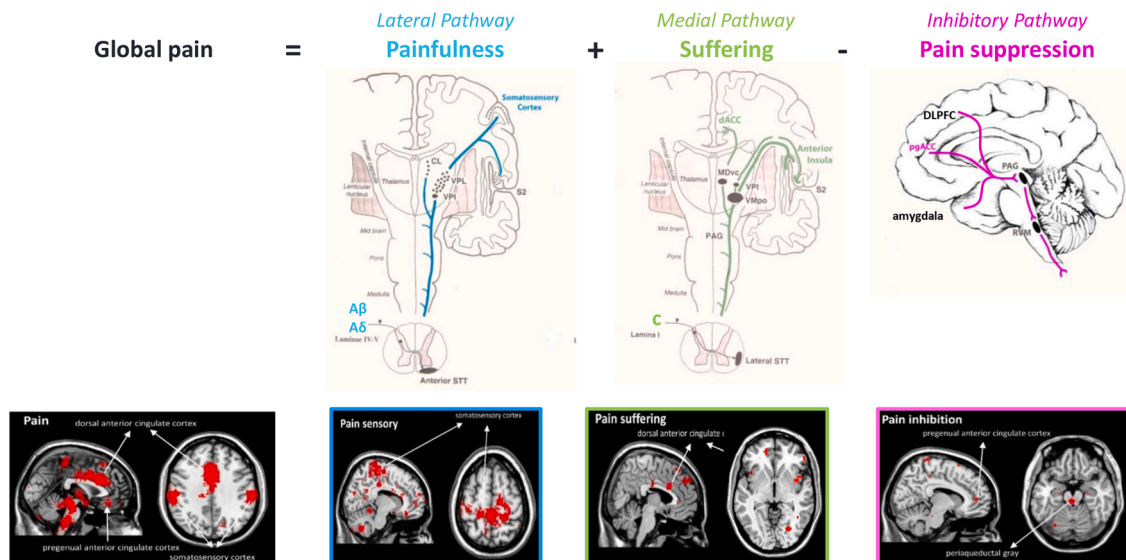

Fig. 1. The anatomical pathways associated with 3 different aspects of pain (painfulness, suffering and presence). A neurosynth meta-analysis of functional imaging studies confirms the anatomy related to the clinical pain characteristics.

motivational circuit is dependent on unmyelinated (C-) fibres, as the hagfish and lamprey lack myelin in their central and peripheral nervous system (de Bellard, 2016), which has remained so throughout evolution. Indeed, even in humans there are two kinds unmyelinated C-fibres associated with pain and pleasure, the low threshold tactile "pleasure" C-fibers (Loken et al., 2009), and the high-threshold "pain" C-fibres. The motivational-affective role of tactile C fibres in humans is an integral part of a thin-fibre afferent homeostatic network for the maintenance of physical and social well-being (Bjornsdotter et al., 2010), encoding pleasantness (Loken et al., 2009), including erotic pleasure (Jonsson et al., 2015). High threshold C fibres likely encode the unpleasantness of pain (Kulkarni et al., 2005).

In summary, unpleasantness and pleasure is transmitted via a phylogenetically old unmyelinated C-fibre network, linked to survival and procreation.

3. The brain anatomy of pain

A stimulus produces an effect on the different sensory receptors, which is being transmitted to the sensory cortex, inducing sensation (De Ridder et al., 2011). Further processing of this sensory stimulation by other brain networks such as the default mode, salience network and frontoparietal control network generates an internal representation of the outer and inner world called a percept (De Ridder et al., 2011). Perception can thus be defined as the act of interpreting and organizing a sensory stimulus to produce a meaningful experience of the world and of oneself (De Ridder et al., 2011).

When a person says he or she is "in pain", what the person actually says is "I have a certain amount of painfulness associated with a certain amount of suffering during a certain amount of time". These 3 components of pain are phenomenological expressions of 3 different pathways involved in pain processing (Fig. 1).

The two main ascending pathways include the anatomically and functionally separated medial and lateral pain pathways (Kulkarni et al., 2005; Price, 2000; Bushnell et al., 2013; De Ridder and Vanneste, 2016). The medial pain pathway involves the rostral to dorsal anterior cingulate (rdACC) and anterior insular cortex. Based on meta-analytical co-activation and functional connectivity profiles the insula is subdivided in 3 separable functional areas (Chang et al., 2013; Uddin, 2015). The posterior insula processes all sensory information (olfactory, gustatory, auditory, somatosensory and pain) (Chang et al., 2013; Uddin, 2015). The anterior ventral area of the insula is involved in emotional and social(face) processing (Chang et al., 2013; Uddin, 2015), and the dorsal anterior area in cognitive processing (Chang et al., 2013; Uddin, 2015).

A meta-analysis has demonstrated that the rdACC is involved in cognitive, emotional, somatosensory and sympathetic autonomic processing (Beissner et al., 2013), and is therefore an area essential for integrating negative emotions and cognitive control of acute and chronic pain (Shackman et al., 2011; Tolomeo et al., 2016; Vogt, 2005; Peyron et al., 2000). The causal relationship has been suggested by the fact that a cingulotomy interferes with processing of negative affect and cognitive control: patients who have undergone a cingulotomy recognize fear, disgust and anger less than healthy controls, but have no impairment in recognizing facial expressions of surprise or happiness (Tolomeo et al., 2016). Strangely enough they have no impairment in recognizing expressions of sadness (Tolomeo et al., 2016).

The rdACC of the medial pathway encodes the unpleasantness (Kulkarni et al., 2005; Price, 2000; De Ridder and Vanneste, 2016; Rainville et al., 1997; De Ridder et al., 2013a), in other words the unpleasant emotional component of the above pain definition (Bonica, 1979). The lateral pathway, which involves the somatosensory cortex (SSC) extending to the parietal area, processes the discriminatory/sensory components of the pain, such as pain intensity, pain localization, and pain character (burning, aching, etc.) (Kulkarni et al., 2005; Bushnell et al., 2013; Flor et al., 1995). The differences at the

cortical level between the lateral and medial pathways can be traced to the thalamus: (chronic low back) pain patients have abnormal connectivity between the ventral lateral/posterolateral nucleus of the thalamus and postcentral gyrus (= somatosensory cortex) and between the dorsal/ventral medial nucleus and insula (Tu et al., 2020), i.e. also at the thalamic level the lateral and medial pathway can be dissociated. The two ascending pain pathways are balanced by a descending pain inhibitory pathway (Fields, 2004; Kong et al., 2010a), involving the rostral and pregenual anterior cingulate cortex (pgACC), the periaqueductal gray, the parahippocampal area, hypothalamus, and rostral ventromedial brainstem (Fields, 2004; Kong et al., 2010a; Eippert et al., 2009). An animal study has demonstrated that the descending pain inhibitory pathway starts from the amygdala, from which it connects to the pgACC, and further relayed to the PAG and brainstem/spinal cord (Huang et al., 2019). The central amygdala also receives pain related information from the spinal cord via the parabrachial nucleus, predominantly right lateralized (Allen et al., 2021). This pathway is serotoninergic and noradrenergic (Huang et al., 2019). The amygdala also sends opioidergic (as well as somatostatin and corticotropin) pain inhibitory signals to the parabrachial nucleus (Raver et al., 2020). Human meta-analytic studies in pain have shown amygdala activation (Simons et al., 2014), confirming the amygdala involvement in pain processing. The ventrolateral prefrontal cortex is also involved in the descending pain inhibitory pathway and is dopaminergic (Sheng et al., 2009; Tang et al., 2009). This descending pain inhibitory pathway is responsible for context dependent pain perception (Leknes et al., 2013), placebo analgesia (Eippert et al., 2009; Bingel et al., 2006; Amanzio et al., 2013; Petrovic et al., 2002), and is deficient in pain syndromes characterized by global pain such as fibromyalgia (Jensen et al., 2013). Thus, the descending pain inhibitory pathway reflects the capacity of the brain to suppress acute or ongoing pain, and it can be assumed that a fully functioning system suppresses all pain, that a completely dysfunctioning system results in constant pain, and a deficient system results in fluctuating pain.

A neurosynth meta-analysis of pain incorporating 516 studies demonstrates that these 3 pathways are not merely an anatomical abstraction, but correlate with functional imaging findings (Fig. 1). Indeed, the neural correlates of (global) pain involve many areas, but these can be separated and subdivided into a sensory 'painfulness' component, a 'suffering' affective component and inhibitory component, consistent with the clinical phenomenology of pain. The sensory component of pain involves predominantly the somatosensory cortex, the suffering component the rdACC and anterior insula, and the inhibitory component the rostral to pregenual ACC and the periaqueductal grey (Fig. 1). These constitute an almost perfect match with the anatomical model described above. Yet, that does not yet permit to accept this simplified model as a true neuroanatomical basis for the understanding of pain. This requires an objective measure for the presence or absence of chronic pain, purely data driven, for which artificial intelligence, using machine learning can be employed. Such a machine learning approach has generated a neural signature for acute pain based on fMRI with 94 % accuracy (Wager et al., 2013). The neural signature included the bilateral dorsal posterior insula, the secondary somatosensory cortex, the anterior insula, the ventrolateral and medial thalamus, the hypothalamus, and the dorsal anterior cingulate cortex (Wager et al., 2013).

A similar approach has yielded a neural signature of chronic pain, based on EEG, with a similar accuracy of 93 % (Vanneste et al., 2018), with almost similar areas. In this study the parahippocampal area, a part of the descending pain inhibitory pathway (Kong et al., 2010a), was included, but the thalamus and hypothalamus were excluded, as EEG cannot pick up deep seated thalamic and hypothalamic activity.

A neurosynth meta-analysis of 92 studies on chronic pain shows that the lateral and medial pain pathway involvement are still present, but activity in the descending pain inhibitory pathway is not present anymore This is compatible with the concept that chronic pain may be the result of a deficiency in pain suppression, rather than pain input, in
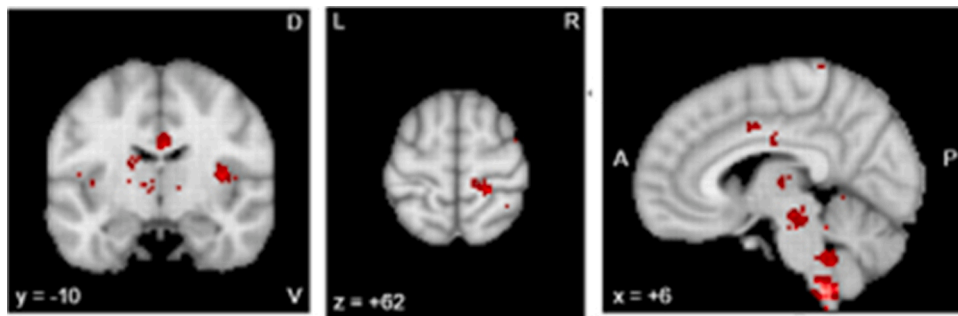
Fig. 2. Neurosynth meta-analysis of chronic pain. The pregenual to subgenual anterior cingulate component is absent, suggesting that chronic pain is related to lost inhibition.

agreement with earlier reports centering on the thalamus that chronic pain may be the result of lost inhibition (Henderson et al., 2013) (Fig. 2). The deficiency of the pgACC, as main hub in the descending pain inhibitory system, in the development of chronic pain has been well described in one form of chronic pain: fibromyalgia (Jensen et al., 2013; De Ridder and Vanneste, 2017; Vanneste et al., 2017).

In summary, the anatomical tracts, the meta-analysis of the functional imaging data combined with the purely data driven machine learning approach demonstrate that pain can indeed be reduced to 3 hubs (pgACC, dACC, SSC) as expressions of the 3 pathways (descending, medial, lateral).

4. Chronic pain, central sensitization, centralized pain: an integrative approach

Nociceptive pain is the result of a protective activation of physiological pain pathways to noxious stimuli, i.e., stimuli that can cause potential or real tissue damage. This activation is triggered by chemical, mechanical or thermal stimuli and the clinical expression of pain serves to protect the damaged region until it can heal (Meacham et al., 2017). Injury to tissue and nerves initiates an inflammatory response that is intended to contain pathogens, clear damaged tissues and promote repair (Ren and Dubner, 2010). Repeated or persistent noxious stimulation results in an enhanced responsiveness, lowered threshold and the development of background activity, known as peripheral sensitization (Perl et al., 1976). Clinically it manifests as pain hypersensitivity. This peripheral sensitization is linked to the release of inflammatory mediators such as chemokines/cytokines as well as neuropeptides (such as CGRP and substance P) (Ren and Dubner, 2010). It serves as a predictive signal of actual or potential harm associated with that stimulus. The peripheral sensitization may subsequently trigger a central sensitization in the spinal cord mediated by upregulation of both ionotropic and metabotropic glutamate receptors, downregulation of GABA receptors, and modifications in sodium and potassium channels, as well as neuroinflammatory changes (Greenwald and Shafritz, 2018; Julius and Basbaum, 2001; Levine and Alessandri-Haber, 2007; Scholz and Woolf, 2002; Tsuda et al., 2003). The neuroinflammatory changes sensitize lamina I neurons, normally responding only to pain-specific stimuli, to also start responding to non-nociceptive inputs, phenomenologically expressed as allodynia (Scholz and Woolf, 2002; von Hehn et al., 2012). Furthermore, associated neuroinflammatory cytokine release determines whether someone is more or less vulnerable to develop chronic

Fig. 3. Overview of factors involved in the transition from acute to chronic pain. Genetic polymorphisms influence gene expression related to a noxious stimulus directly, and environmental factors influence genetic expression indirectly (via epigenetics), resulting in transient or persistent neuroinflammation. The microbiome also modulates the neuroinflammatory response. Neuroinflammation leads to peripheral and central sensitization. Under influence of negative psychological features mediated through the accumbens, anterior cingulate and insula acute pain can transition to chronic pain.

pain (Vasic and Schmidt, 2017). Whereas IL6, IL1 and TNFα lead to vulnerability to chronic pain, IL10, IL4 and TGFβ are associated with resilience (Vasic and Schmidt, 2017). Central sensitization manifests not only as allodynia, but also pain hypersensitivity, secondary punctate or pressure hyperalgesia, aftersensations, and enhanced temporal summation (Woolf, 2011).

Central sensitization may lead to centralized pain syndromes such as fibromyalgia, temporomandibular joint disorders, chronic pelvic pain and migraine (Harte et al., 2018). The centralization is mediated via infraslow oscillations within the ascending pain pathway, resulting from altered neural astrocyte coupling (Alshelh et al., 2016). These pain syndromes are characterized by more widespread or less well localized pain, fatigue, mood and sleep disturbances, and poor quality of life (Eller-Smith et al., 2018). They also tend to be comorbid to other centralized pain syndromes and irritable bowel syndrome (Eller-Smith et al., 2018). These centralized pain syndromes are often associated with childhood adversity (You and Meagher, 2018), such as sexual abuse (Spiegel et al., 2015), non-violent or violent childhood traumas (Pierce et al., 2020).

Centralized pain has been used interchangeably with central pain and even central sensitization (Dydyk and Givler, 2021), yet central pain may better be defined as pain resulting from lesions anywhere along the spino-thalamo-cortical pathway, such as in multiple sclerosis, Parkinson's disease, spinal cord lesions and thalamic strokes (Devulder et al., 2002; Canavero and Bonicalzi, 2007).

Central sensitization can also lead to chronification, i.e., a transition from acute to chronic pain (Fig. 3). Central sensitization during the acute phase resolves for many patients but is a precursor to the transition to chronicity when combined with negative psychological features (Klyne et al., 2019). Systematic reviews demonstrate that depression, anxiety, fear avoidance and catastrophizing are associated with the risk of pain chronification (Hruschak and Cochran, 2018; Theunissen et al., 2012). This may be mediated via the brain's emotional learning circuitry. Indeed, the transition to chronic pain is associated with progressively more involvement of the reward/learning and emotional pathways and less involvement of somatosensory pathways, as demonstrated by structural and functional imaging studies and confirmed at a meta-analytic level (Friebel et al., 2011; Baliki et al., 2012; Mansour et al., 2013; Mansour et al., 2014). Based on a review of the pain literature in adolescents it has been proposed that poor diet and adverse childhood events may trigger prolonged inflammation and microglia activation leading to sensitization of the pain system, and stress induced alterations to hypothalamic-pituitary-adrenal axis, both of which are associated with chronic pain (Salberg et al., 2020). Environmental toxins, medications, diet, and psychological stress can alter epigenetic processes such as DNA methylation, histone acetylation, and RNA interference which may guide the transition from acute to chronic pain (Buchheit et al., 2012). Adverse childhood events are known to induce epigenetic modification of DNA expression, especially via DNA methylation. DNA methylation is altered in the glucocorticoid (stress response) receptor gene, NR3C1, which has been associated with depression, childhood stress, low socioeconomic status, and chronic pain (Aroke et al., 2019). Transgenerational epigenetic inheritance describes how parental life experiences and environmental exposures influence mental and physical health across generations (Jawaid et al., 2021). Adverse childhood experiences, especially physical neglect, are prevalent among parents of youth with chronic pain (Beveridge et al., 2020), suggesting that epigenetic mechanisms may underly the transition from acute to chronic pain. This suggests that patients without risk genes who are exposed to childhood adverse events may be prone to chronification of pain due to DNA methylation or other known epigenetic processes (histone modifications, chromatin remodelling, non-coding RNA) (Buchheit et al., 2012). However, there are also risk genes that are more common in patients with chronic pain. Genetic susceptibility to chronic pain has been linked to genes activated in inflammation and signal transmission in the nervous system, as shown

by meta-analyses (Chidambaran et al., 2020; Hoofwijk et al., 2016; Veluchamy et al., 2018). These patients may develop chronic pain without a history of childhood adversity, analogous to what has been described for depression and schizophrenia (Hoffmann et al., 2017).

But apart from the genetic and epigenetic influences involved in the neuroinflammatory component of central sensitization, a third modulator of the neuroinflammatory component may be of relevance for the transition of acute to chronic pain: the microbiome (Guo et al., 2019). Microbiota produce numerous signalling molecules, such as metabolites, neurotransmitters, and neuromodulators, which act on nociceptors and regulate the peripheral and central sensitisation, which in turn mediate the development of chronic pain (Guo et al., 2019; Lagomarsino et al., 2021; Li et al., 2020). Furthermore, the signal molecules modulate brain activity and connectivity directly, via spinal pathways as well as via the vagal nerve, and indirectly, via the circulation (Guo et al., 2019; Lagomarsino et al., 2021; Li et al., 2020). The microbiota derived signal molecules also modulate the immune cells and can either increase or decrease the neuroinflammatory response and thus modulate peripheral and central sensitization (Guo et al., 2019). Furthermore, it has been shown that the method of delivery at birth, infant feeding, genetics, diet, medication (antibiotics, antipsychotics, antidepressants, proton pump inhibitors), toxins, maternal stress, early life adversity and trauma can change the microbiome, resulting in a gut dysbiosis (Felice and O'Mahony, 2017; Sherwin et al., 2019; Maier and Typas, 2017). Furthermore, alterations in the gut microbiome regulate epigenetic modifications like DNA methylation or histone methylation and/or acetylation (Shock et al., 2021).

Multiple working mechanisms exist to explain the transition from acute to chronic pain (Chapman and Vierck, 2017): 1) persistent noxious signalling in the periphery in some but not all patients (Birbaumer et al., 1997); 2) neuroinflammatory mediated central sensitization; 3) compromised inhibitory modulation of noxious signalling in medullary-spinal pathways; 4) descending facilitatory modulation; and 5) maladaptive brain remodelling in function, structure, and connectivity (Chapman and Vierck, 2017). These 5 mechanisms may be responsible individually or in a combined way.

In summary, genetic polymorphisms (risk or susceptibility genes) related to immune responses as well as neurotransmission directly influence peripheral and central sensitization via peripheral inflammation and neuroinflammation. Furthermore, psychological factors, such as childhood adversity, even transgenerational, or physical traumas, whether toxic or dietary could indirectly modulate neuroinflammation, via epigenetic modification of DNA expression. The genetic and environmental factors also influence the microbiome, which via a direct effect on the immune system and indirectly by modulating epigenetics can modulate the neuroinflammatory response. The neuroinflammation triggers peripheral sensitization, which can evolve into central sensitization. When central sensitization is combined with negative psychological features it can lead to chronic pain. It is evident that this heuristic multistep/multifactorial pathophysiological model is still in its infancy, but it is in alignment with other neurological and psychiatric disorders. Whereas neuroinflammation in pain is a hot research topic with about 200,000 manuscripts being published on neuroimmunology and pain between 2000 and 2019, only 111 papers were clinical human trials, which means that the translation is virtually non-existent, with a 1/1800 ratio (Grace et al., 2021).

5. Pain and suffering are different

The sensation of pain(fullness) can lead to suffering via the associated feeling of unpleasantness and catastrophizing (Wade et al., 2011). Pain catastrophizing is characterized by 1. The tendency to magnify the threat value of the pain stimulus, 2. To feel helpless in the context of pain, and by 3. A relative inability to inhibit pain-related thoughts (rumination) (Osman et al., 1997). As such, pain catastrophizing can be seen as an amplifier on unpleasantness and pain intensity by deficient
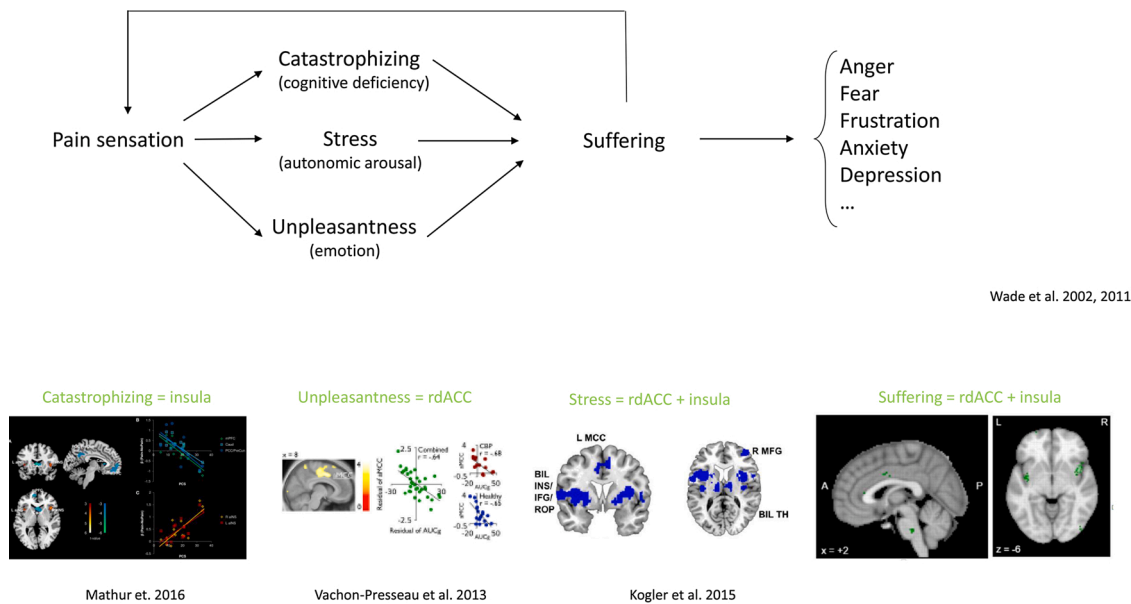
Fig. 4. A chronic painful stimulus leads to a cognitive, emotional, and autonomic response, which phenomenologically expresses as catastrophizing, attention paid to the pain, unpleasantness, fear, anger or frustration with pain and distress. These phenomenological aspects all correlate with altered activity in the medial pathway.
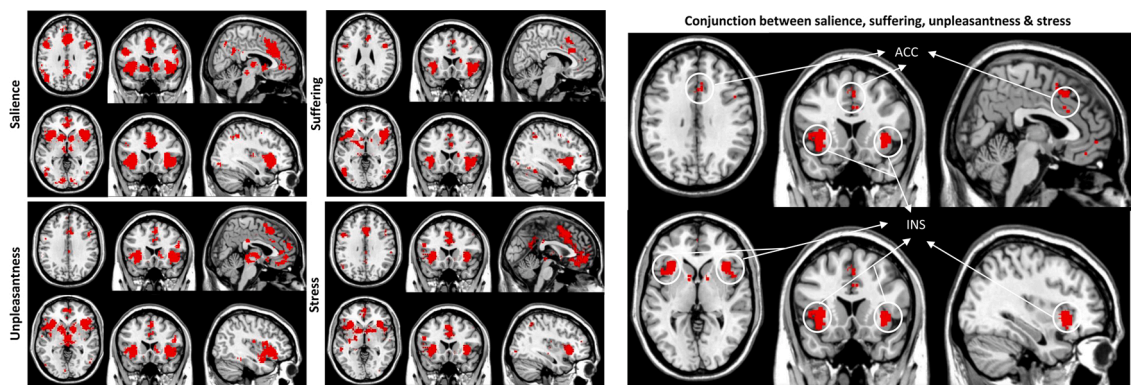

Fig. 5. Neurosynth meta-analyses of salience, suffering, unpleasantness, and stress. These different aspects of pain overlap in the rostral dorsal anterior cingulate cortex and anterior insula, i.e., the medial pathway.

cognitive coping strategies. The combination of the perceived unpleasantness and catastrophizing leads to suffering, which can express in different behaviors, including anger, fear, frustration, anxiety and depression (Wade et al., 2011; Wade and Hart, 2002; Bustan et al., 2015) as well as functional disability (Severeijns et al., 2001) (Figs. 4 and 5). Suffering can thus be defined as an unpleasant experience associated with negative cognitive, emotional and autonomic impact leading to changes in behavior and functional disability. The Global Burden of Disease Study 2013 evaluated "years lived with disability" (YLDs) for a broad range of diseases and injuries in 188 countries (Rice et al., 2016). The single greatest cause of YLDs around the world was chronic low back pain, followed by major depressive disorder, i.e. one expression of suffering. Other frequent causes of YLDs include chronic neck pain, migraine, osteoarthritis, other musculoskeletal disorders, and medication overuse headache (Rice et al., 2016).

Since the beginning of scientific research on stress, pain has been recognized as a prototypical stressor (Selye, 1936). Physiological stress can be defined as an unpleasant sensory, emotional and subjective experience that is associated with potential damage of body tissue and bodily threat (Kogler et al., 2015), especially when an environmental demand exceeds the natural regulatory capacity of an organism (Koolhaas et al., 2011). Stress results in an immediate adaptive short-lived

response of the autonomic nervous system and slower protracted activation of the hypothalamic-pituitary adrenal endocrine axis (Ulrich-Lai and Herman, 2009). Acute elevations in cortisol levels are beneficial to promoting survival of the fittest as part of the fight-or-flight response. However, chronic exposure to stress results in reversal of the beneficial effects, with long-term cortisol exposure becoming maladaptive, which can lead to a broad range of problems including the metabolic syndrome, obesity, cancer, mental health disorders, cardiovascular disease and increased susceptibility to infections (Russell and Lightman, 2019). The mental health disorders associated with chronic stress include depression (Russell and Lightman, 2019; Staufenbiel et al., 2013), anxiety (Staufenbiel et al., 2013), and anger (Gilam et al., 2017), in other words suffering. These behavioral expressions of suffering are most extreme and present in a combined way in the ultimate stress disorder, PTSD (Fonzo, 2018).

For pain unpleasantness and pain catastrophizing no meta-analytic studies have been performed to delineate the neural correlates, but individual studies have, looking both at healthy volunteers and chronic pain patients. Pain unpleasantness correlates with activity in the rdACC in healthy volunteers (Rainville et al., 1997; Girard-Tremblay et al., 2014; Vachon-Presseau et al., 2013) and chronic pain patients (Vachon-Presseau et al., 2013). In healthy controls it also correlates with
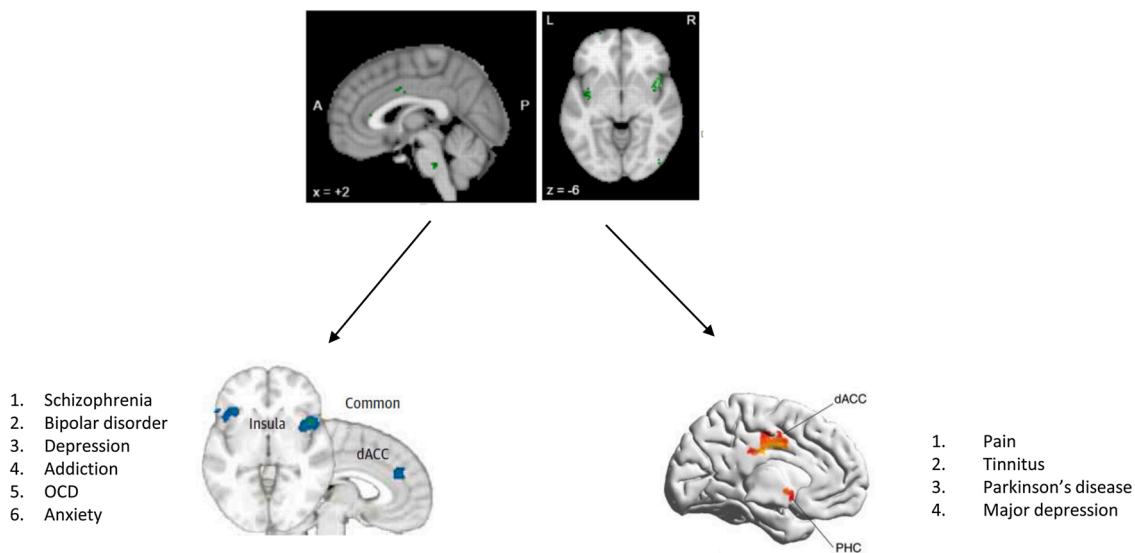
Fig. 6. The rostral dorsal anterior cingulate cortex and insula are involved in many psychiatric disorders and the rostral dorsal anterior cingulate cortex is also implicated in the thalamocortical dysrhythmias. It is proposed that this reflects the neural substrate of suffering.

the anterior insula (Kornelsen et al., 2019; Schreckenberger et al., 2005). Pain catastrophizing in chronic pain patients correlates with activity in the cognitive dorsal anterior insula (Mathur et al., 2016), as well as with decreased functional connectivity between the nucleus accumbens and the right insula (Ikeda et al., 2018), but without correlation to the rdACC (Cottam et al., 2016). In a systematic review without meta-analysis in patients as well as healthy controls, catastrophizing not only is associated with activity in the anterior insula, but also in the rdACC and somatosensory cortex (Galambos et al., 2019). These results suggest that the neural correlates of pain unpleasantness and pan catastrophizing may be somewhat different in chronic pain patients from healthy controls. When we perform a neurosynth meta-analysis of 124 studies of suffering in general, it correlates with rdACC and insula activity. The neural correlates of physiological stress, as evidenced by a meta-analysis also involve the rdACC and anterior insula (Kogler et al., 2015). More in detail, the increased cortisol in stress results in unpleasantness by its modulation of the rdACC (Vachon-Presseau et al., 2013).

The suffering and painfulness of pain can be modulated independently, demonstrating that these pathways are separable. This was already recognized during frontal lobotomies performed in the treatment of chronic pain. It was noted that "The operation does not abolish physical pain but tends to change the menta1 attitude so that the patient does not suffer as he did before (Lyerly, 1951)". Similar observations were made following cingulotomies for chronic pain (Foltz and White, 1962), and are currently observed with electrode implants in the rdACC (Boccard et al., 2014a, 2017). But apart from surgical modulation of the affective component of pain, also non-surgical approaches can modulate the affective or sensory components selectively (Bushnell et al., 2013). Manipulating the attentional state primarily alters the perceived intensity of the pain sensation without significantly altering the perceived unpleasantness of the pain. By contrast, altering the mood state alters the perceived unpleasantness of the pain without altering the intensity of the sensation (Bushnell et al., 2013; Villemure and Bushnell, 2009).

Patients with congenital insensitivity to pain do not experience painfulness to nocuous stimuli, but their medial 'suffering' pathway is activated by seeing others in pain (Danziger et al., 2009), i.e. their medial pathway is functional. This pain(fullness) insensitivity may be related to an overactive opioidergic descending pain inhibitory system, as naloxone, an opioid antagonist can result in pressure and pain perception in those patients (Yanagida, 1978; Minett et al., 2015). Patients with pain asymbolia on the other hand have normal pain

thresholds, but lack an associated emotional and protective withdrawal response (Berthier et al., 1988). This is associated with insular lesions (Berthier et al., 1988). The opposite syndrome, in which patients during a simple partial epileptic seizures of the mid-to posterior insula, present with an emotional and withdrawal response without pain sensation has been described as 'symbolism for pain' syndrome (Hagiwara et al., 2020).

In summary, pain consists of a sensory painfulness component, encoded by the lateral pathway, and a suffering component, encoded by the medial pathway. Suffering involves a cognitive, emotional and autonomic component, all encoded by parts of the medial pathway. The medial and lateral pathway are separable and consequently, one may have pain(fullness) without suffering and suffering without pain (fullness).

6. Suffering involves salience and context

In his opus magnum, Phenomenology de la Perception (Merleau-Ponty, 1945), Merleau-Ponty describes that an object of perception cannot be seen in isolation because it is embedded in a context. It exists in relationship to other things, which gives it its meaning in the world. Perception is embodied, i.e., always related to the self, because the self is required to engage with the environment, the context. Thus, the context determines the meaning, and the meaning determines the way the stimulus is perceived.

Some practical examples clarify this philosophical concept. There is no relationship between the extent of the injury and experienced pain in wounded soldiers evacuated from the frontline in the Second World War (Beecher, 1956). This makes intuitive sense, as surviving is more salient, more behaviorally relevant than pain perception when wounded in the front line. Suffering from pain could lead to immobilization, and thus prevent appropriate measures to be taken to stay alive. "The intensity of suffering is largely determined by what the pain means to the patient" (Beecher, 1956), in other words "the intensity of the suffering is largely determined by the salience of the pain in this specific context". Thus, the suffering, and more specifically the unpleasantness depends on the context (Leknes et al., 2013). And indeed, in sado-masochism pain can be perceived as pleasant, the opposite of suffering. Yet, the painfulness is only perceived as pleasant in the very specific erotic context. For the sadomasochist hitting his finger with a hammer will feel equally unpleasant and cause the same amount of suffering as for a non-sadomasochist.

Context thus changes the perception of identical pain stimulus (Leknes et al., 2013). Pain perceived as pleasant by contextual modulation activates the descending pain inhibitory pathway and reward (accumbens caudate) system, whereas unpleasant pain activates dACC and insula, in other words the medial 'suffering' pain pathway (Leknes et al., 2013), which overlaps with the salience network. And indeed, the neurosynth meta-analysis of suffering, and its constituent components unpleasantness and stress, and the salience meta-analysis overlap (Fig. 4).

The same is seen in masochists. An erotic context dramatically alters the affective component of pain (Kamping et al., 2016): Masochists feel less pain and pain is less unpleasant, but only in erotic sadomasochist context (Kamping et al., 2016). This is mediated via the descending and medial pain pathway (rdACC-insula). The contextual influence is demonstrated by the fact that this switch from suffering to pleasure in the sadomasochistic context is controlled by the parahippocampal area, a major hub in contextual processing (Aminoff et al., 2007, 2013; Bar et al., 2008a, b; Ranganath and Ritchey, 2012).

7. Suffering is common in mental disorders and thalamocortical dysrhythmia

A meta-analysis of structural studies looking for a common neurobiological substrate for mental illness identified the rdACC and anterior insula, i.e., the salience network, as the common denominator for six different psychiatric pathologies, previously classified as axis 1 pathologies, i.e., schizophrenia, bipolar disorder, depression, addiction, obsessive-compulsive disorder, and anxiety (Goodkind et al., 2015) (Fig. 6).

This was confirmed and extended by a meta-connectome analysis of meta-analytic studies of even more psychiatric pathologies, including Alzheimer's Disease, attention deficit hyperactivity disorder, autism spectrum disorder, bipolar disorder, depressive disorder, mild cognitive impairment, multiple sclerosis, obsessive-compulsive disorder, Parkinson's Disease, post-traumatic stress disorder, and schizophrenia (Sha et al., 2018). These common structural and connectivity changes in psychiatric pathologies are also reflected functionally. A meta-analysis of functional imaging studies confirmed that the salience network is disrupted in emotional processing across psychiatric disorders including schizophrenia bipolar and unipolar major depression, anxiety, OCD, PTSD, and substance use disorders (McTeague et al., 2020). This common network is associated with symptomatic distress/suffering and cognitive deficiency (McTeague et al., 2016).

Furthermore, in a study looking at the common neural substrates of Parkinson's disease, pain, tinnitus and depression, also known as thalamocortical dysrhythmias (Llinas et al., 1999), machine learning extracted the common core of these pathologies, found to be beta activity in the rdACC and parahippocampal area (Vanneste et al., 2018) (Fig. 6). Thalamocortical dysrhythmia was proposed as a common pathophysiological model underlying pain as well as other pathologies such as tinnitus, slow wave epilepsy, depression and Parkinson's disease (Llinas et al., 1999). It posits that in a deafferented state, the physiological thalamocortical resting state alpha rhythm (8−12 Hz) slows down to theta (4−7 Hz) (Llinas et al., 1999) band frequencies. As a result, GABA$_A$ mediated lateral inhibition is reduced (Llinas et al., 2005; Di Pietro et al., 2018), inducing gamma (>30 Hz) band activity (Llinas et al., 1999) surrounding the deafferented theta area, also known as the edge effect (Llinas et al., 2005). These thalamocortical changes may not be limited to the lateral pathway, but also extend to the medial pathway (Tu et al., 2020; Prichep et al., 2018; Groh et al., 2018), and involve low frequency oscillations, as shown by resting state fMRI in low back pain (Tu et al., 2020) and migraine (Hodkinson et al., 2016). It is of interest that no increase in infraslow oscillations are present within the ascending pain pathway during acute noxious stimuli in healthy individuals, suggesting that increased infraslow oscillatory activity within the ascending pain pathway may be critically related to increased and

self-sustaining thalamocortical dysrhythmia, phenomenologically expressed as constant perception of pain (Alshelh et al., 2016).

What all these psychiatric and neurological disorders may have in common is suffering, and it is likely that what the meta-analyses and machine learning picked up was not pathology specific, but the common suffering core, intrinsic to all these pathologies. And indeed, a neurosynth meta-analysis of 'suffering', demonstrates that suffering is characterized by activity in the right insula, dACC, sgACC extending into the orbitofrontal cortex and right inferior parietal area (Fig. 6). Furthermore, in the psychiatric meta-analysis, there were few diagnosis-specific effects, distinguishing only schizophrenia and depression from other diagnoses (Goodkind et al., 2015), suggesting that the common areas might indeed express a common phenomenology, and similarly, what differentiated the individual thalamocortical dysrhythmias was determined by the specific involvement of the associated cortex: the auditory cortex in tinnitus, the motor cortex for Parkinson's disease, and the subgenual anterior cingulate for depression (Vanneste et al., 2018).

In summary, the medial pathway overlaps with the salience network, explaining that behavioral relevance determines the suffering associated with painfulness, but also with other symptoms.

8. A Bayesian perspective on pain as an imbalance between pain input and pain suppression

In 1664, in Treatise of Man, René Descartes theorized the first mechanical/physiological explanation for pain, influenced by Galileo Galilei's concept of a fully mechanistic universe (Benini and DeLeo, 1999). He proposed that pain is the consequence of activation of a pain pathway (hollow tubes) that transmits painful stimuli (via Galenic animal spirits) to Herophilus' pineal gland, where the nocuous stimuli were translated into the feeling of pain (Benini and DeLeo, 1999; Lopez-Munoz et al., 2012). Textbook pain physiology still follows this same basic principle. However, in real world circumstances there is no perfect correlation between the pain stimulus and the perceived pain, as the soldiers coming back from the frontline and the sado-masochist pain perception demonstrate. These two expressions of context mediated pain perception, as well as the concept of placebo in pain suggest that the perceived pain may be a balance between Cartesian pain input and contextual activation of the pain inhibitory pathway.

This balance concept for chronic pain has been proposed more than 50 years ago to exist at the level of the spinal cord, between large Abeta and small fibers (Adelta and C-fibers), called the pain gate hypothesis (Melzack and Wall, 1965). More recently intracortical changes in the balance of excitation and inhibition have also been proposed to exist at the level of the somatosensory cortex and underlie chronic neuropathic pain (Harding and Salter, 2017). Based on preliminary findings on source-localized EEG it has been that chronic pain can be seen as an imbalance between the two (medial and lateral) ascending pain pathways and the descending pain inhibitory pathway (De Ridder and Vanneste, 2016). When the current density in the rdACC and somatosensory cortex equals the current density (x2) of the pregenual ACC, i.e. when activity in the pain input equals the activity in pain inhibition there is no pain, as noted in healthy controls (De Ridder and Vanneste, 2016). However, in chronic pain patients the input is increased in comparison to the pain suppression, leading to the perception of pain (De Ridder and Vanneste, 2016). As seen above, in fibromyalgia, and chronic pain in general the descending pain inhibitory pathway seems to be deficient. Using machine learning it can be demonstrated that the balance between (rdACC + SSC)/pgACCx2 can better detect the presence pain (89.3 % accuracy) than the activity in the somatosensory cortex alone (68.8 %), and better than the activity in the somatosensory cortex plus rdACC (79.3 %) (Vanneste and De Ridder, 2021; De Ridder and Vanneste, 2021), suggesting that this balance concept is a worthwhile avenue in the quest to find an objective measure for a fundamentally subjective state. It does so, by integrating context-based activation of the pain inhibitory pathway into the equation, which now
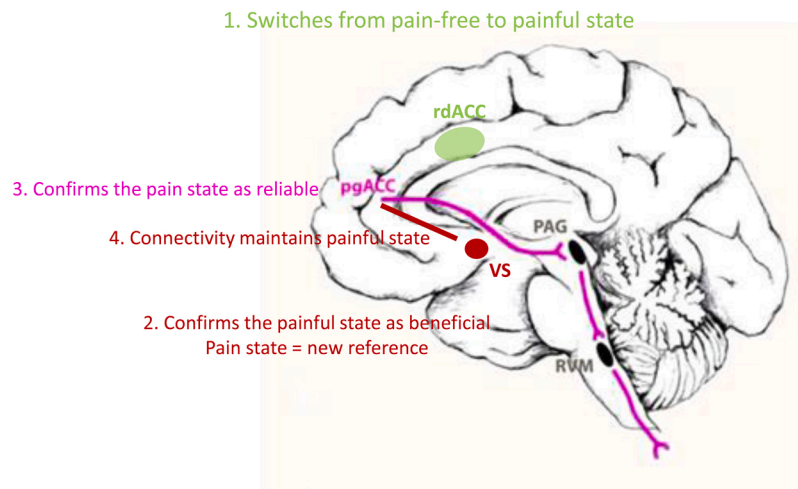
Fig. 7. The neural correlates of a chronic pain as predicted by a Bayesian brain model.

only involves painfulness and unpleasantness. This context-based influence via the descending pain inhibitory pathway is in keeping with Merleau-Ponty's philosophical stand on perception in general. Further improvements, e.g., by incorporating anterior insula activity, could also integrate catastrophizing into the model.

A balance, by definition, requires communication between the rdACC and pgACC and somatosensory cortex. The functional connectivity between the rdACC and pgACC is anti-correlated (Margulies et al., 2007), i.e. when the rdACC is more active the pgACC is less active (Fox et al., 2005). The sensorimotor cortex is co-activated with the rdACC but anti-correlated with the pgACC (Margulies et al., 2007), in keeping with the fact that rdACC and somatosensory cortex encode the motivational/affective and physical characteristics of the pain stimulus, and that the pgACC is involved in the descending pain inhibitory system.

It has been proposed that balance between the ascending pain pathways and the descending pain inhibitory pathway is under control of the reward system (De Ridder and Vanneste, 2016; Leknes and Tracey, 2008; Yu et al., 2020). This is based on the fact that the transition from acute to chronic pain is associated with increased structural and functional connectivity between the nucleus accumbens and the pregenual anterior cingulate cortex, which predicts the development of chronic pain by more than 80 % (Baliki et al., 2012; Mansour et al., 2013). This nucleus accumbens-pregenual anterior cingulate cortex functional connectivity is maintained during the chronic pain state (Makary et al., 2020). Furthermore, a smaller nucleus accumbens volume predates the development of chronic pain and remains unchanged when pain becomes chronic (Makary et al., 2020). This fits with the concept that the transition to and continuation of chronic pain is dependent on the state of motivational/learning and reward mesolimbic-prefrontal circuitry of the brain (Baliki et al., 2012; Mansour et al., 2013; Denk et al., 2014). The nucleus accumbens its involvement in this transition can be theorized in terms of its function in behavior in general, linked to the Bayesian brain concept (Barrett and Simmons, 2015; De Ridder et al., 2014; Friston, 2010). The reward system is based on the ventral tegmental area, and in patients with chronic pain the functional connectivity between the ventral tegmental area (VTA) and the pgACC is decreased, and the decreased functional connectivity correlates with the pain severity and duration (Yu et al., 2020). The pain severity increase results from decreased functional connectivity between the parahippocampus and the VTA (Yu et al., 2020). This is compatible with the concept that chronic pain may be (a reward driven) maladaptive learning process (Apkarian et al., 2009).
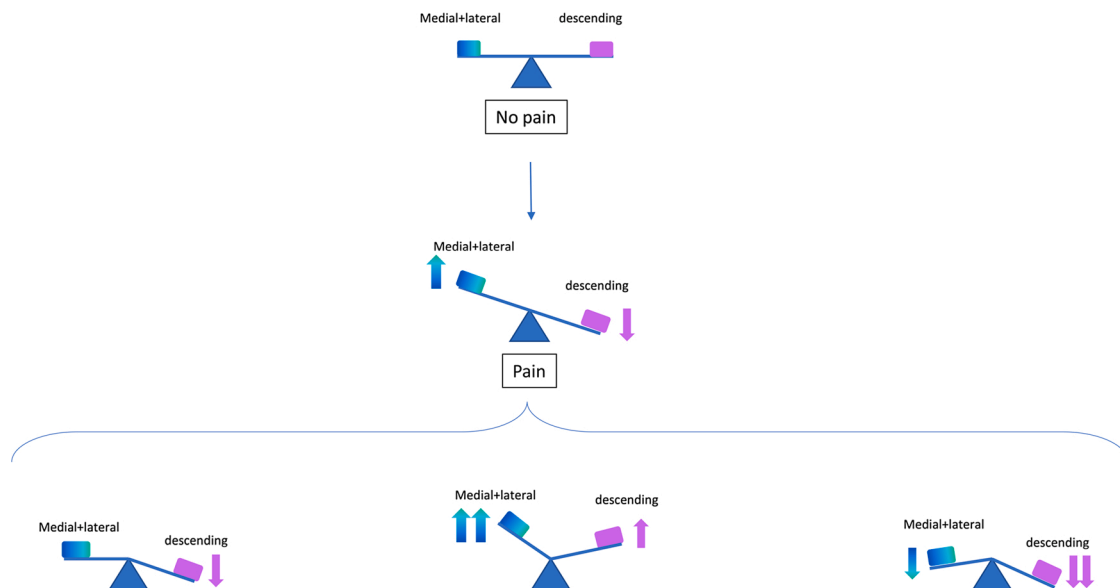

Fig. 8. Pain as an imbalance explains why on functional imaging the descending pain inhibitory pathway is also activated, as compatible with the middle lower figure.

In the Bayesian brain model the brain is conceptualized as a probability machine that constantly makes predictions about the world and then updates them based on what it actively seeks in the environment using the different senses (Fletcher and Frith, 2009; (De Ridder, 2014)). The brain can make multiple predictions in parallel (De Ridder et al., 2013b; Donoso et al., 2014) and the prediction which best fits the sensory sampling survives and becomes the next percept (De Ridder et al., 2013b). The reliability of the current behavioural strategy, e.g., the pain-free state is encoded by ventral medial prefrontal cortex and pregenual anterior cingulate cortex (Donoso et al., 2014), while the reliability of alternative behavioural strategies is encoded by lateral frontopolar cortex. When the reliability of the current strategy decreases, the behavioural strategy switches to the alternative. This switching is encoded by rostral to dorsal anterior cingulate cortex, and the rejection of the current strategy is encoded by ventrolateral prefrontal cortex, while the confirmation of new behavioural strategy as actor is encoded by ventral striatum, i.e. nucleus accumbens (Donoso et al., 2014). Translating this general neuroanatomical model of behaviour to chronic pain, it can be proposed that in chronic pain the dorsal anterior cingulate cortex switches the current pain-free state to a painful state. The accumbens confirms the painful state as beneficial, i.e. as the new reference state. The pregenual anterior cingulate cortex confirms the painful state as reliable and the increased functional connectivity between the nucleus accumbens and pregenual anterior cingulate cortex maintains the painful state, i.e. chronifies the pain (Mansour et al. (2013); Baliki et al. (2013)) (Fig. 7).

It is important to realize that a simple balance model will be insufficient to explain all subtypes of pain. A broken balance may actually be more of a rule than an exception. This could be explained by a simple model in which pain input is increased, but with an attempt of the brain to suppress pain by activating the descending pain inhibitory pathway. As long as the inhibition is less than the input will pain ensue (Fig. 8).

In summary, based on the concept of the Bayesian brain as well as functional and structural imaging a model can be proposed in which pain (and suffering) is the consequence of an imbalance between the ascending and descending pain inhibitory pathways. This balance is theorized to be under control of the reward system.

9. Sex differences in pain and suffering

There is a widespread belief that the sex undergoing parturition would require higher pain tolerance (Mogil, 2020). Contrary to this belief, experimental acute pain studies demonstrate that women have a lower pain threshold and pain tolerance, and perceive pain stimuli as more intense, as well as more unpleasant (Mogil, 2012; Day et al., 2020). Furthermore, women catastrophize pain more than men (Day et al., 2020), suggesting they suffer more for the same pain stimulus. Painful stimuli elicit differential responses in the autonomic nervous system as well. Women demonstrate higher galvanic skin responses(Aslaksen et al., 2007) and more pupil dilation (Ellermeier and Westphal, 1995), i. e. more sympathetic activation during experimental pain than men. And similar responses are identified in chronic low back pain (Tousignant-Laflamme and Marchand, 2006). Yet, it is still unclear whether women have more sympathetic responses to painful stimuli because the same pain stimuli exert more emotional responses in women, or whether it is the other way around (Melchior et al., 2016).

The question arises whether laboratory studies on emotion processing and acute pain can teach us anything about chronic pain, as chronic pain may not just be a temporal extension of acute pain (Kuner and Flor, 2016)?

The prevalence of chronic pain is approximately 6 times higher in women than in men (Mogil, 2012; Fillingim et al., 2009). This is reflected by more tension headache and migraine, fibromyalgia, rheumatoid arthritis, musculoskeletal pain, chronic regional pain syndrome (CRPS), procedural and postoperative pain, and temporomandibular pain (Shansky and Murphy, 2021; Midavaine et al., 2021). Women not

only experience more pain, but also suffer more. They have twice the lifetime rates of depression and most anxiety disorders (Kessler et al., 1994; Gater et al., 1998; Weissman et al., 1996; Altemus et al., 2014; Davis et al., 1999; McCarthy et al., 2017). In addition to higher rates of affective disorders that meet full diagnostic criteria, subclinical anxiety and depression symptoms are also more common in women (Nolen-Hoeksema et al., 1999; Hankin, 2009).

For the same diagnosis, pain levels within chronic pain syndromes are markedly higher in women than men (Ruau et al., 2012). This could explain why women use health care services more frequently than men for both painful and non-painful disorders (Briscoe, 1987), suggesting women may suffer more in general. Higher pain intensity results in more frustration and fear in women, in contrast to generating anxiety and depression among men (Riley et al., 2001). Higher pain unpleasantness results in depression and frustration among women, as compared to frustration among men (Riley et al., 2001).

But apart from increased unpleasantness perception by women, a meta-analysis has also shown that major and minor life events result in more stress and is perceived as more intense in females compared to males (Davis et al., 1999), which explains why anxiety, depression and PTSD is more common in women than men in relation to the same or similar events, such as cancer (Unseld et al., 2019), sexual trauma (Tannahill et al., 2020) or the Covid-19 pandemia (Liu et al., 2020).

These clinical differences between acute and chronic pain perception being worse in women than men is in striking contrast to most preclinical work, which involves exclusively male animals, and clinical studies overwhelmingly do not include sex as a factor for analysis (Shansky and Murphy, 2021). For example, 80 % of the pain studies published in the PAIN journal in 2015 were carried out in male rodents only (Mogil, 2016). The 'sex as a biological variable' policies, introduced in 2014 and implemented in 2016 in the USA, are being increasingly adopted by funding agencies (Tannenbaum et al., 2019), generating a wealth of data demonstrating not only the epidemiological and clinical differences in acute and chronic pain, but also the underlying mechanisms, at a genetic, molecular, immunological, cellular, cognitive and social levels (Mogil, 2020). Consequently, different theories have been proposed to explain the differences in pain processing between men and women. The most common theories for these sex-based differences in acute and chronic pain perception include 1. Structural and functional differences in brains between men and women, as well as in pain processing pathways, 2. Hormonal influences in pain processing, 3. Autonomic nervous system involvement differences, 4. Genetic differences, 5. Sociocultural and 6. Immunological differences (Mogil, 2020, 2012; Melchior et al., 2016; Midavaine et al., 2021). These are not mutually exclusive but may become integrated into one sex-based theory of pain. Brains of men and women are different, both genetically determined and epigenetically adjusting to environmental factors (McCarthy et al., 2017). Meta-analytic studies have shown that males have larger total brain volumes than females (Ruigrok et al., 2014). Regional sex differences in volume and tissue density include the amygdala, hippocampus and insula (Ruigrok et al., 2014), i.e. especially in the medial pain pathway/salience network. Furthermore, sex-specific differences in structural connectivity exist. In all supratentorial regions, males have greater within-hemispheric connectivity, whereas between-hemispheric connectivity and cross-module participation predominates in females (Ingalhalikar et al., 2014). But more important than structural differences between men and women are functional differences, both in brain activity and functional connectivity. Functional resting state connectivity in healthy individuals is different between the sexes within the medial pain pathway between the anterior insula and rdACC (Dai et al., 2018), as well as between the periadequctal grey, insula and rdACC (Coulombe et al., 2016; Kong et al., 2010b), i.e. between the medial pathway and the descending pain inhibitory pathway. Furthermore, men have pain evoked PAG functional connectivity to the amygdala, putamen and caudate nucleus, unobserved in women (Linnman et al., 2012). These could lead to differential brain activation in men and

women on stimulus presentation, whether emotional or pain stimuli. Emotional stimuli indeed exert a different neural brain response in men and women, at the medial prefrontal cortex, anterior cingulate cortex, frontal pole, and mediodorsal nucleus of the thalamus, i.e. the medial pathway, as shown by meta-analytic evaluation (Filkowski et al., 2017).

These structural and functional differences between sexes in brain anatomy is in part genetically encoded. Thirty seven percent of all genes exhibit sex-biased expression in at least one tissue, and the brain and spinal cord are highly sex differentiated (Oliva et al., 2020),The differences between male and female brains are partly mediated via a sex-specific release of hormones as well as differential involvement of the immune system, with microglia masculinizing and T cells feminizing brains (McCarthy et al., 2017). This differential mechanism is similar to what has been described in pain. Mechanical pain hypersensitivity has been shown to be generated by different mechanisms at the level of the spinal cord, by microglial involvement in males and T cells in females (Sorge et al., 2015). Microglia mediate pain signaling in neuropathic and inflammatory pain conditions in males, while adaptative T cells are mainly involved in pain signaling in females (Dance, 2019). In bone cancer pain, microglia are involved in pain signaling in both sexes, while T cells are found only in males (Midavaine et al., 2021). In all three pain conditions, neurons and astrocytes are involved in pain signaling in a sex-independent manner (Midavaine et al., 2021).Based on microglial involvement in many brain disorders (Salter and Stevens, 2017) it can be hypothesized this mechanism might also extend to other pathologies such as depression and anxiety, i.e. suffering. And indeed, gene activation studies in humans in depression have shown an opposite effect in men and women for gene expressions that control microglial activation (Seney et al., 2018). This is confirmed in rats exposed to in utero and later in life stress who demonstrate anhedonia/depression. In the nucleus accumbens the microglia are atrophic in female rats and hypertrophic in male rats, and neurons show a similar response (except for neurons in females in late stress exposure) (Gaspar et al., 2021).

The genetic differences between sexes in brain structural and functional anatomy in general have also been evaluated in pain processing, more specifically using genome wide association studies. For example, in multisite chronic pain, in women 31 genes are identified that are associated with the chronic pain, and in men 37 genes (Johnston et al., 2021). Six genes are associated with chronic pain only in women, and 4 genes only in men, demonstrating that there is a genetic basis for differential pain processing in men and women (Johnston et al., 2021). These genetic differences result in differential activation of pain areas on the application of painful stimuli. In men, painful stimuli elicit activation of the secondary somatosensory cortex and parietal cortex in contrast to women (Melchior et al., 2016). In women, these stimuli evoke activity in the thalamus and anterior cingulate cortex (Melchior et al., 2016), possibly explaining the higher unpleasantness. And indeed, unpleasantness in painful stimulation correlates with the canonical rdACC activation in women (Girard-Tremblay et al., 2014; Monroe et al., 2015), whereas for men a decrease in sgACC may be more relevant (Girard-Tremblay et al., 2014). In both men and women the primary somatosensory cortex, primary motor cortex and premotor cortex are activated on pain stimuli (Melchior et al., 2016). These differences are also present in chronic pain. A meta-analytic study demonstrated more prominent primary sensorimotor structural and functional alterations in female chronic pain patients compared with male chronic pain patients, differences in the nature and degree of insula alterations, with greater insula reactivity in male patients, and differences in the degree of anterior cingulate structural alterations (Gupta et al., 2017).

But not only brain activity in response to painful stimuli is different between sexes, also functional connectivity between the pain processing brain areas differs.

Using a machine learning approach to assess how accurately participants' sex can be classified based on spatially specific resting state brain connectivity, it was shown that brain regions displaying the highest sex classification accuracies were mainly located along the

anterior cingulate cortex and insula among others (Weis et al., 2020), and these areas overlap with the medial pathway. These functional connectivity differences in the rdACC and sgACC are also present in chronic pain. Women exhibit stronger connectivity with the rdACC and sgACC, whereas men show more connectivity with the somatosensory cortex (Fauchon et al., 2021).

The differences in pain processing are mediated by sex hormones, as suggested by the fact that in early childhood, before puberty, there are no differences in pain processing between boys and girls (Melchior et al., 2016), and in postmenopausal women there exist no differences in pain thresholds and unpleasantness (Monroe et al., 2015, 2018; Riley and Gilbert, 2001), Furthermore, in chronic pain the differences in catastrophizing are less obvious postmenopausally (Racine et al., 2020; Wheeler et al., 2019). However, during puberty, between the ages of 12 and 14, differential pain responses arise, characterized by lower pain thresholds for girls, and the development of more chronic pain, even though no sex differences are identified in conditioned modulation (Melchior et al., 2016). During adulthood women become more sensitive to pain. Pain thresholds are lower in women, as is pain tolerance, and conditioned pain modulation is less efficient (Melchior et al., 2016). In hypogonadal men, 6 months of testosterone replacement therapy improves chronic bodily pain and mental health (Kato et al., 2020), confirming the epidemiological and clinical data. Higher total testosterone levels are also associated with less pain in the operated knee in men and women undergoing total knee replacement (Freystaetter et al., 2020). But testosterone not only modifies painfulness perception, but also suffering. During noxious stimulation, participants with low testosterone levels perceive higher painfulness, unpleasantness, anxiety and fear than participants with higher testosterone levels (Choi et al., 2017). The pain suppression effect of testosterone is mediated via the pgACC, i. e. the descending pain inhibitory pathway (Choi et al., 2017). Similarly, patients with chronic pain are more depressed and anxious and have a diminished quality of life, which is influenced by cytokines and testosterone (Corriger et al., 2019). Progesterone dissociates pain intensity and unpleasantness by influencing the medial pathway (Vincent et al., 2018).These anatomical, neurophysiological, immunological and hormonal differences can explain the clinical differences between men and women, but importantly also suggest that treatments may need to become sex-specific.

Translating preclinical studies only performed on male animals into the clinical realm may lead to inappropriate treatment approaches for female patients. Morphine, for example, has a differential effect in the periaqueductal gray, part of the descending pain inhibitory pathway. Morphine is metabolized into morphine-6-glucuronide, especially in males, which binds to μ opioid receptors and elicits an analgesic response. Morphine however, also metabolizes in morphine-3-glucuronide, especially in females, which binds to Toll-like receptor 4 and elicits a neuroinflammatory response (Shansky and Murphy, 2021). Therefore, morphine may be less effective in females (Shansky and Murphy, 2021), and generate more neuroinflammation induced sensitization, important for chronification. A meta-analysis suggests that men and women may indeed differ in the response to opioids for pain relief, but these differences as well as similarities are significantly influenced by factors like age and comorbid mental disorders (Pisanu et al., 2019), as evident from the above paragraphs showing a hormonal influence and different sex-dependent prevalence in anxiety and depression.

Interestingly, not all treatments for chronic pain show a clear sex-dependent effect. A meta-analysis has demonstrated that psychological treatments seem to have a similar effect on boys and girls (Boerner et al., 2017). Yet, also here, a hormonal influence may be of importance, as this meta-analysis evaluated pain in children and adolescents. Similarly, a meta-analysis of the response to triptans for migraine identified no sex differences for 2 -h headache and pain-free responses, but men had a lower risk for headache recurrence (van Casteren et al., 2021).

In summary, women have lower pain thresholds and pain tolerance, and therefore perceive pain as more intense and more unpleasant than
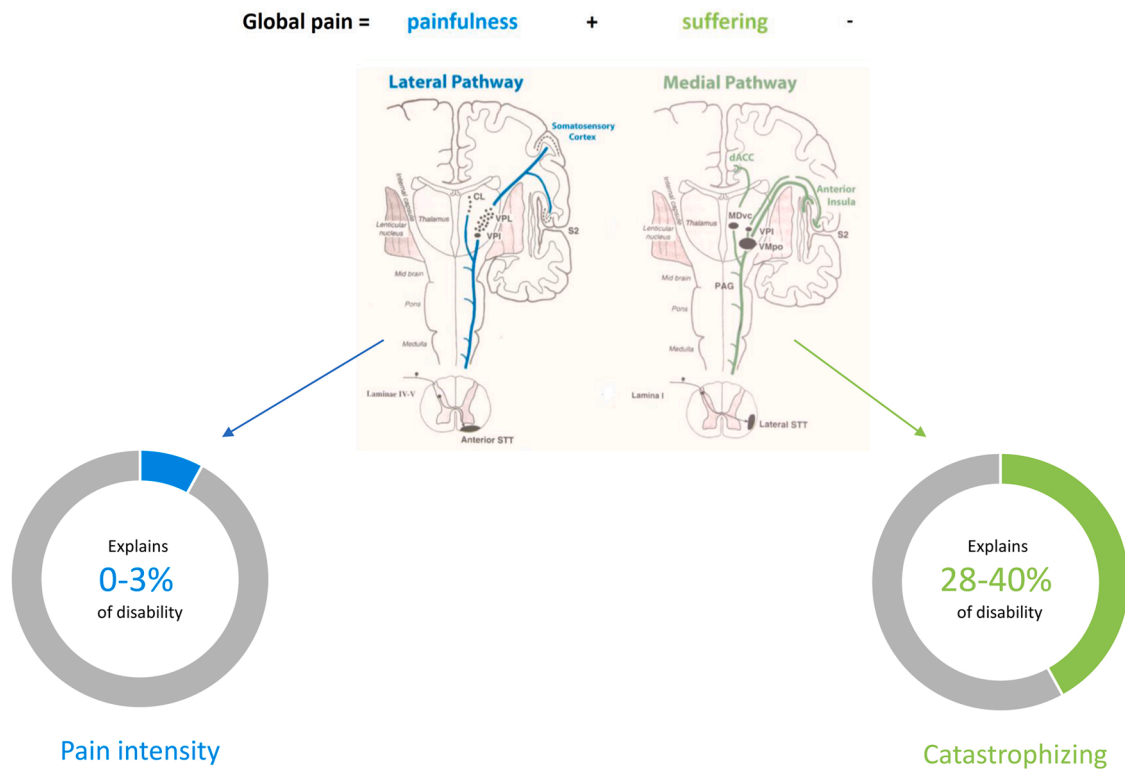
Fig. 9. Pain disability correlates highly with suffering, but not so with painfulness.

men, resulting in more suffering, as expressed by increased prevalence of depression, anxiety and stress. Women also have higher chronic pain prevalence than men. This is mediated via a differential activation and connectivity of the medial pathway. The differences in the medial pathway are genetically encoded, and dependent on differential hormonal and immunological modulation of pain processing in the nervous system. These sex differences in pain processing may lead to different sex-dependent treatment approaches for pain.

10. Implications for the treatment of pain and suffering

The perceived chronic pain related disability strongly correlates with suffering, as expressed by catastrophizing (Besen et al., 2017; Kovacs et al., 2011), explaining between 28–40 % of the disability. In contrast, painfulness correlates only weakly (Besen et al., 2017; Kovacs et al., 2011; Garbi Mde et al., 2014), explaining only 0–3 % of the disability (Fig. 9).

Therefore, it would intuitively make sense to focus the treatment of pain on reducing overactivity in the medial 'suffering' pathway, rather
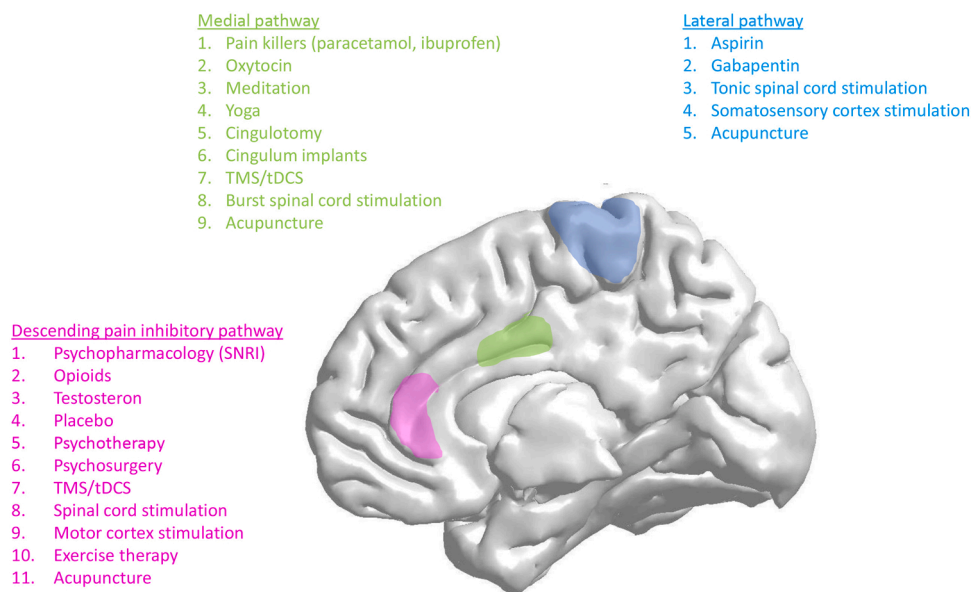

Fig. 10. The categorization of therapeutic modulations of the medial, lateral, and descending pathways. This permits to select complementary therapies to address the pain balance model, by reducing lateral and medial pathway influence and increasing descending pain inhibitory pathway activity.

than the lateral 'painfulness' pathway. The balance concept, which is critically based on the 3-pathway model, has important implications for the treatment of pain and suffering. First of all it suggests that Nobel laureate Paul Ehrlich's magic bullet (Winau et al., 2004) may not be applicable to treat pain and suffering, except if one drug would simultaneously influence the three pathways. Ehrlich envisioned that analogous to a bullet fired from a gun aiming to hit a specific target, there must be a pharmacological way to specifically target a symptom or disease. Based on the concept of pain as an imbalance in the brain it is more sensible to combine a drug that activates the descending pain inhibitory pathway, with another one that suppresses the medial pathway and a third that suppresses the lateral pathway. This cocktail approach is similar to what is very successfully used in for example AIDS pharmacotherapy, keeping the disease under control in 85–90 % of patients (Lu et al., 2018). The beauty of the 3-pathway imbalance concept is that pain and suffering cocktails can be rationally designed, based on a categorization of drugs using their demonstrated brain mechanism by pharmaco-imaging (Fig. 10). This is in keeping with the nascent discipline of network science (Milo et al., 2002; Albert and Barabasi, 2000; Strogatz, 2001; Watts and Strogatz, 1998). Network science has shown that random attacks cannot disrupt a network efficiently, and thus cannot disrupt the emergent property of the network (Albert et al., 2000), e.g. pain. However, a targeted attack, focusing on the critical hubs can dissolve the network, and thus the emergent property (Albert et al., 2000). Approaching pain treatments based on network science suggests that a combination of treatments that target the 3 described pathways simultaneously may be optimal to dissolve the persisting pain network in chronic pain. The following list describes some of the most common treatments for chronic pain and the pathway that is predominantly modulated by the described treatment. This may aid to develop rational treatment combinations as to influence all 3 pathways simultaneously.

10.1. Modulation of the descending (pain) inhibitory pathways?

1 Pharmacological therapy for suffering (anxiety and depression). A meta-analysis of functional and structural neuroimaging studies of pharmacological therapies has shown that increased baseline activity in the pregenual anterior cingulate is predictive of a higher likelihood of improvement. As well, increased baseline activation in the insula and striatum is associated with higher likelihood of a poorer clinical response (Fu et al., 2013). This suggests that the effect of psychopharmacological therapies may depend on the modulation of the pgACC (Fu et al., 2013), as confirmed on pre-post pharmacological evaluations.
2 Pharmacological treatment for pain.

Opioids. Opioid receptors are expressed at high levels in the pgACC, and the pgACC mediates the analgesic effects of opioids (Eippert et al., 2009; Petrovic et al., 2002). But opioids do not only modulate the descending pain inhibitory pathway. Fentanyl, a mu opioid receptor agonist, is known to influence the pgACC, rdACC, insula and somatosensory cortex, i.e. all 3 pathways, associated with similar changes (+/−50 %) in both pain intensity and pain unpleasantness (Casey et al., 2000). Opioids reduce functional coupling between the dACC and bilateral anterior insula/putamen and the rACC and right insula (Gorka et al., 2014), i.e., between the descending pain inhibitory system and the medial pathway.

Serotonin and noradrenalinereuptake inhibitors. Serotonin and Noradrenaline Receptor Inhibitors like duloxetine also modulate the descending pain inhibitory pathway, which is not only opioidergic but also serotoninergic and noradrenergic (Malfait and Schnitzer, 2013). And indeed, the pain suppressing effect of duloxetine depends on the activation of the pgACC (Watanabe et al., 2018; Lopez-Sola et al., 2010). It has been recently postulated that this pain suppressing effect of duloxetine consists of 2 components: a rapid and centrally mediated

effect via the descending pain inhibitory pathway and a delayed, peripheral effect relying on the anti-neuroimmune action of chronic antidepressant treatment (Kremer et al., 2018).

Testosterone also mediates its pain inhibitory effect via activation of the pgACC (Choi et al., 2017).

3 Placebo analgesia is critically dependent on opioidergic activation of the descending pain inhibitory pathway, including the pgACC and PAG (Eippert et al., 2009; Bingel et al., 2006; Petrovic et al., 2002; Levine et al., 1978).
4 Psychotherapy is first-line treatment for depression and anxiety disorders but ineffective for as many as 50 % of patients (Cuijpers et al., 2014a, b). A longitudinal meta-analyses of brain activity changes accompanying psychological therapy demonstrates that treatment success depends on the modulation of the pgACC (Marwood et al., 2018).
5 Non-invasive brain stimulation using transcranial magnetic stimulation (O'Connell et al., 2018) or transcranial direct current stimulation (Zortea et al., 2019) are also used for the treatment of depression and anxiety, and treatment response also depends on the pgACC. The pgACC becomes thicker in patients who respond favorably to DLPFC rTMS and thinner in patients with a less favorable response (Boes et al., 2018). Furthermore, the response depends on the functional connectivity from the pgACC to the parietal area (Ge et al., 2020).
6 Invasive neuromodulation for pain and suffering. Intractable neuropathic pain can sometimes be treated by electrodes implanted on the motor cortex (Lima and Fregni, 2008) and somatosensory cortex (De Ridder et al., 2007a, b). A meta-analysis of functional imaging studies has shown that motor cortex stimulation exerts its effect via the descending pain inhibitory system, as pain suppression depends on modulation of the pgACC and periaqueductal grey (Volkers et al., 2020). Implantation of the subcallosal (= subgenual) ACC has been promoted as a neurosurgical treatment for intractable depression (Mayberg et al., 2005). Six-month response rates hover around 50 % in open-label trials (Dandekar et al., 2018), even though a systematic review and meta-analysis on the effectiveness of deep brain stimulation in depression is still inconclusive (Kisely et al., 2018). For the treatment of suffering in major depression the glutamate concentration in the pgACC seems to determine the response to subcallosal deep brain stimulation (Clark et al., 2020).
7 Psychosurgery by lesioning. The development of stereotactic approaches in 1947 permitted smaller and better targeted lesions, resulting in 4 kinds of psychosurgery: cingulotomy, anterior capsulotomy, subcaudate tractotomy and limbic leucotomy, which is a combination cingulotomy and subcaudate tractotomy (De Ridder et al., 2016a). Based on modern structural imaging using tractography it has become evident that these 3 targets functionally converge on the pregenual anterior cingulate (Schoene-Bake et al., 2010). Anatomically, this convergence may derive from the superolateral branch of the medial forebrain bundle, a structure that connects these frontal areas to the origin of the mesolimbic dopaminergic 'reward' system in the midbrain ventral tegmental area (Schoene-Bake et al., 2010), a possible final common pathway for the different techniques. Thus cingulotomies, subcaudate tractotomies and anterior capsulotomies modulate the balance between the medial and descending pain pathways, i.e., the suffering network. It could also explain the current interest in the nucleus accumbens as a target for the treatment of mental disorders (De Ridder et al., 2016a).
8 Spinal cord stimulation for neuropathic pain. A fMRI study performed during tonic spinal cord stimulation has demonstrated that tonic stimulation modulates predominantly the lateral pain pathways, as fMRI changes are noted in the somatosensory cortices (Stancak et al., 2008). This was confirmed by a more

recent study showing changes in the thalamus, primary sensori-motor area, posterior insula and secondary somatosensory cortex (Moens et al., 2012). However, more importantly, the amount of pain suppression resulting from spinal cord stimulation is related to the amount of activation in the pregenual anterior cingulate cortex (Moens et al., 2012), i.e. how much the descending pain inhibitory pathway was activated. This is confirmed by evoked potentials elicited by painful stimulation, recorded with and without SCS. SCS results in consistent attenuation of evoked potentials in primary and secondary somatosensory cortex but less so in the dorsal anterior cingulate cortex (Polacek et al., 2007), suggesting that tonic stimulation predominantly modulates the lateral pathway, as well as the descending pain inhibitory pathway, ultimately responsible for improving the imbalance by increasing the descending pain inhibitory pathway component of the equation.

9 Exercise therapy can improve pain by activating the descending pain inhibitory pathway. Both Tai Chi, baduanjin and stationary cycling activate the pgACC in knee osteoarthritis pain patients (Liu et al., 2019).

10 Acupuncture blocks pain by activating the descending pain inhibitory system, as shown in both animal (Takeshige et al., 1992; Lv et al., 2019) and human studies (Lv et al., 2019; Egorova et al., 2015; Li et al., 2016). Indeed, acupuncture normalizes abnormal functional connectivity between the PAG and medial prefrontal and AG and hippocampal areas (Egorova et al., 2015) in chronic (knee) pain. Similarly, acupuncture normalizes functional connectivity between the PAG and rACC and ventral striatum (nucleus accumbens) in migraine (Li et al., 2016).

In summary, improvement of pain or suffering by psychopharmacotherapy, psychotherapy, non-invasive and invasive neuromodulation, psychosurgery by brain lesioning, as well as tonic spinal cord stimulation, exercise therapy and acupuncture seems to critically depend on modulation of the pgACC as main hub of the descending (pain) inhibitory pathway, thereby rebalancing the imbalance between pain evoking pathways and pain inhibitory pathways.

10.2. Modulating of the medial 'suffering' pathway

1 Pain killers. Paracetamol, an over-the-counter pain killer modulates the rdACC and insula directly, as well as the periaqueductal grey (Pickering et al., 2015; De Coster et al., 2020). But paracetamol does not only reduce physical pain, also the affective social component of pain, i.e., the suffering, can be reduced, associated by a modulation of the medial pathway (Dewall et al., 2010). Yet interestingly, not only suffering is attenuated by paracetamol, but also pleasure, suggesting that paracetamol functions as a dimmer on the medial suffering pathway (Mischkowski et al., 2016, 2019). Also non-steroidal anti-inflammatory drugs seem to exert their effect by modulating the medial pathway. Whereas a non-specific cox inhibitor ibuprofen predominantly acts via activation of the descending pain inhibitory pathway (Hodkinson et al., 2015), the selective cox2 inhibitor parecoxib modulates the medial pain (and lateral) pathways (Herrndobler et al., 2009).

2 Oxytocin. Whereas most psychopharmaca seem to exert their effect by increasing the activation of the descending pain inhibitory pathway, some drugs do seem to modulate the medial 'suffering' pathway more directly. Oxytocin is such an example. Even though a systematic review of randomized controlled trials evaluating the effect of intranasal oxytocin on anxiety and depressive symptoms is still inconclusive, improvement is associated with functional connectivity changes between the rdACC-anterior insula and amygdala, only in patients with anxiety and depression, not in healthy controls (De Cagna et al., 2019). Thus, oxytocin seems to modulate the medial pathway directly.

3 Meditation. A meta-analysis has demonstrated that meditation results in structural changes in the rdACC (Fox et al., 2014). This is accompanied by acute functional changes in the same area as well as the anterior insula during meditation, but also in the somatosensory cortex (Zeidan et al., 2011). This can explain why meditation influences unpleasantness (Zeidan et al., 2011; Perlman et al., 2010) and catastrophizing (Gamaiunova et al., 2019; Andersen and Vaegter, 2016), as well as sometimes the painfulness (Zeidan et al., 2011). Indeed, meditation not only changes arterial spin labeling fMRI signals in the rdACC and insula correlated to attenuated unpleasantness, but also changes pain evoked potentials in the rdACC, associated with reduced unpleasantness ratings (Brown and Jones, 2010).

4 Anterior cingulate implants for chronic pain. rdACC implants reduce the affective 'suffering' component of chronic pain (Boccard et al., 2014a, 2017; Boccard et al., 2015, 2013; Boccard et al., 2014b). However, with the current tonic stimulation designs the result only seems to last for 6 months (Boccard et al., 2017, 2013). The same rdACC target is also used to treat the suffering in tinnitus (De Ridder et al., 2016b), alcohol addiction (De Ridder et al., 2016c; Leong et al., 2020) and OCD (De Ridder et al., 2016d). When using burst stimulation instead of tonic simulation the benefit seems to last longer (De Ridder, Manning et al. 2016).

5 Non-invasive neuromodulation using transcranial magnetic stimulation has also been used to target the rdACC. This target can be reached using a double cone coil (Hayward et al., 2007; Vanneste et al., 2012) or H-coil (Tzabazis et al., 2013). A comprehensive review of rdACC targeted double cone coil stimulation demonstrated that it seems beneficial for depression and anxiety (Kreuzer et al., 2018) as well as the distress component in tinnitus (Vanneste and De Ridder, 2012).

6 Burst spinal cord stimulation. To mimic naturally occurring burst firing, burst stimulation was developed to treat intractable pain (De Ridder et al., 2013a, 2010; De Ridder et al., 2015). Burst stimulation exerts a similar effect on the ascending lateral and descending pain inhibitory pathway as tonic stimulation (De Ridder and Vanneste, 2016), but is unique in that it also modulates the medial pain pathway, as confirmed by source localized EEG (De Ridder and Vanneste, 2016; De Ridder et al., 2013a) and PET scan (Yearwood et al., 2019). A systematic review and pooled analysis demonstrated that burst spinal cord stimulation is associated with a clinical improvement in suffering, as demonstrated by reductions in pain catastrophizing and other affective measurements of chronic pain (Chakravarthy et al., 2019). And what is curious, is that the reductions are so powerful that they fall below population norms, suggesting that burst spinal cord stimulation may make people resilient to suffering, as indexed by catastrophizing (Deer et al., 2020).

7 Acupuncture modulates the rdACC and anterior insula of the medial pathway (Chae et al., 2013).

In summary, over the counter pain killers such as paracetamol and ibuprofen seem to exert their effect predominantly by treating the suffering, as does oxytocin. More direct approaches such as non-invasive transcranial magnetic stimulation or transcranial direct current stimulation as well as invasive cingulotomy or cingulum stimulation also modulate the affective suffering component. Surprisingly, even spinal cord stimulation can treat suffering, on the condition burst stimulation is used.

10.3. Modulating of the lateral 'painfulness' pathway

1 Aspirin. Aspirin 1000 mg predominantly modulates the latter pathway (Herrndobler et al., 2009).

2 Gabapentin exerts the same effect on the lateral pathway (Wanigasekera et al., 2016) and some effect on the insula as well (Iannetti et al., 2005).

3 Somatosensory cortex stimulation has been performed to treat intractable neuropathic pain (De Ridder et al., 2007a, b; De Ridder and Van de Heyning, 2007). This targets the lateral pathway directly, in contrast to motor cortex stimulation, which seems to exert its effect via the descending pain inhibitory pathway.

4 Tonic spinal cord stimulation. Tonic spinal cord stimulation as a treatment for intractable pain was developed more than 50 years ago. A fMRI study performed during tonic spinal cord stimulation has demonstrated that tonic stimulation modulates predominantly the lateral pain pathways, as fMRI changes are noted in the somatosensory cortices (Stancak et al., 2008). This was confirmed by a more recent study showing changes in the sensory thalamus, primary sensorimotor area, posterior insula and secondary somatosensory cortex (Moens et al., 2012), but not in the medial pathway.

5 Yoga modulates the somatosensory part of the insular cortex and posterior midcingulate cortex, permitting yogi to tolerate pain twice as long as non-yogi (Villemure et al., 2014).

6 Acupuncture also modulates the lateral pain pathway, both the somatosensory and posterior insula components (Chae et al., 2013), as well as the medial pathway, including the rdACC and anterior insula (Chae et al., 2013).

In summary, the lateral pathway can be modulated by aspirin and gabapentin, as well as by somatosensory cortex stimulation, spinal cord stimulation, but also by yoga and acupuncture.

11. Outlook and future research

Current deficiency in our understanding of acute-to-chronic pain transition remains a hurdle for developing effective treatments against chronic pain (Ho et al., 2020). Based on this review many promising research avenues can be proposed for further intense investigation that may benefit our understanding of chronic pain: 1 Neuroinflammation, 2. Network science, 3. Autonomic nervous system involvement, 4. Environmental/epigenetic influences, 5. Microbiome relationship with pain

Based on the above discussion of the involvement of peripheral inflammation and neuroinflammation in the generation of peripheral and central sensitization it appears that a better understanding of these inflammatory responses to noxious stimuli may be highly beneficial for the development of novel treatments. Recent evidence suggests that neuroinflammation, i.e. a local inflammation of tissue within the peripheral and central nervous system, characterized by infiltration of immune cells, activation of glial cells and production of inflammatory mediators, such as chemokines and cytokines, as well as neuroactive substances, plays an important role in the transition from acute to chronic pain, as well as in the persistence of chronic pain (Ho et al., 2020; Ji et al., 2014; White et al., 2005; Ellis and Bennett, 2013; Gao and Ji, 2010; Kawasaki et al., 2008). Neuroinflammation could be induced by altered C-fiber activity, aka neurogenic inflammation (Xanthos and Sandkuhler, 2014; Hathway et al., 2009) or local neurons in the spinal cord.

Whereas a large body of evidence exists in preclinical studies, there are still few human studies looking at the involvement of chronic neuroinflammation in chronic pain (Grace et al., 2021). The development of the translocator protein (TSPO) PET imaging has begun to fill this gap (Grace et al., 2021). TSPO can serve as a marker of neuroinflammation because this protein is dramatically upregulated in activated microglia and astrocytes. Using TSPO PET scanning 2 conclusions can already be drawn: (1) In chronic pain the frequency of painfulness is associated with a neuroinflammation of the lateral pathways (Albrecht et al., 2019a) and the suffering is related to neuroinflammation of the medial pathways (Albrecht et al., 2019b). (2) The neuroinflammation is somatotopically restricted, depending on the pain pathology. For example the neuroinflammation is restricted to the lumbar spine primary somatosensory cortex cortical representation in chronic low back pain (Loggia et al., 2015), in a ventrolateral aspect of the primary somatosensory cortex, compatible with the face area in migraine (Albrecht et al., 2019b), and in a large portion of the sensorimotor strip in patients suffering from widespread body pain (fibromyalgia) (Albrecht et al., 2019c).

The sympathetic and parasympathetic nervous system are involved in inflammation. The sympathetic system can be both pro-inflammatory or anti-inflammatory (Pongratz and Straub, 2014; Carr et al., 2003), whereas the parasympathetic nervous system is generally considered anti-inflammatory (Czura et al., 2003; Pereira and Leite, 2016). Modulation of the sympathetic and parasympathetic nervous system is used in pain management. Sympathectomies have been performed for neuropathic pain and CRPS, but a Cochrane meta-analysis concluded that surgical and chemical sympathectomy for neuropathic pain and CRPS is based on very little high-quality evidence. It results in about 50 % pain relief (Straube et al., 2010), but in some patients the same pain worsens or is replaced by an another kind of pain (Kapetanos et al., 2003). The meta-analytic evidence for sympathetic blocks in CRPS is equally unclear (O'Connell et al., 2016), and may benefit from a physiological approach, eg by selecting patients based on measures of autonomic nervous system functioning such as heart rate variability or galvanic skin responses.

Vagal nerve stimulation, which essentially modulates the parasympathetic nervous system has been applied for chronic pain as well, especially for fibromyalgia, pelvic pain, and headaches (Chakravarthy et al., 2015). Non-invasive vagal nerve stimulation has shown functional imaging confirmed (Zhang et al., 2021) and meta-analytic evidence to benefit migraine and episodic but not chronic cluster headaches (Lai et al., 2020; de Coo et al., 2019). Analgesia is potentially mediated by two mechanisms: (1) vagal afferents inhibit spinal nociceptive reflexes and transmission and (2) vagal nerve stimulation has strong anti-inflammatory properties (Chakravarthy et al., 2015). The involvement of the microbiome in the pathophysiology of chronic pain is currently investigated (Guo et al., 2019; Li et al., 2020), both for the painfulness and the suffering, such as anxiety and depression (Guo et al., 2019; Li et al., 2020). The microbiome's influence on neuroinflammation and thus central sensitization may be a worthwhile to further investigate, as this may also lead to novel therapies or preventive measures in the fight against chronic pain, such as nutritional or pharmacological approaches that can increase microbiota diversity (Nijs et al., 2020; Elma et al., 2020).

Epigenetic modulation of DNA expression in chronic pain may also be a worthwhile avenue of research in chronic pain, as there are many pharmacological and non-pharmacological approaches that could modulate the epigenetic influences on chronic pain. Several studies, mostly in animals, revealed that inhibitors of DNA methylation, activators and inhibitors of histone modification and modulators of miRNAs reverse a number of pathological changes in the pain epigenome, which are associated with altered expression of pain-relevant genes (Niederberger et al., 2017). Some pharmacological treatments for chronic pain exert their beneficial effect partially via epigenetic modifications, such valproate, celecoxib, amitriptyline, fluoxetine and opioids (Niederberger et al., 2017). N_2O (Bessiere et al., 2021) and ketamine (Potter and Choudhury, 2014) both modulate NMDA receptors, but their therapeutic effect may also involve epigenetic mechanisms, such as microRNA and methionine synthase regulation. But other drugs can influence epigenetic DNA and RNA changes, as have been shown in cancer research and psychiatry, and could potentially become repurposed for chronic pain treatment. Furthermore, specific epigenetic immunemodulators are being tested for pain, such as the histone deacetylases trichostatin A, vorinostat, givinostat, quisinostat and romidepsin, the histone acetyltransferase inhibitor anacardic acid, and the DNA methyltransferase inhibitors 5-azacytidine and decitabine (Niederberger et al., 2017).
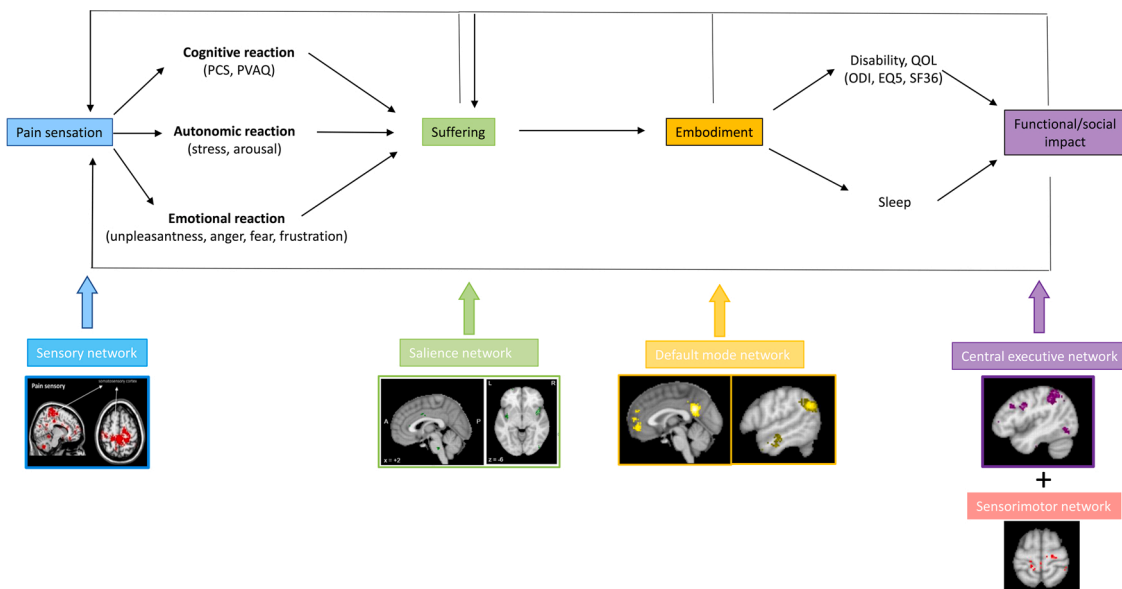
Fig. 11. The presence of a painful stimulus in the lateral somatosensory pathway, can lead to a cognitive, emotional, and autonomic response, encoded by the medial salience pathway expressed by suffering. When the pain and suffering become chronic, they become embodied, i.e., part of the self, mediated via connectivity of the somatosensory cortex to the default mode network. The embodied pain and suffering can subsequently lead to physical and cognitive disability, possibly mediated via dysfunctional connectivity with the motor and the central executive network, respectively.

Network science is commonly used to evaluate resting state networks in brain disorders, including chronic pain. This has shown that the default mode network is involved in chronic pain (Baliki et al., 2008, 2014; Alshelh et al., 2018), and it can be hypothesized that in chronic pain the default mode network, which controls self-representational processing may become pathologically connected to pain provoking networks (Pei et al., 2020), in keeping with Merleau-Ponty's above-mentioned concept (Merleau-Ponty, 1945). As such, the pain becomes embodied, i.e., an integral part of the self, thereby making treatments more difficult. When the suffering is chronic, the fear can turn into anxiety and the sadness into depression. This can lead to a decrease in quality of life and the development of pain associated disability, both physical and cognitive disability. It is proposed that each aspect of the pain is the result of connectivity changes between the lateral pathway, i. e. somatosensory network and another resting state network, such as the salience network (suffering), the default mode network (embodiment) and central executive network (cognitive disability) and motor network (physical disability) (Fig. 11). Changes in the sensorimotor, salience, default mode and central executive network have been shown in patients with failed back surgery syndrome (Kolesar et al., 2017), migraine (Yu et al., 2017) and low back pain (Pei et al., 2020), however these were not correlated to specific aspects of the pain. Chronic low back pain is characterized by hyperconnectivity of the primary somatosensory cortex to the default mode and executive control network (Pei et al., 2020). These connections between the somatosensory network and the salience network as well as the default mode are somatotopic, restricted to the homuncular cortical representation of the painful body area (Kim et al., 2019). Furthermore, increased connectivity between the default mode network and anterior insula of the salience network correlates with increasing pain (Kim et al., 2019). This progressive involvement of multiple resting state networks calls for studies that correlate specific clinical aspects of pain with activity and connectivity measures and predict that large scale studies including and lumping together patients with and without suffering, with and without embodiment of the pain and suffering and with and without disability, may not be able to reveal the involvement of these resting state networks. Thus, further clinically well documented patient populations may shed light on this approach of better understanding the supratentorial mechanisms involved in the different aspects of pain.

Furthermore, in a healthy state, the salience network, which overlaps with the medial pathway and the stress network is anti-correlated with the default mode network (Fox et al., 2005). In chronic pain this anti-correlation is lost (Hemington et al., 2016). Targeting the functional connections between the salience and default mode network could be a therapeutic avenue for treating chronic pain as well.

It is of interest that the salience network and the sympathetic central control overlap in the brain (Taylor et al., 2016), and the central component of the brain's parasympathetic nervous network partially overlaps with the default mode network (Babo-Rebelo et al., 2016). This could lead to a fusion of the abovementioned neuroinflammatory approach and a more network science-based approach and autonomic neuroscience approach. Thus, integrating systems neuroscience, autonomic nervous system science, network science and neuroimmunology could be a worthwhile avenue for gaining an integrated understanding of how acute pain becomes chronic and lead to novel treatment approaches.

12. Conclusion

Pain is processed by three separable but interacting networks, each encoding a different pain characteristic. The lateral pathway, with as main hub the somatosensory cortex is responsible predominantly for painfulness. The medial pathway, with as main hubs the rdACC and insula are involved in the suffering component, and the descending pain inhibitory pathway is possibly related to the percentage of the time that the pain is present. One may have pain(fullness) without suffering and suffering without pain(fullness). Chronic pain is likely the result of an imbalance between the ascending pain provoking pathways and the descending pain inhibitory pathways. This balance concept suggests that a combination therapy of different approaches may be the preferred way of treating chronic pain, on the condition that for each treatment it is known what pathway it predominantly modulates.

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