Understanding the relationship between chronic pain and emotional disorders

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Abstract

Although frequent coexistence of chronic pain and emotional disorders is well documented, exact mechanisms of comorbidity are not fully understood. The overarching aim of this thesis was to advance our knowledge of the mechanisms that link chronic pain and emotional disorders.

Results of the literature review suggest that nosologically different conditions might coexist if they share common transdiagnostic risk factors that predispose individuals to several disorders. Using this transdiagnostic approach, a theoretical model explaining the relationships between different risk factors and how they might contribute to comorbidity between chronic pain and emotional disorders has been developed. According to the proposed model, one of the most fundamental transdiagnostic risk factors associated with both conditions is uncontrollable stress. It does not cause chronic pain or emotional disorders directly but promotes development of other risk factors, such as helplessness, negative affectivity, hypersensitivity to pain, dysregulation of stress response, and cognitive deficits. Importantly, these risk factors are not disorder specific. They equally predispose individuals to depression, anxiety, and chronic pain. Development of a specific disorder is determined by the influence of environmental and biological moderators that transform pre-existing risk factors into specific disorders.

Considering that the sequence of pathological processes leading to psychopathology and/or chronic pain starts from the experience of uncontrollable stress, it is important to identify neural mechanisms that could mediate its effects. There is evidence suggesting that the frontal pole comprising of the rostromedial prefrontal cortex (rmPFC) and rostrolateral prefrontal cortex (rlPFC) plays an essential role in evaluation of controllability. Dysfunction of this area may increase the sense of uncontrollability, thereby promoting development of transdiagnostic risk factors. Both subregions of the frontal pole are parts of the neural networks that perform higher-order processing and modulation of nociceptive and emotional reactions. Thus, increased sensitivity to pain and heightened negative affect in

patients with chronic pain disorders might be mediated by impaired interaction of the rmPFC and rlPFC with low-level nociceptive and emotional circuits.

To test this hypothesis, resting-state functional and effective connectivity of the rmPFC and rlPFC was investigated in two chronic pain conditions: chronic low back pain (CLBP) and osteoarthritis (OA).

Functional connectivity (FC) of the rmPFC and rlPFC in CLBP. CLBP patients displayed decreased FC of the rmPFC with retrosplenial cortex (RSC), posterior part of the ventral pallidum (VP), and mediodorsal (MD) thalamus. Diminished interaction with these regions may hinder retrieval of positive episodic memories of control and attribution of positive outcomes to personal actions. This may negatively influence patients' belief about their ability to cope with stress, increase the sense of perceived uncontrollability. CLBP patients also showed reduced FC of the rmPFC with the medial pulvinar nucleus of the thalamus, midbrain reticular formation, and periaqueductal grey. These structures are parts of the ascending reticular activating system (ARAS) that regulates the level of arousal in the central nervous system. Reduced modulation of the arousal system by the rmPFC may result in development of a hyperarousal state and amplification of nociceptive and emotional responses leading to hyperalgesia and increased negative affectivity. There was no difference in FC of the rlPFC between CLBP patients and healthy controls.

Effective connectivity analysis in CLBP. Causal interactions between the rmPFC, stress-related brainstem structures (dorsal raphe nucleus, ventral and dorsal periaqueductal grey), and memory systems (ventral striatum, hippocampus, amygdala) were investigated using the spectral dynamic causal modelling (spDCM). Consistent with the results of the FC analysis in CLBP, the spDCM also found altered interaction between the rmPFC and memory systems. Specifically, patients showed weaker connectivity of the rmPFC with hippocampus and stronger connectivity with the amygdala. Such pattern of connectivity may lead to inaccurate evaluation of the probability of control based on past experiences, overgeneralization and impaired extinction of fears. Patients also demonstrated hyperactivation of the dorsal raphe

nucleus, ventral and dorsal periaqueductal grey (parts of the ARAS) that may contribute to hyperalgesia and increased negative affectivity.

Functional connectivity of the rmPFC and rlPFC in OA. In this study FC of the rmPFC and rlPFC was compared between patients with shorter duration of OA (<7 years), patients with longer duration of OA (>7 years), and healthy volunteers. Only patients with longer duration of OA showed increased negative FC of the rmPFC with multiple brainstem nuclei, such as the parabrachial complex, locus coeruleus, dorsal and median raphe nuclei, ventral tegmental area, midbrain reticular formation, and periaqueductal grey, that together comprise the ARAS. Negative FC between the rmPFC and ARAS may reflect increased compensatory inhibition of the activating system by the rmPFC in attempts to suppress pain-induced arousal and negative affect. Despite longer duration of pain, patients did not show signs of hyperalgesia or emotional distress. Perhaps, effective suppression of the brainstem arousal system demonstrated by OA patients was due to preserved connectivity between the rmPFC and memory systems. Both groups of OA patients also showed reduced FC of the rlPFC with the multiple demand network that may contribute to development of another transdiagnostic risk factor, i.e., cognitive deficit.

Results of all three studies presented in this thesis suggest that chronic stress may cause development of transdiagnostic risk factors such as negative affectivity and hyperalgesia via hyperactivation of the brainstem arousal system that augments nociceptive and emotional responses. Impaired regulation of the arousal system by the rmPFC, which evaluates controllability of the stress based on previous experiences, may contribute to hyperactivation of the ARAS. Reduced interaction between the rmPFC and memory systems may obstruct retrieval and utilization of positive memories of control, thereby increasing the sense of uncontrollability, facilitating hyperarousal, and contributing to development of transdiagnostic risk factors. In contrast, preserved connectivity between the rmPFC and memory systems may oppose the negative effects of chronic stress and help patients to maintain a belief that they are capable of coping with the stress.

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I. Literature review

1.0 Introduction

1.1 Pain taxonomy and classification

Definition of pain. The International Association for the Study of Pain (IASP) defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (Aydede, 2019). Pain is thought to be a protective biological mechanism that motivates organisms to withdraw from harmful situations, protect damaged body parts, and avoid painful experiences in the future. It is also a major symptom of many pathological processes in the body and one of the most common reasons to seek for medical help (Mäntyselkä et al., 2001).

Pain mechanisms. Pain syndrome can develop via several mechanisms. The IASP distinguishes "neuropathic", "nociceptive", and "nociplastic" mechanisms. Neuropathic pain is described as "pain caused by a lesion or disease of the somatosensory nervous system" (Trouvin and Perrot, 2019). Pain syndrome in diseases such as stroke, multiple sclerosis, and diabetes has a neuropathic mechanism of development.

Nociceptive pain is induced by pathological processes that affect tissues outside of the somatosensory system. The IASP defines it as "pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors." It is the most common type of pain that can be caused, for example, by inflammation as a result of infection or action of certain chemical and physical agents (Trouvin and Perrot, 2019).

Nociplastic mechanism has been proposed only recently (Kosek et al., 2016). The authors of the new term defined nociplastic pain as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain." The rationale behind the new descriptor is based on the existence of a group of chronic pain disorders that

cannot be fully explained by nociceptive (damage to non-neural tissue) or neuropathic (damage to somatosensory system) mechanisms. Pain disorders with poorly understood etiology and pathophysiology, such as fibromyalgia (FM), chronic regional pain syndrome (CRPS), non-specific chronic low-back pain (CLBP), irritable bowel syndrome (IBS), and other "functional" visceral pain disorders, are suggested to have the nociplastic mechanism of development (Kosek et al., 2016). According to the authors, pain syndrome in these disorders is a result of altered processing of nociceptive signals due to pathological changes in structure, function, and connectivity of certain brain regions involved in pain processing. Notably, disorders with initial nociceptive mechanism of pain, such as osteoarthritis, may later develop additional nociplastic mechanism caused by accumulation of pathological changes in the brain. The main clinical manifestation of nociplastic mechanism is hypersensitivity to pain. However, the authors also admit that it is difficult to differentiate normal sensitivity from hypersensitivity as even in healthy individuals there is a significant variance in pain sensitivity (Kosek et al., 2016).

Acute and chronic pain. Regardless of the mechanisms, pain can also be classified into acute and chronic forms. The temporal border between acute and chronic pain is arbitrarily taken to be 3 months, which is consistent with temporal cut-offs of other chronic pathological conditions (Treede et al., 2015). Such differentiation is necessitated by many clinical and physiological differences between short-lasting and prolonged pain (Tracey and Bushnell, 2009). Acute pain, in comparison with chronic pain, is more directly related to tissue damage, serves useful protective and warning functions. It gradually recedes during the healing process (Grichnik and Ferrante, 1991). However, in some patients pain may outlast the healing time and persist despite the absence of recognizable tissue damage. Phantom limb pain (Kikkert et al., 2018) and complex regional pain syndrome type 1 (CRPS 1) (Goh et al., 2017) are vivid examples of such pain. Although in some chronic diseases, such as rheumatoid arthritis (RA), persistence of pain may be partly explained by progression of the pathological process, the severity of pain and the level of pain-related distress may become disproportionate to the actual damage (Wolfe et al., 2014). Chronic pain in its late phases may lose the association

with the underlying cause and no longer serve its useful function (Raffaeli and Arnaudo, 2017). Therefore, chronic pain was previously described by the IASP as "pain without apparent biological value that has persisted beyond the normal tissue healing time".

Recently, it has been suggested that such definition of chronic pain is more applicable to pain after surgery or trauma where the normal tissue healing time can be approximately estimated (Treede et al., 2019). However, it is less suitable for other conditions (e.g., chronic headache, osteoarthritis) where the healing process per se is difficult to define. Consequently, it is not quite possible to measure the normal healing time for such disorders (Treede et al., 2019). In addition, in some chronic pain disorders, such as osteoarthritis, pain may still play a protective role as it, for example, limits the ability to perform physical activities that may cause additional harm to already damaged tissues (e.g., long-distance walking, running) (Lamb et al., 2000). There is also an opinion that the biologically useful function of chronic pain, from the evolutionary perspective, is to maintain a state of hypervigilance for threat. Such hypervigilance can be helpful for survival as it compensates for increased vulnerability due to functional limitations, especially after disfiguring and disabling injuries (Walters and Williams, 2019). Therefore, the IASP has omitted the concepts of healing time and biological value from the latest definition. Now, it is based purely on the temporal criterion: chronic pain is a pain that lasts or recurs for longer than 3 months (Treede et al., 2019).

Classification of chronic pain disorders. Prolonged experience of pain is marked by many functional, structural, and neurochemical changes in the central and peripheral nervous systems (Henry et al., 2011; Tracey and Bushnell, 2009). Growing evidence of such changes has convinced some of the researchers to consider chronic pain as an independent disease state where pain is caused by dysfunction of the nervous system (Fine, 2011; Tracey and Bushnell, 2009). In line with this idea, the American Academy of Pain Medicine has proposed a new terminology for pain: "eudynia" and "maldynia" (Dubois et al., 2009). The term "eudynia" translates as "good pain" and refers to pain as a symptom of an underlying somatic disorder. Chronic intractable "eudynia" may eventually

transform into “maldynia” (“bad pain”) – a separate disease process that occurs as a result of pathological changes and malfunction of the neural systems involved in pain processing. However, the pain-as-a-disease theory has been criticized for its weak conceptual foundation and for the absence of unique set of symptoms that would establish chronic pain as a separate disease (Cohen et al., 2013). It is not quite clear how to differentiate between “good” and “bad” pain. Various changes in the brain associated with chronic pain may represent the effects of pain itself, but they may also reflect adaptive processes or pre-existing biological and psychological features that predispose to persistence of pain (Cohen et al., 2013; May, 2011).

Despite the ongoing debate, a separate diagnostic code has been assigned to chronic pain in the 11th International Classification of Diseases (ICD-11) (Treede et al., 2015). According to the new classification, chronic pain is now divided into primary and secondary pain syndromes. Chronic primary pain category consists of diagnostic entities with poorly understood etiology and pathophysiology, such as fibromyalgia (FM), migraine, chronic low back pain (CLBP), irritable bowel syndrome (IBS), and others. Importantly, chronic primary pain is now considered as a disease in its own right with a nociplastic mechanism of development (Nicholas et al., 2019; Treede et al., 2019). This category is further subdivided into chronic widespread pain (e.g., FM), complex regional pain syndrome, chronic primary headache or orofacial pain (e.g., migraine), chronic primary visceral pain (e.g., IBS), and chronic primary musculoskeletal pain (e.g., CLBP). Diagnostic criteria for chronic primary pain disorder include: 1) persistence or recurrence of pain for longer than 3 months, 2) presence of significant emotional distress (e.g., anxiety, depression) and/or functional disability, and 3) absence of the evidence suggesting that pain is better accounted for by other diagnosis (Treede et al., 2019).

Chronic pain that can be attributed to some underlying medical condition (e.g., cancer, trauma, infection) is classified as a chronic secondary pain syndrome. If, for example, a patient diagnosed with cancer additionally suffers from persistent pain caused by the tumour itself or by its treatment, a second diagnosis of chronic secondary cancer-related pain will be added to the first cancer diagnosis. If cancer was successfully treated, but chronic pain remained, such condition will be coded as

chronic secondary cancer-related pain alone. The diagnosis of secondary pain disorder may change to primary pain disorder after development and persistence of significant emotional distress or occurrence of apparent dissociation between the extent of the actual tissue damage and clinical characteristics of pain, for example if pain appears in body parts that were not affected by the underlying disease. The severity of primary and secondary pain, relevant psychosocial factors (such as catastrophizing, fear, avoidance, impact on work or social relationships) are also included into the diagnosis (Treede et al., 2019).

Introduction of primary and secondary chronic pain syndromes, inclusion of pain intensity, emotional distress, and functional limitations as well as psychosocial factors into the diagnosis are expected to promote multimodal treatment and improve pain research due to more accurate grouping of study participants. Addition of chronic pain into the ICD also reflects a growing acknowledgment of the burden that chronic pain disorders impose on society and individuals (Treede et al., 2019).

1.2 The impact of chronic pain

Chronic pain is a frequent condition affecting approximately 20% of the population worldwide (Goldberg and McGee, 2011). Although most of the diseases associated with persistent pain are not immediately life-threatening, there is evidence suggesting that chronic pain patients have increased risk of cardiovascular pathology and mortality (Andersson, 2009; Torrance et al., 2010).

Significant functional limitations caused by chronic pain make it a leading source of disability in the world (Rice et al., 2016). Due to high national and individual expenses associated with disability and treatment, chronic pain has become one of the most economically burdensome medical conditions (Gaskin and Richard, 2012). In addition, people with chronic pain are 30% less productive and absent from the workplace 40% more often than individuals without it (Mesas et al.,

2014). 10-20% of patients eventually lose their jobs because of chronic pain condition (de Buck et al., 2006; de Sola et al., 2016).

Income-related problems, physical limitations of chronic pain patients negatively affect their social status, personal relationships, and mental health (de Sola et al., 2016; McCarberg et al., 2008). Diminished sense of perceived self-efficacy (personal judgment of one's ability to cope with adversities) due to pain-related disability promotes development of depressive symptoms (Turner et al., 2005). Financial and physical dependence very often leads to the sense of worthlessness which has also been strongly associated with depression and suicidal ideation (Jacobi et al., 2003; Kowal et al., 2012). It has been estimated that chronic pain patients have nearly two times higher risk of death by suicide (Tang and Crane, 2006). Chronic pain is also linked with increased risk of major depressive disorder (MDD), dysthymia (DYS), anxiety disorders, substance abuse disorders as well as cognitive impairments, sleep and sexual disorders (Fine, 2011). Development of psychiatric comorbidities in addition to chronic pain can significantly obstruct effective management of chronic pain and amplify the negative socio-economic consequences (Bair et al., 2003).

1.3 The relevance of studying comorbidity between chronic pain and emotional disorders

Prevalence of depression among chronic pain patients is significantly higher than in general population. Magni et al. (1990) found that 18% of subjects with chronic pain also suffer from depression, whereas in subjects without chronic pain the prevalence of depression is 8%. Another population-based study reported similar rates (19.8 % in chronic pain vs 5.9% in pain-free population) and found chronic pain to be the strongest predictor of MDD (Currie and Wang, 2004). Interestingly, disorders with known underlying cause (secondary pain syndromes) have lower occurrence of depression than disorders with unknown etiology (chronic primary pain syndromes) (Bair et al., 2003). For example, MDD affects 13–42% of patients with rheumatoid arthritis (RA) (Margaretten et al., 2011) and 62–86% of

patients with fibromyalgia (Gracely et al., 2012). Nevertheless, results of multiple studies indicate that even in secondary pain disorders the rates of depression are higher than in general population (5-8%) (Bair et al., 2003).

Patients with a primary diagnosis of MDD very often complain of persistent pain too. In the study by Bair et al. (2003) the mean prevalence of concurrent pain disorder in patients with depression in psychiatric settings was 65%. Similar results were reported by Arnow et al. (2006) who investigated the prevalence of chronic pain in MDD patients in primary care settings. More patients with MDD had additional chronic pain disorder than those without MDD (66% versus 43%, respectively). Another large longitudinal cohort study has shown that depressive symptoms at baseline can predict future episodes of low back pain, neck-shoulder pain, and musculoskeletal pain symptoms (Leino and Magni, 1993).

Depression is not the only emotional disorder that often coexists with chronic pain. Demyttenaere et al. (2007) carried out 18 surveys in 17 countries with a total of 85 080 participating adults. Results of their research showed that, in addition to MDD, chronic pain is strongly associated with dysthymia, generalized anxiety disorder (GAD), agoraphobia, panic disorder (PD), social anxiety disorder (SAD), and post-traumatic stress disorder (PTSD). Prevalence of anxiety disorders among patients with primary and secondary pain disorders is also significantly higher than in general population (Fietta et al., 2007; McWilliams et al., 2003; Raphael et al., 2006).

Notably, clinical characteristics and negative socioeconomic consequences of chronic pain are substantially aggravated when pain coexists with emotional disorders. For example, anxiety and depression in chronic pain patients have been associated with more intense pain, longer duration of pain, greater functional limitations and disability (Bair et al., 2003; Berrahal et al., 2017; Sharma et al., 2016; Steiner et al., 2017). Also, comorbidity significantly increases health care utilization and overall cost (Sharma et al., 2016). For example, Engel et al. (1996) found that patients with coexistent CLBP and depression, compared with patients who suffered from chronic pain only, had more primary care follow-up visits, more pain–related radiographs, more pain medication refills, and higher total costs. Impairments in social functioning, higher unemployment rates among chronic pain patients also

significantly correlate with depression (de Buck et al., 2006; de Sola et al., 2016). Some researchers have suggested that depression has greater impact on outcomes of chronic pain than other clinical factors (Burton et al., 1995; Linton, 2000). A recent meta-analysis showed that emotional factors (such as anxiety and depression) and cognitive-behavioral risk factors (e.g., avoidance, catastrophizing) are better prognostic indicators for worse long-term physical functioning than pain-related factors (pain intensity, chronicity) (Tseli et al., 2019).

1.4 Summary and general aim

Chronic pain is a heterogeneous and highly disabling medical condition that negatively effects many aspects of patients' life and represents a significant burden for society and economy (Turk et al., 2011). There is still an ongoing debate on how to conceptualize chronic pain. Some investigators suggest that it should be put in the realm of a disease state (Tracey and Bushnell, 2009); others think that it is only a symptom of an underlying disease (Cohen et al., 2013). The latest classification of chronic pain conditions takes into consideration both accounts by introducing new concepts - chronic primary pain and chronic secondary pain (Treede et al., 2015). Primary pain, in contrast to secondary pain, is considered as an independent disease with a nociplastic mechanism of development characterized by altered nociceptive processing and hypersensitivity to pain. Significant emotional distress (e.g., depression or anxiety) is one of the criteria that defines primary pain and determines a possible transition from secondary to primary pain (Treede et al., 2019). Patients with both types of pain are at high risk of developing emotional disorders, however, the risk is higher for patients with primary pain (Bair et al., 2003; Demyttenaere et al., 2007). Coexistence of chronic pain and emotional disorders is characterized by increased pain sensitivity, greater functional limitations and disability, substantially aggravated negative socioeconomic consequences, and poorer outcome (Tseli et al., 2019).

Considering the relevance of comorbid emotional disorders for differential diagnosis of chronic pain conditions, negative influence of comorbidity on the

clinical and socioeconomic aspects of chronic pain, the overarching aim of the thesis is to advance our understanding of the mechanisms that contribute to the development of emotional disorders in chronic pain patients. More specifically, the following questions will be addressed further in the review:

1) Why chronic pain disorders often coexist with mood and anxiety disorders?
2) What are the mechanisms of comorbidity between chronic pain and emotional disorders?

2.0 The problem of comorbidity

2.1 Comorbidities between emotional disorders

Comorbidity of chronic pain with a wide range of mood and anxiety disorders raises important clinical questions: do they have independent pathways of development and, therefore, should they be treated separately; or, maybe, one condition is a consequence of another condition, if so, what disorder should be treated first; or is there a common underlying etiological mechanism, targeting of which may have therapeutic effects on both conditions. Adding to the complexity of the problem, chronic pain often coexists with several mood, anxiety and substance abuse disorders at the same time (Barry et al., 2016) making clinical management of such patients even more challenging. The problem of comorbidity is particularly significant in psychiatry where comorbidity is more the rule than the exception (Dell'osso and Pini, 2012). Perhaps, the mechanisms explaining the comorbidity within the group of mental health disorders could also explain the comorbidity between chronic pain and emotional disorders.

It is well-documented that anxiety disorders are usually accompanied by another anxiety or depressive disorder and rarely appear in isolation (Brown et al., 2001; Kessler et al., 2005). For example, Merikangas et al. (2003) followed a large cohort (N=4547) of patients with emotional disorders for 15 years and found that cases of anxiety or depression alone were relatively rare. Patients with a "pure" (i.e., no comorbidity) anxiety disorder at the baseline developed either depression

or combined anxiety and depression as the disorder progressed. Similar longitudinal study examined stability of anxiety disorders in 447 patients with pure panic disorder, agoraphobia, social anxiety disorder, and GAD over a 6-year period. Results showed that anxiety disorders have low longitudinal stability and high rates of transition between all diagnoses (Hovenkamp-Hermelink et al., 2016).

A cross-sectional study by Brown et al. (2001) examined 1127 patients with a principal anxiety or mood disorder and found that 55% of the patients had at least one additional current anxiety or mood disorder. 77% of them had a history of another anxiety or mood disorder experienced previously. Diagnoses with the highest overall comorbidity were PTSD, MDD, dysthymia (DYS), and GAD. Current comorbidity rates in specific phobias (SP), PD, and SAD were relatively low, however lifetime comorbidity rates were still quite high - 65%, 75%, and 72% for SP, PD, and SAD, respectively.

Clinical and epidemiological studies consistently report that mood and anxiety disorders have many overlapping symptoms (Möller et al., 2016; Preisig et al., 2001; Schoevers et al., 2003). A recent study by McElroy and Patalay examined a large clinical sample (N = 37,162) of children and adolescents diagnosed with either anxiety, depression, or specific phobias. Using a network analysis and community detection algorithm, the authors demonstrated weak clustering of symptoms into distinct communities and widespread cross-community associations, indicating considerable symptom overlap between anxiety, depression, and phobias (McElroy and Patalay, 2019).

Anxiety disorders and depression are also characterized by common dysfunctional cognitive processes, often referred to as cognitive vulnerabilities. For instance, Hong and Cheung (2015) conducted a meta-analytic structural equation modelling examining a relationship between cognitive factors most commonly associated with either major depression (i.e., ruminative style, pessimistic inferential style, and dysfunctional attitudes) or anxiety disorders (i.e., intolerance of uncertainty, anxiety sensitivity, and fear of negative evaluation). Results of the study showed that all cognitive factors were moderately to strongly correlated with each other suggesting that anxiety and depression have common dysfunctional cognitive processes (Hong and Cheung, 2015).

Collectively, all these findings have recently created a shift in conceptualization of mood and anxiety disorders from categorical to more transdiagnostic approach. Transdiagnostic approach implies that many emotional disorders share some core pathological processes that underlie frequent comorbidity and easy transition between the emotional disorders (Barlow et al., 2014b; Norton and Paulus, 2017). Studies trying to identify such fundamental factors involved in development of multiple disorders have become increasingly prominent in recent years (Barlow et al., 2014a; Norton and Paulus, 2017; Wahl et al., 2019).

2.2 Transdiagnostic approach to explain comorbidity

Transdiagnostic models of emotional disorders do not claim that all emotional disorders are identical, but rather focus on similarities and common factors present in many disorders (Norton and Paulus, 2017). One of the advantages of such approach is that intervention targeting a transdiagnostic factor may positively impact all of the disorders associated with that factor (Harris and Norton, 2018).

Many transdiagnostic models of emotional disorders have been proposed so far (Aldao et al., 2010; Barlow et al., 2014b; Cludius et al., 2020; Fairburn et al., 2003; Harvey et al., 2011; Norton and Paulus, 2017). Although all of them are transdiagnostic in nature, each model focuses on different factors, such as catastrophizing (Norton and Paulus, 2017), neuroticism/negative affectivity (Barlow et al., 2014b), emotion regulation (Hofmann et al., 2012), avoidance (Hayes et al., 2004), sleep disturbances (Harvey et al., 2011), and others.

However, the list of putative transdiagnostic factors is quite long and heterogeneous (Clark and Taylor, 2009; Dudley et al., 2011). Multiple studies have demonstrated that cognitive-behavioural factors such as selective attention and memory, recurrent memories, interpretation and expectancy biases, emotional reasoning, recurrent negative thinking (worry and rumination), certain metacognitive beliefs, thought suppression, experiential avoidance, safety

behaviours, intolerance of uncertainty, anxiety sensitivity, and perceived control are all involved in development of various anxiety and mood disorders (Harvey et al., 2004). Many psychobiological factors such as sleep disturbances, executive control deficits, dysregulated stress response, and emotion regulation deficits may be considered as transdiagnostic factors too (Sanislow et al., 2010). Several environmental factors such as sexual, physical and emotional abuse, especially during childhood, neglectful parenting, parental psychopathology have also been associated with many emotional disorders (Dozois et al., 2009; Maniglio, 2009). Thus, the diversity of transdiagnostic factors and little understanding of the causal relationships between them make it difficult to decide which of them should be prioritized and selected for targeted therapy.

Another limitation of many existing transdiagnostic models is that they do not fully address the problem of divergent trajectories, i.e., why the same transdiagnostic factor leads to one set of symptoms in one person and to different set of symptoms in another person (Nolen-Hoeksema and Watkins, 2011). For example, it is not clear how stress, which is related to many different disorders, including depression, anxiety, and alcohol abuse, contributes to development of depression in some people, anxiety in others, and alcohol abuse in others.

Considering these issues, Nolen-Hoeksema and Watkins (2011) proposed a heuristic for developing transdiagnostic models of emotional disorders. The authors have organized all transdiagnostic factors into those that are causally more distant from the onset of psychopathology – distal risk factors (e.g., congenital biological factors, history of childhood abuse); and those that are causally closer to the disorder – proximal risk factors (e.g., hypothalamic-pituitary-adrenal (HPA) axis dysfunction, neuroticism/negative affectivity, biased attention to threat, avoidance). Distal factors do not necessarily result in occurrence of psychopathology, they only contribute to the development of proximal factors which, in turn, may cause psychopathology. Possible mechanisms by which distal transdiagnostic risk factors lead to proximal processes include observational learning, classical and operant conditioning (Clarke et al., 2008), and formation of cognitive schemas (Cicchetti and Toth, 2004). For example, repeated childhood abuse (distal factor) may promote hypervigilance towards threat (proximal factor)

via negative reinforcement of hypervigilance, as it may be advantageous to stay alert in order to avoid potential abuse (mechanism connecting distal and proximal factors). Importantly, these distal and proximal factors are not disorder-specific. They are equally implicated in the development of many disorders.

The authors also proposed possible environmental and biological moderators that interact with proximal risk factors and determine what specific disorder may eventually occur. For example, individuals with high neuroticism (proximal factor) may be more likely to develop an anxiety disorder if their current environment is threatening and uncertain (LeDoux, 2000). Different types of threat may lead to different types of anxiety disorders. For example, people with social phobia frequently report having experienced traumatic social embarrassment prior to developing their phobias (McCabe et al., 2003). In contrast, neurotic individuals who had experienced a series of important losses, failures, or rejection may be more prone to develop depression than anxiety (Nolen-Hoeksema and Larson, 1999; Williamson et al., 2005). Several biological factors may also determine what symptoms are likely to occur. For example, hyperreactivity of the autonomic arousal system may contribute to development of anxiety (Roy-Byrne et al., 2006); or dysfunction of the reward circuitry may promote development of MDD (Höflich et al., 2019).

In summary, anxiety and mood disorders are highly comorbid conditions that have complex relationships. A growing body of evidence suggests that frequent comorbidity between emotional disorders is due to shared transdiagnostic risk factors, such as genetic abnormalities, personality traits, dysregulated stress response, cognitive biases, emotion regulation deficits, and many others (Aldao et al., 2010; Barlow et al., 2014b; Cludius et al., 2020; Fairburn et al., 2003; Harvey et al., 2011; Norton and Paulus, 2017). Several transdiagnostic models have been introduced so far, however, most of them do not consider causal and temporal relationships between the factors and do not explain why some people with same transdiagnostic factors may develop different disorders. Nolen-Hoeksema and Watkins (2011) have offered a heuristic that addresses these issues. As described in the previous section, chronic pain often coexists with anxiety and mood disorders suggesting that same transdiagnostic processes found in emotional disorders might

also be implicated in the pathogenesis of chronic pain disorders. In the next section the heuristic developed by Nolen-Hoeksema and Watkins (2011) will be used for development of a theoretical model that could explain the comorbidity between chronic pain and emotional disorders.

2.3 Transdiagnostic approach to comorbidity between chronic pain and emotional disorders

Several transdiagnostic models of chronic pain and emotional disorders have already been proposed. For example, Linton et al. (2013) suggested that avoidance, catastrophic worry, and suppression are the main transdiagnostic processes common between chronic pain and emotional disorders. Asmundson and Katz (2009) developed a shared vulnerability model that focuses on comorbidity between chronic pain and PTSD. According to their model, comorbidity with PTSD occurs when negative events both traumatic and painful in nature happen to individuals with certain psychological (high anxiety sensitivity, low perceived control) and biological (low threshold for alarm reactions) vulnerabilities. However, both suggested models do not elaborate on the problem of divergent trajectories described previously. Therefore, a model based on the heuristic proposed by Nolen-Hoeksema and Watkins (2011) could better describe transdiagnostic processes that may underpin the comorbidity between chronic pain and various emotional disorders.

Distal transdiagnostic risk factors. According to the heuristic, distal factors predict many disorders, but they are distant from the onset of psychopathology in probability and mechanism. Distal factors can be divided into biological and environmental categories. Biological factors are mainly represented by genetic predisposition to certain disorders that influence brain function or structure, thereby determining individual's development and interaction with the environment (Nolen-Hoeksema and Watkins, 2011).

Recently, Meng et al. (2020) examined genetic correlations of eight pain phenotypes (headache, facial pain, neck pain, back pain, abdominal pain, hip pain, knee pain, and pain all over the body) with depressive symptoms and neuroticism in

500 000 people from the UK Biobank database. Results showed that all pain phenotypes showed significant genetic correlations with each other. In addition, all pain phenotypes, except hip and knee pain, had significant and positive genetic correlations with depression and neuroticism (Meng et al., 2020). Another large twin study on the relationship between emotional disorders (MDD, GAD) and chronic pain disorders (FM, IBS, and migraine) also reported shared genetic vulnerability between these disorders (Kato et al., 2009).

The second group of distal risk factors consists of environmental adversities that can be collectively categorised as uncontrollable stress. These adversities include chronic childhood abuse, history of sexual, physical, or emotional abuse, and other traumatic events that had significant negative impact. Chronic uncontrollable stress has been reliably associated with many psychiatric disorders (Monroe, 2008). However, there is also a strong association with chronic pain disorders (De Benedittis et al., 1990; Ghosh and Sharma, 2010; Klenerman et al., 1995; Young Casey et al., 2008). For example, adverse childhood experiences, such as verbal and sexual abuse, parental psychopathology, and early parental loss, are predictive of pain-related medical conditions in adulthood (Sachs-Ericsson et al., 2017). Physical abuse regardless of the age when it was experienced is another distal risk factor associated with chronic pain (Ellsberg et al., 2008).

It is important to note that the presence of a distal factor does not guarantee subsequent occurrence of psychopathology or pain-related disorder. For example, not everyone with a history of childhood abuse eventually develops chronic pain or emotional disorder (Sachs-Ericsson et al., 2017). Several intermediate proximal factors caused by distal factors must occur before that.

Proximal transdiagnostic risk factors. Environmental adversities combined with genetic abnormalities may trigger certain interrelated psychological and biological processes that are more directly involved in causation of clinical symptoms. The above-mentioned study by Meng et al. (2020) found a strong relationship between genetic factors (distal risk factor), neuroticism (proximal risk factor), chronic pain, and depression. Neuroticism also referred to as negative affectivity, is a heritable personality trait characterized by a tendency to experience frequent and intense negative emotions in response to various sources of stress.

Increased negative emotionality of a neurotic person probably originates from hyperreactivity of the limbic structures (e.g., the amygdala) due to weaker top-down control of limbic circuits by prefrontal areas (Barlow et al., 2014a). Not only genetic but also environmental distal factors may contribute to neuroticism. For instance, experience of chronic uncontrollable stress, such as repeated abuse during childhood, correlates with neuroticism in adulthood (Gamble et al., 2006; Roy, 2002). Negative affectivity is a well-established proximal risk factor of anxiety and mood disorders (Barlow et al., 2014a). However, it has also been associated with development of chronic pain disorders, such as headache, neck or shoulder pain, back pain, and FM (Ashina et al., 2017; Bru et al., 1993; Malin and Littlejohn, 2012). Higher negative affectivity of chronic pain patients has been associated with greater disability, increased pain reactivity, greater suffering, and the use of passive pain-coping strategies (Kadimpati et al., 2015).

Another proximal transdiagnostic factor commonly associated with development of both chronic pain and emotional disorders is helplessness. Helplessness is a behavioural phenomenon that occurs in both humans and animals after being repeatedly exposed to uncontrollable stress. Exposure to uncontrollable stress and multiple unsuccessful attempts to escape it may result in passive behaviour (passive coping strategies) that reflects formation of a belief that one has no control over aversive events (Maier and Seligman, 2016). Importantly, such belief and behaviour initially formed in response to a certain type of uncontrollable stress generalizes over other types of stressors too. In addition to passive coping mechanisms, helplessness is characterized by development of anhedonia and anxiety or depression-like behaviour (Maier and Seligman, 2016). Experimentally induced helplessness is one of the strongest animal and human models of emotional disorders (Maier and Seligman, 2016; Wang et al., 2017). In the laboratory settings, helplessness model can produce 8 out of 9 symptoms of major depression specified in the Diagnostic and Statistical Manual of the American Psychiatric Association Fourth Edition (DSM-IV), with the only exception being suicidal thoughts (Maier and Seligman, 2016). A considerable number of studies have demonstrated the major role of helplessness as a risk factor for chronic pain and depression (Keefe et al., 1990; Samwel et al., 2006). Prospective studies on

patients with rheumatoid arthritis also support this idea indicating a strong predictive value of helplessness for the level of pain, functional disability, depression, and even mortality (Callahan et al., 1996; DeVellis and Blalock, 1992; Smith et al., 1994).

Chronic uncontrollable stress, subsequent increase in negative affectivity and helplessness may contribute to overload and dysregulation of the HPA axis, which is a common feature of stress-related psychiatric disorders (Leistner and Menke, 2018; Rohleder et al., 2010) and chronic pain disorders (Hannibal and Bishop, 2014; Macedo et al., 2008; Vachon-Presseau et al., 2013). Multiple studies have found a strong correlation between childhood abuse (distal factor), dysregulated stress response in adulthood (proximal factor), and predisposition to emotional disorders (Doane et al., 2013; Heim and Nemeroff, 2001; Kuras et al., 2017). One of the key mechanisms underlying dysregulation of the HPA axis is impaired function of glucocorticoid receptors. Hyperactivity of the HPA axis due to repeated stress and maintenance of such hyperactivity by increased attention towards threat in neurotic individuals may result in reduced sensitivity of glucocorticoid receptors leading to abnormal concentrations and altered fluctuations of peripheral cortisol levels (Leistner and Menke, 2018). Diurnal rhythm of the HPA axis is flattened in both emotional (Gaffey et al., 2019) and chronic pain disorders (Heim and Nemeroff, 2001). Flattening of the diurnal rhythm can predict subsequent development of emotional (Doane et al., 2013) as well as chronic pain disorders (McBeth et al., 2007) in individuals who are at high risk suggesting that dysregulation of the HPA axis is a transdiagnostic proximal risk factor rather than a symptom of a disease.

Chronic uncontrollable stress and hyperactivity of the HPA axis with elevated cortisol levels may negatively impact cognitive functions, as prolonged hypercortisolemia is associated with structural changes in various brain regions (e.g., hippocampus and prefrontal cortex) involved in cognitive operations (Shansky and Lipps, 2013; Yuen et al., 2012). Basic cognitive abnormalities, such as deficits in attention, impaired memory processes, slower speed of information processing, and changes in executive functions, are all displayed by patients with chronic pain (Moriarty et al., 2011) and emotional disorders (Ferreri et al., 2011; Zuckerman et

al., 2018). However, cognitive deficits might exist even before the onset of chronic pain and emotional disorders. For example, a prospective study by Attal et al. (2014) on surgical patients showed that persistence of clinically meaningful pain at 6 and 12 months after the surgery can be predicted by poorer performance on cognitive flexibility and memory tasks. Similarly, there is evidence suggesting that cognitive deficits are already present in patients with the first episode of major depression (Lee et al., 2012) and in their first-degree relatives (MacKenzie et al., 2019). Cognitive impairments can predict increases in depressive symptoms (Letkiewicz et al., 2014) and persist beyond depressive episodes (Austin et al., 2001). Taken together, these studies support the idea that cognitive deficit might be a transdiagnostic proximal risk factor that predisposes to both chronic pain and emotional disorders.

Chronic stress has also a major impact on pain processing. Depending on the controllability, intensity, and duration of the aversive stimulus, nociceptive responding is either reduced (stress-induced analgesia (SIA)) or exacerbated (stress-induced hyperalgesia (SIH)) during and/or following exposure to stress (Ferdousi and Finn, 2018). SIA typically occurs following intense and acute stressful stimulus which triggers release of endogenous opioids. However, prolonged or repeated exposure to physical or psychological stress may result in 'exhaustion' of the analgesic effect and exaggerated nociceptive responding in animals and humans (Olango and Finn, 2014). Altered pain processing is present not only in chronic pain disorders (Kosek et al., 2016), but also in animal models of anxiety and depression (Bravo et al., 2012; Burke et al., 2010), and in patients with emotional disorders (Asmundson and Katz, 2009; Nitzan et al., 2019; Rhudy and Meagher, 2000; Zambito Marsala et al., 2015). Moreover, altered pain processing, specifically hyperalgesia, can be induced in healthy individuals without emotional disorders or chronic pain by subjecting them to uncontrollable psychosocial stress (Crettaz et al., 2013). Thus, altered pain processing is not necessarily a consequence of chronic pain or emotional disorder but might be one of the outcomes of uncontrollable stress, i.e., a proximal transdiagnostic risk factor.

Altogether, these findings suggest that chronic pain and emotional disorders indeed share many distal and proximal risk factors that may underlie frequent comorbidity and transition among these disorders.

Mechanisms connecting distal and proximal risk factors. Considering a strong relationship between stress and emotional disorders, genetic studies have focused on identification of specific genetic variants that determine individual reactions to stress. Caspi et al. (2003) found that polymorphism in the promoter region of the serotonin transporter (5-HTTLPR) gene moderates the effect of childhood maltreatment and stressful life events on the risk of depression. More than fifty studies tried to replicate Caspi's findings, but results have been contradictory (McGuffin and Rivera, 2015). For example, a meta-analysis by Karg et al. (2011) supports the hypothesis that 5-HTTLPR moderates the relationship between stress and depression. However, the most recent and larger meta-analysis of genetic data from 38802 subjects did not find such evidence (Culverhouse et al., 2018). Therefore, exact genetic mechanisms that connect distal and proximal risk factors are still largely unknown.

Besides hereditary mechanisms, observational learning of parental behaviour may also play important role in the development of proximal factors. Genetically determined maladaptive behaviours of parents with emotional disorders may be modelled or copied by their children (Eisenberg et al., 2010). Similarly, parental pain-related behaviours can be modelled by children and contribute to development of chronic pain disorders later in adolescence or adulthood. For example, in a study by Wilson et al. (2014) parental pain catastrophizing exclusively explained frequency of pain, somatic complaints, and pain-related disability in their children (Wilson et al., 2014). This is consistent with other findings suggesting that parental beliefs about pain may influence pain perceptions and beliefs about pain in their children (Vowles et al., 2010).

Another mechanism is a classical conditioning, which is an essential component of many theories of emotional disorders (Lissek et al., 2005; Nees et al., 2015). Conditioning is a learning process through which a neutral conditioned stimulus (CS) that was paired with aversive or rewarding unconditioned stimulus

(US) acquires the capacity to elicit emotional reactions (Pavlov, 2010). Many emotional disorders are characterized by facilitated fear conditioning. For example, in GAD, fear responses that were initially elicited only by a specific conditioned stimulus inappropriately overgeneralize to other perceptually similar stimuli. Such overgeneralization maintains neuroticism and increased attention to threat, which are proximal risk factors, by increasing the number of neutral stimuli able to trigger fear response (Lissek et al., 2014). Many theoretical models of chronic pain, such as the fear-avoidance model, also assign a central role to classical conditioning (Harvie et al., 2017). In such models, acute pain serves as an unconditioned stimulus, whereas various neutral stimuli repeatedly associated with pain, e.g., movement, are considered as conditioned stimuli that can elicit anticipatory fear. Similar to GAD, overgeneralization of fear of movement has been observed in chronic pain patients too (Vlaeyen and Linton, 2000). This mechanism plays important role in development of such proximal risk factors as experiential avoidance, hypervigilance, and negative affectivity (Vlaeyen and Linton, 2012).

Development of proximal transdiagnostic factors from distal factors is also mediated by cognitive schemas. Schemas are relatively stable structural representations of multiple past experiences that direct identification, interpretation, categorization, and evaluation of current experiences. It is an abstract gist of knowledge derived by extraction of regularities from multiple episodic memories and loss of more specific aspects of each event (Bowman and Zeithamova, 2018; Gilboa and Marlatte, 2017). For example, repeated abuse or threat may result in formation of threat-related schemas (e.g., “The world is a dangerous place” or “All people are untrustworthy”). Such schemas are often present in people with high negative affectivity (Barlow et al., 2014a). Repeated failures and losses may result in negative schemas about the self and future (e.g., “I am worthless” or “I will never succeed”) typical for depressed people (Clark and Beck, 2010). Interpretation of past or current events and prediction of future events are performed through the lens of existing cognitive schemas. Thus, negative schemas can bias towards negative interpretation of events. Negativity bias interferes with processing of schema-incongruent information, for example

information indicating safety or possible positive outcome, thereby maintaining pessimistic inferential style, hypervigilance, selective attention to threat, experiential avoidance, and other proximal risk factors (Clark and Beck, 2010). In relation to pain processing, Lim et al. (2020) have demonstrated that repeated painful experiences can also be schematically represented in memory and that evaluation of subsequent painful stimulations is influenced by pain-related schemas. The authors also showed that evaluation of pain intensity is biased by schema-based threat predictions in people with high pain catastrophizing (Lim et al., 2020). Besides pain-related schemas, chronic pain patients often demonstrate cognitive schemas that are typical for depression or anxiety disorders. For example, Saariaho et al. (2012) found that in comparison with healthy controls, significantly larger group of chronic pain patients (without comorbid clinical anxiety or depression) displayed cognitive schemas of failure, dependency, incompetence, defectiveness, shame, and vulnerability.

To sum up, emotional and chronic pain disorders have many overlapping distal and proximal risk factors that may underlie frequent comorbidity between these conditions. The final major component of the heuristic is moderators that shape the vulnerability created by proximal transdiagnostic factors into specific symptoms.

Moderators of the effects of proximal risk factors. Moderators act upon proximal risk factors and direct them towards specific disorders. As mentioned previously, certain environmental conditions may determine whether individuals will experience depressive or anxiety symptoms. For example, threatening or uncertain circumstances (e.g., possibility to lose income) facilitate development of anxiety disorders, whereas experiences of loss (e.g., break up in a relationship) determine occurrence of depressive symptoms (Nolen-Hoeksema and Watkins, 2011). In relation to chronic pain disorders, various medical conditions with acute clinical pain as a main symptom (e.g., acute low back pain, OA, RA, injury, surgery, et cetera) (Mills et al., 2019) may be considered as moderators that lead to chronic primary or secondary pain disorder when combined with pre-existing distal and proximal risk factors. Acute pain does not always transform into chronic pain

disorder. For instance, a study by Klenerman et al. (1995) reported that approximately 10% of patients with an acute attack of low back pain develop a chronic low back pain 12 months later. The authors also found that risk factors such as passive coping strategies, personality traits, previous stressful life events are better predictors of chronification of pain than clinical or demographical factors (Klenerman et al., 1995). Similarly, Casey et al. (2008) found that cumulative traumatic past events, negative beliefs about pain, depressed mood in the early stages of a new pain episode significantly contribute to chronification of acute back pain. Even in diseases that cannot be completely cured, such as OA, not all patients have chronic pain syndrome. Hannan et al. (2000) found that only 47% of 319 people with radiographic changes corresponding to the 2-4 stage of knee OA have pain and only 61% of them had been diagnosed with OA by their clinicians. Altogether, these findings suggest that somatic diseases with acute pain are more likely to transform into chronic pain disorder if patients already have pre-existing distal and proximal transdiagnostic risk factors.

Biological factors may also predispose to development of specific disorders. For example, innate hyperactivity of the fight/flight system or dysfunction of the basal ganglia may promote PD (Del-Ben and Graeff, 2009) and OCD (Rauch et al., 2007) respectively. Innate or acquired dysfunction of the endogenous pain modulation system may contribute to chronification of acute pain in somatic disorders (Ossipov et al., 2014; van Wijk and Veldhuijzen, 2010). Considering that altered pain processing is a characteristic feature of primary pain disorders (Treede et al., 2019), dysfunction of the endogenous pain modulation system might be a biological moderator that determines development of primary pain disorders.

It should be noted that the same environmental or biological factors may act as either distal risk factors or moderators of proximal risk factors (Nolen-Hoeksema and Watkins, 2011). For example, chronic childhood abuse can be a distal risk factor that causes dysregulated stress response (Gonzalez, 2013) (proximal risk factor). But in individuals whose stress response is already dysregulated due to other distal factors (e.g., genetic abnormalities), abuse in adulthood may become a moderator leading to emotional disorder. In a similar way, a somatic disease (e.g., OA or RA)

with acute or episodic pain syndrome can either be a distal risk factor or moderator. Depending on the severity of a disease, its controllability by medications, presence or absence of certain socioeconomic factors (e.g., financial stability or social support), and effectiveness of coping mechanisms somatic disease may remain as a distal risk factor with only episodic or intermittent pain that does not cause significant disability and distress (Schaible, 2012). Alternatively, poor controllability of pain syndrome, negative socio-economic consequences of the disease may promote development of proximal risk factors, such as helplessness, neuroticism, dysregulated stress response, hyperactivity of the limbic system, and dysfunction of the endogenous pain modulation system, that would contribute to further progression of acute somatic disease into chronic pain disorder. Various adversities, for example traumatizing social stress, acting upon these proximal factors may result in development of a comorbid chronic pain and social anxiety disorder. Likewise, chronic social stress can be a distal risk factor that induces the same proximal risk factors, i.e., helplessness, neuroticism, dysregulated stress response, and hyperactivity of limbic system. In this case, occurrence of a painful somatic disease will act as a moderator of the proximal factors and lead to chronification of acute pain and comorbidity between social anxiety and chronic pain disorder. This is consistent with the findings that chronic pain can precede as well as follow the development of emotional disorders (Bair et al., 2003). Thus, chronic pain patients may develop various comorbid emotional disorders at different points in time depending on specific environmental or biological factors that increase the probability of a certain disorder.

2.4 Summary

Chronic pain patients often develop various psychiatric comorbidities, including MDD, DYS, GAD, SAD, SP, PD, PTSD, and OCD (Demyttenaere et al., 2007; Fine, 2011). Although emotional and chronic pain disorders have been traditionally viewed as separate nosological entities with distinct etiologies, emerging evidence suggests that they might share common transdiagnostic processes and risk factors

that form the basis for their comorbidity (Asmundson and Katz, 2009; Linton, 2013). According to Nolen-Hoeksema and Watkins (2011), all transdiagnostic factors can be categorized into distal and proximal risk factors depending on causal and temporal relation to the pathology they predict. Distal and proximal factors are not disorder-specific, they are associated with a wide range of disorders. Specific environmental, psychological, and biological moderators shape vulnerabilities formed by distal and proximal factors into specific disorders. Schematic model of the development of comorbidity between chronic pain and emotional disorders is presented in Fig.1. Comorbidity can develop via multiple pathways. For example, a person with a history of chronic childhood abuse or another uncontrollable stress (Distal factors box in Fig.1) may generalize multiple unrelated stressful experiences and unsuccessful attempts to avoid them into a cognitive schema (Mechanisms box in Fig.1) that he/she has little control over adverse events (Cicchetti and Toth, 2004). Such cognitive schema may result in helpless behavior (passive coping mechanisms), biased interpretation of various stressful situations encountered later in life in more negative way leading to high neuroticism (negative affectivity), dysregulation of the HPA axis activity and cortisol function (Clark and Beck, 2010; Gilboa and Marlatte, 2017; Maier and Seligman, 2016). Chronic stress and dysregulation of stress response can cause alterations in pain processing and cognitive impairments (Olango and Finn, 2014; Shansky and Lipps, 2013) (Proximal factors box in Fig.1). Further trajectory of a pathology depends on the interaction between specific environmental or biological moderators (Moderator Boxes in Fig.1) and proximal transdiagnostic factors. Various combinations of such moderators may result in various combinations of comorbidities. Moderators and consequent comorbidities can either be unrelated or connected with each other. For instance, occurrence of acute somatic disease or injury may shift the proximal factors towards development of chronic pain disorder. If a person does not have any other biological or environmental moderators that could cause additional comorbidities, then a person will suffer only from chronic pain disorder. Alternatively, having a chronic pain disorder could make patients' environment more uncertain as he/she might encounter income or employment related problems and concerns regarding one's future. Such circumstances may trigger

additional symptoms of anxiety. Later, patients' functional disability, loss of income, strained personal relationships may promote additional depressive symptoms. In this case, all three comorbid disorders (chronic pain, anxiety, and depression) are strongly interconnected. However, the moderators and respective comorbidities can also be causally independent from each other. For example, a person with a history of childhood abuse and all subsequent proximal risk factors may develop chronic pain disorder following, for example, a surgery. The same individual might later become a victim of abuse and develop a PTSD. In this case the trajectories of chronic pain and PTSD will be independent, only indirectly related to each other via common proximal factors.

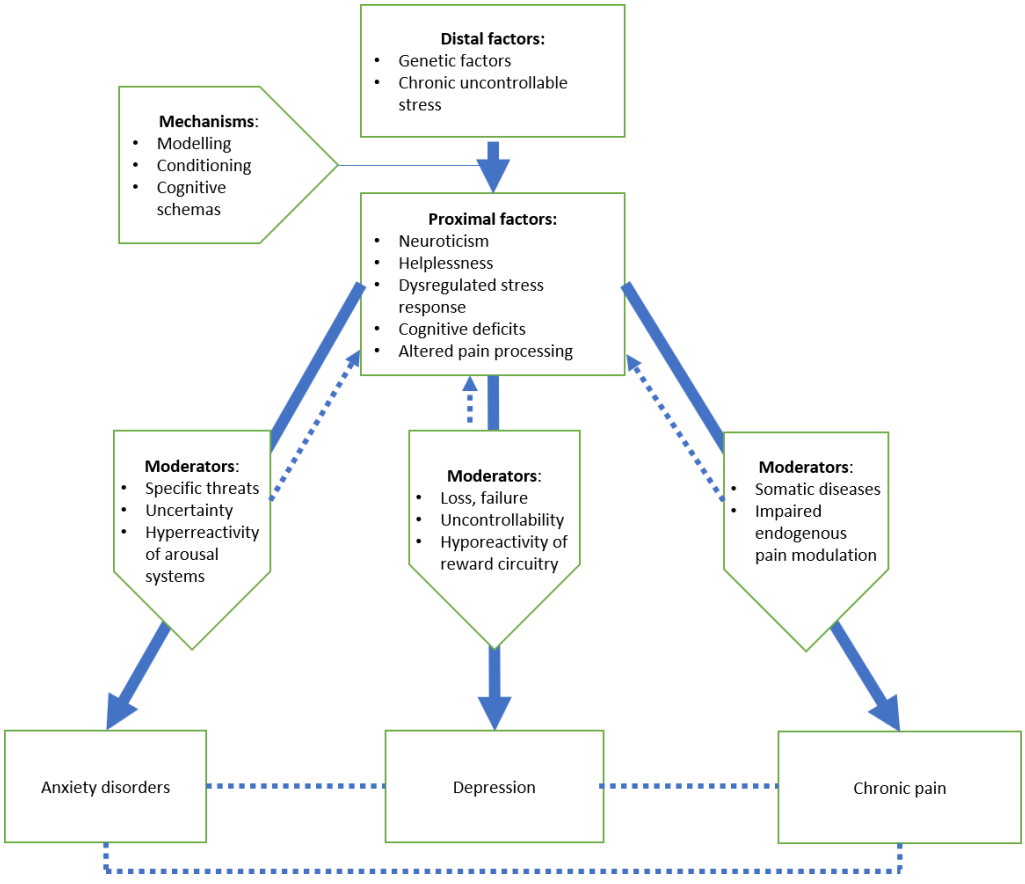


Figure 1. Transdiagnostic model of chronic pain and emotional disorders. Solid arrows indicate causal relationships between distal factors, proximal factors, and multiple disorders. Dotted arrows indicate a possible action of moderators specific for certain disorders on proximal risk factors. Dotted lines represent possible combinations of comorbidities.

Thus, distal and proximal transdiagnostic risk factors play important roles in the pathogenesis of both emotional and chronic pain disorders. Interventions

aiming to prevent development of proximal risk factors may be effective in prevention of chronic pain as well as emotional disorders. Therefore, it is important to identify neural mechanisms of pain and emotion that could also be involved in development of proximal risk factors.

In the next chapter will focus on the following questions:

1) What are the neural mechanisms of pain processing?
2) What are the neural mechanisms of emotions?
3) What brain structures and mechanisms involved in processing of pain and emotions might mediate between uncontrollable stress and proximal transdiagnostic factors?

3.0 Neural mechanisms of pain

3.1 Neuroanatomy of pain pathways

Typically, pain starts with the activation of specialized receptors (nociceptors) by painful (noxious) stimulus. There are two types of nociceptors: 1) high-threshold mechanoreceptors, which respond to mechanical input and 2) polymodal nociceptors, which react to a variety of agents, such as cytokines, bradykinin, prostaglandins, histamine, and leukotrienes, produced by various cells as a result of tissue damage or inflammation (Millan, 1999). These mediators connect to the nociceptors, activating and sensitizing them. Then, nociceptors convert noxious stimulation into action potentials that are carried via Aδ- and C-fibres towards the spinal cord. Cell bodies of these primary afferent nerve fibres are located either in the dorsal root ganglia or in the trigeminal ganglion and project to the dorsal horn of the spinal cord. Excitatory and inhibitory interneurons of the dorsal horn interact with each other allowing early modulation of pain already at the spinal level. In addition, the dorsal horn receives descending modulatory projections from the brain (Dubin and Patapoutian, 2010; Gangadharan and Kuner, 2013).

Ascending pathways. The axons of the second-order neurons of the dorsal horn transmit noxious information to the brain regions via multiple ascending pathways that have complex neuroanatomical organisation (Almeida et al., 2004; Millan, 1999; Willis and Westlund, 1997). They can be separated into two phylogenetically different systems. The first, older one, runs through the medial region of the brainstem and consists of the paleospinothalamic, spinoreticular, spinomesencephalic, spinoparabrachio-amygdaloid, spinoparabrachio-hypothalamic, and spinohypothalamic bundles. The other system, phylogenetically more recent, occupies the lateral region of the brainstem and consists of the neospinothalamic bundle, spinocervical bundle, and postsynaptic dorsal column pathway (Millan, 1999). Collectively, both systems carry noxious signals to the brainstem and diencephalon including the thalamus, periaqueductal grey, parabrachial region, reticular formation of the medulla, amygdaloid complex, septal nucleus, hypothalamus, and others (Almeida et al., 2004). Depending on cortical and subcortical areas they innervate, some of these pathways are involved in sensory-discriminative aspects of pain (intensity, location, pattern) others are associated with affective, cognitive, autonomic, or motor reactions to painful stimuli (Almeida et al., 2004; Millan, 1999). The thalamus is a key structure for processing noxious information. Axons of the lateral and medial tracts terminate in their respective medial and lateral thalamic nuclei and from here neurons project to the primary and secondary somatosensory cortices, insula, cingulate cortex, and prefrontal cortex (Almeida et al., 2004; Millan, 1999; Willis and Westlund, 1997).

Descending pathways. Descending pathways play an important role in modulation of nociceptive signalling. The modulatory circuit includes several cortical and subcortical areas such as the medial prefrontal cortex (mPFC), perigenual anterior cingulate cortex (pgACC), amygdala, and hypothalamus. All these structures project to the periaqueductal grey (PAG) in the midbrain which, in turn, sends projections to neurons of the nucleus raphe magnus and nucleus reticularis gigantocellularis in the rostral ventromedial medulla (RVM). Two neuronal subpopulations within the RVM known as “on” and “off” cells are thought to respectively enhance or inhibit nociceptive transmission changing the experience

of pain through their connections with the dorsal horn (Fields, 2004; Ossipov et al., 2010). It is thought that malfunction of this endogenous system may underlie some chronic pain states (Tracey and Bushnell, 2009).

To sum up, neuroanatomical studies suggest that experience of pain is a complex phenomenon involving multiple stages of processing in the peripheral and central nervous systems. Nociceptive information delivered by several ascending pathways is analysed in a distributed set of cortical and subcortical brain regions. The resultant subjective experience of pain can also be inhibited or facilitated by the descending modulatory system.

3.2 The pain matrix

Although the basic structures involved in pain processing have been identified, specific roles of multiple constituents of these pathways in pain processing remain obscure (Davis et al., 2015). Multiple theories of pain have been proposed so far, but none of them completely explains all aspects of pain perception (Moayedi and Davis, 2013). Pain was once considered to be a hard-wired system in which noxious information was transmitted by sensory pathways to a specific pain centre, whereas pain-related motivational, emotional, and cognitive phenomena were considered as separate reactions to pain (Garcia-larrea et al., 2013). Only in 1968, Melzack and Casey (1968) suggested that subjective experience of pain is a combination of interacting sensory, affective, and cognitive dimensions. Today, most of the researchers agree that there is no designated "pain centre'' and that perception of pain is a multidimensional phenomenon collectively produced by a distributed group of brain regions known as the pain matrix (Garcia-larrea et al., 2013). The key regions of the pain matrix are the thalamus (Th), primary and secondary somatosensory cortices (S1 and S2), insular cortex (IC), anterior and midcingulate cortices (ACC, MCC), and medial prefrontal cortex (mPFC) (Apkarian et al., 2005). Other cortical and subcortical regions like the posterior cingulate cortex (PCC), posterior parietal cortex, amygdala, hippocampal formation, PAG, ventral

tegmental area (VTA), nucleus accumbens (NAc), and cerebellum are also associated with the experience of pain, but activations in these areas are less frequently observed in pain inducing experiments (Bushnell et al., 2013; Navratilova et al., 2016).

Specific roles of different parts of the matrix are only partially understood. Although subjective experience of pain and objective intensity of noxious stimulation correlate with activity of the pain matrix (Bornhovd et al., 2002; Coghill et al., 1999), its main regions, such as the MCC, anterior insula, prefrontal and posterior parietal areas, can also be activated by innocuous stimulation in a wide range of experiments (Davis et al., 2015; Iannetti and Mouraux, 2010; Ploghaus et al., 1999). For example, activation of the pain matrix has been observed during social rejection experiments (Eisenberger, 2012) and in response to non-painful sensory stimuli (auditory, somatosensory, visual) (Iannetti et al., 2013). It has recently been demonstrated that many pain-responsive regions (including the MCC and insula) are activated by noxious stimulation in individuals with congenital insensitivity to pain (Salomons et al., 2016). Considering these findings, some investigators have strongly criticized the very concept of a specific pain matrix, claiming that most, if not all, of the regions represent a nonspecific salience-detection system, activated by salient, not necessarily noxious stimuli (Iannetti and Mouraux, 2010). However, more sophisticated methods using machine learning and multivariate pattern analysis have provided evidence that activity of the pain matrix (Th, pIC, aIC, S2, dACC, PAG, and other regions) in response to pain can be differentiated from the activity of the same regions in response to non-noxious stimuli (Wager et al., 2013).

3.3 The model of pain processing in the brain

Elaborating on Melzack's theory (Melzack and Casey, 1968), Garcia-Larrea et al. (Bastuji et al., 2016; Garcia-larrea et al., 2013) suggested that the pain matrix is a hierarchically organized network that performs processing of noxious signal in three consecutive phases or levels: nociceptive, perceptive-attentional, and reappraisal-emotional. Accordingly, all regions of the matrix can be separated into 3 interacting groups depending on their involvement in these phases of pain perception.

Nociceptive phase. During the first (nociceptive) phase, noxious stimulation activates the spinothalamocortical tract. Pain signal propagates from the dorsal horn to the posterior thalamus and from the thalamus goes to the posterior insula (pIC), somatosensory cortices, posterior mid-cingulate cortex (pMCC), and supplementary motor area (SMA). In parallel, nociceptive signal via the spinoparabrachial pathway also reaches the amygdala. Electrophysiological studies show that the earliest pain-related activity in the brain occurs in these regions (Bastuji et al., 2016; Garcia-larrea et al., 2013). Electrical stimulation of the pIC and inner operculum can trigger a sensation of pain (Mazzola et al., 2012, 2006). Conversely, lesion to this area may result in selective pain deficits (Garcia-Larrea, 2012). Similarly, pain can be triggered by stimulating thalamic regions projecting to the pIC and operculum (Lenz et al., 1995). Recently, Wager and Barret (2017) conducted a meta-analysis of studies reporting insular activations and found that the pIC, S2, and portions of the parietal operculum, are distinctly activated by pain (Wager and Barrett, 2017). First-level processing of nociceptive information starts simultaneously in the medial (pMCC, amygdala) and lateral (S2, pIC) nociceptive subsystems (Bastuji et al., 2016). Activation of the lateral subsystem is thought to represent encoding of the sensory-discriminative components of pain (location, intensity) (Talbot et al., 2019). Neural responses in the pMCC may represent an early reflexive motor reaction that orients body towards salient sensory stimulation (Vogt, 2016). The amygdala is responsible for initiation of autonomic reactions and processing of the affective component of pain (Bastuji et al., 2016). Thus, first-order

sensory-discriminative, orienting, and affective aspects triggered by nociceptive input are processed in parallel by the pIC/S2, pMCC, and amygdala respectively. However, the transition from cortical registration of noxious signal to full conscious experience of pain with multiple attentional-cognitive modulations requires recruitment of a second set of cortical networks (Garcia-larrea et al., 2013).

Perceptive-attentional phase. The next step of pain processing is performed mainly by the anterior insular cortex (aIC), anterior MCC (aMCC), and frontoparietal network represented by the dorsolateral prefrontal cortex (dlPFC) and posterior parietal cortex (PPC) (Garcia-larrea et al., 2013). Electrophysiological recordings show that this group of regions respond later than the first group. They are involved in attentional modulation and conscious perception of pain (Bastuji et al., 2016; Garcia-larrea et al., 2013). A posterior-to-anterior flow of sensory information within the insula reflects the transformation of sensory inputs into somatic reactions and associated internal feelings (Craig, 2002). It has been suggested that convergence of multimodal input in the most anterior portions of the insula contributes to emotional awareness and conscious perception. Therefore, the aIC may represent a core system that integrates affective and sensory information, and contributes to subjective feeling of pain (Craig, 2010). Results of the study by Bastuji et al. (2018) support this suggestion. Using intracranial recordings during nociceptive stimulation, the authors found that pIC and amygdala respond to painful input almost at the same time, whereas activation of the aIC appear later, suggesting that sensory information from the posterior insula and affective information from the amygdala converge in the anterior insular region. The dorsal part of the anterior insula is thought to be involved in direction of attention towards salient stimuli (Wager and Barrett, 2017). Anterior and posterior regions of the insula have bi-directional functional and anatomical connections (Bastuji et al., 2016; Garcia-larrea et al., 2013). Hence, attention to noxious stimuli driven by the activity of the dorsal aIC may enhance activity in posterior sensory regions (S2, pIC) and increase perceived intensity of pain (Wiech et al., 2008). Another area activated during the second phase of pain processing is the aMCC. The aMCC is thought to be

involved in preparation, implementation, and evaluation of potential or performed actions, such as avoidance or withdrawal (Vogt, 2016).

The second-order processing results in conscious perception of pain which may happen only when activity of the sensory regions is synchronized with a widespread cortical network consisting of frontal, temporal, and parietal areas (Bastuji et al., 2016). The frontoparietal network is crucial for consciousness (Bor and Seth, 2012). Functional coupling of stimulus-specific (sensory) areas with the frontoparietal network represents entry of sensory information into consciousness (Dehaene et al., 2006; Nani et al., 2019). Conscious perception of noxious information makes it available for high-level processes, such as cognitive appraisal, conceptualization, and memorization, that occur during the third phase.

Reappraisal-emotional phase. Finally, noxious information undergoes the reappraisal-emotional phase of processing associated with activations in the hippocampus, ventral posterior cingulate cortex (vPCC), mPFC, perigenual cingulate (pgACC), and rostrolateral prefrontal cortices (rlPFC) (Garcia-larrea et al., 2013). During this step, initial sensory, affective, motivational aspects of ongoing noxious stimulation are reappraised based on previous memories and various contextual factors. Such contextual reappraisal can significantly modulate the experience of pain. For example, in the study by Leknes et al. (2013) participants were asked to evaluate identical noxious stimuli in two different conditions – pain could be either the worst possible outcome (i.e., it was of the highest intensity) or the best possible outcome (i.e., it could be followed by even more intense pain). When pain was considered as the best possible outcome it was evaluated positively and even described as pleasant. Such reappraisal of pain was associated with activation of the mPFC, pgACC, and rlPFC (Leknes et al., 2013). Exact functions of these structures are not fully understood. However, there is evidence suggesting that the rlPFC regulates switching to alternative emotion regulation strategies (e.g., from avoidance to reappraisal) when the current strategy is inappropriate (Koch et al., 2018). The mPFC plays an important role in simulation of future events based on previous experiences (Addis et al., 2009; Dixon et al., 2017). The perigenual ACC is involved in evaluation of the relevance of interoceptive (including noxious) stimuli for well-

being based on personal or conceptual knowledge and contributes to subjective feelings of pleasure or displeasure (Dixon et al., 2017). Importantly, the perigenual cingulate and mPFC cortices, are functionally and anatomically connected with subcortical regions, such as the PAG. Together with the midbrain regions they participate in descending pain modulation (Leknes et al., 2013). The vPCC, which has strong connections with the hippocampal formation, is thought to be predominantly involved in supporting and retrieval of episodic and semantic memories, their maintenance in awareness, conceptual processing, and manipulation for the purposes of problem solving and planning (Leech and Sharp, 2014). Thus, reappraisal of the negative value of pain observed by Leknes et al. (2013) in the above-mentioned study can be schematically described as follows: 1) all previous episodes of pain induction were retrieved and maintained by the vPCC, 2) the mPFC using information from the vPCC predicted that pain could be worse, 3) the rlPFC provided alternative emotion regulation strategy (reappraisal instead of avoidance or suppression), 4) the pgACC reconsidered the value of current noxious sensation from negative to positive and inhibited nociceptive signalling in the dorsal horn via the PAG.

Altered pain processing in chronic pain disorders. It has been noted that in chronic pain conditions compared to acute or experimental pain conditions, pain is associated with stronger involvement of the regions involved in emotional and attentional/cognitive modulation of pain. In a study by Hashmi et al. (2013), brain responses to spontaneous pain were compared between the acute and chronic back pain groups. Brain activation pattern in the acute back pain was similar to the classical pain matrix, whereas in the chronic back pain group results showed greater involvement of emotional circuits including the amygdala and mPFC. Bilateral amygdala hyperactivation was also observed in FM patients with comorbid depression (Giesecke et al., 2005). Another study found that activity of the mPFC correlated with the severity of depressive symptoms and mediated the relationship between depression and the number of painful joints in RA patients (Schweinhardt et al., 2008). Collectively, neuroimaging studies suggest that increased negative affectivity in chronic pain is associated with altered activity of a number of brain

regions, most consistently the mPFC, pgACC, aIC, and amygdala (Wiech and Tracey, 2009). These regions are implicated in emotional and attentional modulation of pain via descending modulatory pathway through the PAG and RVM. Importantly, the PFC may exert both facilitatory as well as inhibitory effects on pain perception depending on context (Bushnell et al., 2013). For example, in the above-mentioned study by Leknes et al. (2013), the mPFC activation was associated with pain relief when pain was considered as best possible outcome. However, in another study Brascher et al. (2016) observed facilitatory influence of the mPFC when pain was perceived as uncontrollable.

3.4 Summary

Garcia-Larrea and Peyron (2013) have proposed a model (Fig.2) which suggests that the experience of pain is a result of 3 consecutive phases of processing. During the nociceptive phase, the posterior insula, somatosensory cortices, amygdala and pMCC process initial sensory-discriminative, affective aspects of nociceptive stimulus and trigger reflexive skeletomotor orientation to the stimulus. The second perceptive – attentional phase of pain processing is carried out in the middle, anterior insular cortices, aMCC, and frontoparietal circuits that determine integration of sensory and affective components, initiation of autonomic reactions, attentional modulation, initiation of action tendencies (withdrawal), and conscious perception. Finally, during the reappraisal-emotional phase, the hippocampus, vPCC, pgACC, mPFC, and rlPFC evaluate emotional significance of the sensation based on personal experience or conceptual knowledge and modulate (inhibit or facilitate) pain perception depending on this knowledge and contextual factors. Chronic pain, in contrast to acute pain, is characterized by greater involvement of the regions that are involved in emotional and attentional modulation of pain perception, such as the amygdala, aIC, pgACC, and medial PFC. Dysfunction of these regions is associated with such proximal transdiagnostic factors as increased negative affectivity as well as with altered pain modulation

leading to hyperalgesia (Bushnell et al., 2013). Thus, these are candidate regions that could mediate the development of proximal transdiagnostic factors.

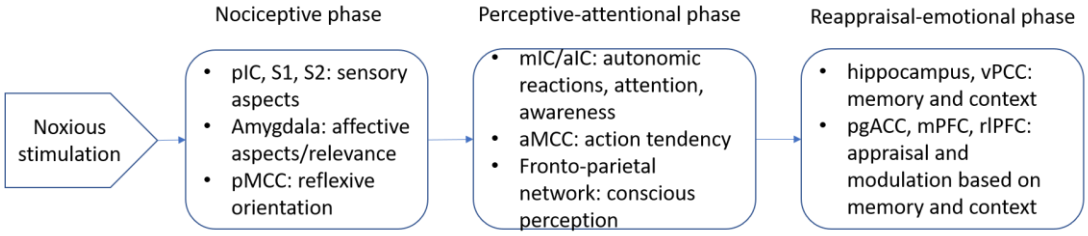


Figure 2. Schematic model of pain processing. pIC - posterior insular cortex; S1-S2 - primary and secondary somatosensory cortex; pMCC - posterior mid-cingulate cortex; mIC - middle insular cortex; aIC - anterior insular cortex; aMCC - anterior mid-cingulate cortex; vPCC – ventral posterior cingulate cortex, pgACC – perigenual anterior cingulate cortex; mPFC – medial prefrontal cortex; rlPFC – rostrolateral prefrontal cortex

4.0 Neural mechanisms of emotions

4.1 Theories of emotion

Despite decades of extensive research there is still an ongoing debate regarding the nature of emotional phenomenon, its structure, psychological and neural mechanisms, and even definition (there are more than 100 scientific definitions of emotion) (Dixon, 2012; Sander and Scherer, 2009). Over the last century, several psychological theories of emotion have been proposed (Sander and Scherer, 2009), including basic emotion theories (Ekman, 1992; Gu et al., 2019; Levenson, 2011), dimensional theories (Barrett, 2006; Posner et al., 2005), constructivist theories (Averill, 1980; Barrett, 2017; Lindquist, 2013), and appraisal theories (Ellsworth and Smith, 1988; Sander et al., 2018; Klaus R. Scherer, 2009)

According to the basic emotion theory, there are 4-8 kinds of basic emotions: happiness, joy, surprise, disgust, anticipation, sadness, fear, and anger, each associated with a prototypical behaviour and innate neural substrate (Ekman, 1992; Gu et al., 2019; Levenson, 2011). These basic emotions are differentially associated with three core affects: reward, punishment, and stress. Different

combinations of the three affects in various proportions result in more complex emotions (Gu et al., 2019).

Dimensional theory is similar to the basic emotion theory in that it postulates that each emotion results from the fusion of six basic forms of feelings: pleasure, displeasure, excitement, inhibition, tension, and relaxation. Later variants of the dimensional theory proposed that all emotions can be arranged in a circle controlled by two independent dimensions: hedonic (pleasure-displeasure) and arousal (rest-activated) (Barrett, 2006; Posner et al., 2005).

Constructivist theories, in contrast to the basic emotions theory, argue that discrete feelings, such as anger, happiness, fear, or sadness, are not independent entities with designated neural substrates for each emotion, but just different conceptualizations (or verbal labelling based on learning and culture) of changes in the single core affect. Constructivist approach suggests that the core affect is always present, similar to body temperature, but it can be altered by emotional events along its two dimensions—valence and arousal (Averill, 1980; Barrett, 2017; Lindquist, 2013).

Recent years have witnessed a heated debate between proponents of the constructivist and basic emotion theories. Lindquist et al. (2012) performed a meta-analysis of neuroimaging studies on emotions in healthy population in order to test whether there are brain regions that are consistently associated with specific emotions. The results of their study showed that discrete emotion categories cannot be consistently and specifically localized to distinct brain regions. Instead, they found that a set of brain regions such as the amygdala, insula, dlPFC, ventrolateral prefrontal cortex (vlPFC), orbitofrontal cortex (OFC), aMCC, subgenual anterior cingulate cortex (sgACC), anterior temporal lobe (ATL), PCC, and PAG are equally associated with all kinds of discrete emotions. In another meta-analysis Lindquist et al. (2016) looked at the neural correlates of positive and negative emotions in general and found that both positive and negative emotions are equally represented by the same distributed network of brain regions, i.e., there are no brain regions specifically activated by positive or negative emotions. According to the authors, both of their meta-analyses disprove one of the main postulates of the

basic emotion theory that each discrete emotion has its own neural signature (Ekman, 1992; Gu et al., 2019; Levenson, 2011), and support the constructivist theory according to which there is only one core affect collectively generated by the abovementioned brain regions (Barrett, 2006; Lindquist, 2013; Lindquist et al., 2015). On the other hand, there is evidence suggesting that it is possible to discriminate local and whole-brain patterns of neural activity that separately represent positive and negative valence as well as discrete emotional states, such as anger, fear, content, disgust, and others, using multivoxel pattern analysis (MVPA) and machine learning (Kragel and Labar, 2013; Kragel and LaBar, 2015; Saarimaki et al., 2016). However, such MVPA studies also showed inconsistent results regarding the exact localization of emotion-specific patterns at the voxel level despite some broad overlap at a larger spatial scale (Kragel and LaBar, 2016). Interestingly, Skerry and Saxe (2015) using the MVPA method have directly compared which of the major theoretical approaches to emotion better predict neural activity during the processing of emotional information and found that both basic and constructivist/dimensional approaches were outperformed by the appraisal theory approach (Skerry and Saxe, 2015).

Appraisal theories emphasize the role of cognitive appraisal in the process of emotion generation and regulation. According to this theory, emotional response occurs only when a stimulus or event is considered as relevant to one's goals, needs, and desires (Ellsworth, 2013; Klaus R Scherer, 2009). Relevance of an event is determined by a set of abstract criteria, called appraisal variables, that include expectedness, goal relevance, goal congruence, goal obstructiveness, causality, urgency, controllability, and other aspects. For example, an event is likely to elicit a feeling of anger if after several conscious or unconscious appraisal checks the event is considered as unexpected, having high goal relevance and goal obstructiveness, being caused by another person, having high outcome probability, high urgency, and being highly controllable. In contrast, the same situation will cause emotion of fear if a person makes similar appraisals with respect to relevance and obstructiveness but considers the situation as uncontrollable (Klaus R. Scherer, 2009). Appraisal of controllability plays important role in the development of

emotional disorders. For example, depression is characterized by consistent underestimation of one's ability to control negative events (Klaus R. Scherer, 2009).

Multiple possible combinations of appraisals determine multiple variants and gradations of emotions. It has been experimentally demonstrated that by changing certain aspects of an event, so that a person will appraise it in a certain way, it is possible to accurately predict what kind of emotion will be experienced (Klaus R. Scherer, 2009). Similarly, it has been shown that two apparently different events can cause identical emotions only if they yield the same appraisals (Gratch et al., 2015). Appraisal theory of emotion is considered as the most influential theory of emotion from the computational neuroscience perspective (Broekens et al., 2008). The next section will describe neural correlates of the appraisal model of emotion in more detail.

4.2 The appraisal model of emotions

Although most of the complex mechanisms of appraisal have been described at the psychological-cognitive level, appraisal theories are now starting to integrate neuroscientific findings and explain brain basis of emotion from their account (Brosch, 2013; Brosch and Sander, 2013; Sander et al., 2018). According to the appraisal theory, emotion can be divided into two major parts: emotion elicitation and emotional response. Emotional response, in turn, consists of four components: 1) expression, 2) autonomic reaction, 3) action tendency, and 4) feeling. Although precise underlying neural mechanisms of these components remain to be elucidated, it is possible to connect certain brain regions and circuits with each component based on already accumulated neuroscientific evidence (Brosch, 2013; Brosch and Sander, 2013; Dixon et al., 2017; Sander et al., 2018).

Simple perception of a stimulus or event is not enough to start an emotional response, some minimal cognitive processing is required to begin the reaction (Brosch, 2013). As mentioned previously, appraisal of the event serves to determine whether a perceived object or situation is relevant to the needs, goals, desires, and

values of an individual (Moors et al., 2013). There are several criteria that an object of appraisal should meet in order to elicit emotional response. Incoming sensory information (including interoception) and internally generated information (thoughts, memories) are constantly checked against these criteria. The appraisal process begins with detection of a change in the external or internal environment which then undergoes an iterative sequence of interpretation and reinterpretation (Cunningham et al., 2007). It may begin with a rapid and relatively coarse low-level appraisal, which is then continuously refined and adjusted by successive processing that takes into account additional information, such as context and past experiences. At the lower level, appraisals are based on prior learning of simple stimulus-outcome or stimulus-stimulus associations. At the higher level, events are evaluated in relation to current internal and external context, semantic knowledge, and autobiographical memory (Cunningham et al., 2007; Sharpe and Schoenbaum, 2016).

Low-level appraisal. It is thought that low-level initial appraisal processes are carried out by the amygdala together with other cortical and subcortical structures, such as the thalamus, hippocampus, and sensory cortices (Brosch, 2013; Y. Sun et al., 2020). Their role in appraisal of emotional stimuli has been extensively investigated in fear conditioning experiments. In such experiments, fear reaction to an innocuous stimulus (e.g., a tone) can be elicited if it has been previously paired with an aversive stimulus (e.g., a footshock). The amygdala plays an important role in conditioning process by binding together two streams of sensory information. Neurons carrying information about the innocuous stimulus and neurons conveying information about the painful stimulus converge on single neurons in the lateral amygdala causing synaptic plasticity that underpins formation of a memory that a given signal is associated with pain (Pape and Pare, 2010). There is evidence suggesting that this memory is initially held in the amygdala itself (Josselyn et al., 2015), but after consolidation, it is transferred to other regions, for example, to the sensory cortices (Cambiaghi et al., 2016). Sensory cortices are reciprocally connected with the basolateral amygdala. Inactivation of the sensory cortex after consolidation of a fear memory impairs the ability to recall the memory and

discriminate between frightening and neutral cues. When sensory cortices detect cues that were paired with aversive stimuli in the past, they trigger activation of the amygdala. Thus, synchronized activity of the sensory cortex and amygdala underlies retrieval of fear memories and activation of all associated physiological and behavioural reactions (Cambiaghi et al., 2016).

Already during the initial low-level appraisal, the amygdala through its connections with multiple systems initiates emotional responses. These responses include changes in action tendency, such as approach vs. withdrawal, physiological changes (e.g., heart rate, skin conductance, secretion of stress hormones), changes in motor expression (in face, voice, and body), and changes in subjective feeling (Brosch, 2013). Each of these elements of emotional response is supported by complex mechanisms and involve multiple regions. The anatomical substrates supporting changes in action tendency include the amygdala-motor cortex pathway, MCC, supplementary motor area (SMA), and basal ganglia (Peron et al., 2013; Sander et al., 2018; Vuilleumier, 2015). Physiological and endocrine reactions triggered by the amygdala are executed by the hypothalamus, cardiovascular and respiratory centres in the medulla oblongata, and other brainstem nuclei (Hopkins and Holstege, 1978; Masaoka and Homma, 2005; Venkatraman et al., 2017). Brainstem structures, such as the pons and PAG, are also implicated in automatic expression reactions (e.g., screaming during a sudden threat) (Holstege, 2014). Finally, the feeling component of emotion closely related to awareness and consciousness is poorly understood, however, there is evidence suggesting involvement of the insular cortex and its synchronisation with sensory areas and frontoparietal network (Nani et al., 2019; Sander et al., 2018). Early appraisals and initial physiological and behavioural reactions based on conditioned associations are then followed by more reflective and contextualized appraisals by higher order cortical regions. Reappraised information from the cortex is then fed back to subcortical regions to refine and regulate (inhibit or facilitate) initial appraisals and reactions (Cunningham et al., 2007).

High-level appraisal. It is suggested that higher-level appraisal and reappraisal processes take place in the association cortices, which are located

between sensory areas. Engagement of the PFC is essential for evaluation of events from multiple perspectives. Dixon et al. (2017) have proposed an 'appraisal-by-content' model of prefrontal functions according to which appraisals of different types of information are carried out in different subregions of the PFC.

According to this model (Dixon et al., 2017), the vmPFC together with the hippocampus and retrosplenial (RSC) cortex evaluates internally generated events, such as episodic memories, simulated future events, and predictions. Activation of the vmPFC during presentation of some external stimulus, may reflect an appraisal of the relevance of memories triggered by the stimulus for person's goals and tasks, rather than appraisal of the stimulus per se (Bechara and Damasio, 2005). The vmPFC is also involved in reconstruction of past events and prediction of future events based on past experiences (Addis et al., 2009; Andrews-Hanna et al., 2014). Thus, it may also evaluate how expected was the stimulus in comparison with such predictions.

In contrast to the vmPFC which assesses internally generated information, the lateral orbitofrontal cortex (lOFC) evaluates the relevance of external sensory information for current physiological needs or goals (Dixon et al., 2017). For example, food related stimulus presented to a hungry person increases activation in the lateral OFC. The same stimulus presented after satiation decreases the activation suggesting that activation of this area represents valuation process (Gottfried et al., 2003; Kringelbach et al., 2003). Lesions to the lateral OFC disrupt the ability to evaluate the pertinence of stimuli for current physiological needs (Murray and Rudebeck, 2013). All sensory areas send direct projections to the lateral OFC. It is also connected with regions that supply signals about current physiological needs, such as the amygdala, hypothalamus, and PAG (Petrides and Pandya, 2007). Additionally, connections with the lateral PFC (Petrides and Pandya, 2007) may provide information about task-related or long-term goals (Dixon and Christoff, 2014). Food presented to a hungry person might be negatively evaluated by the lateral OFC if the person is on diet. In this case, the context of a long-term goal to lose weight represented in the lateral PFC might modulate the appraisal process in the lateral OFC (Dixon et al., 2017).

The subgenual anterior cingulate cortex (sgACC) uses contextual information and past experiences to reappraise the usefulness of initial autonomic (cardiovascular, respiratory, metabolic) and neuroendocrine reactions that were triggered by the amygdala during initial appraisal (Dixon et al., 2017). This area has rich anatomical connections with regions that control physiological responses, including the dorsolateral PAG, several hypothalamic nuclei, lateral parabrachial nucleus, and the bed nucleus of the stria terminalis (Bandler et al., 2000; Drevets et al., 2008). Autonomic reactions to a given situation may be considered as appropriate if, in similar situations in the past, they were associated with a desirable outcome (i.e., avoidance of an aversive outcome, or acquisition of a rewarding outcome) (Dixon et al., 2017).

The perigenual anterior cingulate cortex (pgACC) is involved in processing of interoceptive information (Palomero-Gallagher et al., 2018). According to Dixon et al. (2017), it evaluates the importance of viscero-sensory (interoceptive) signals for one's well-being in accordance with personal experience and conceptual knowledge (Dixon et al., 2017). Appraisal of interoceptive sensations through the lens of one's personal and conceptual knowledge may modulate subjective feelings of pleasure and displeasure (Berridge and Kringelbach, 2011). For example, if some bodily sensations were associated with a disease in the past, current sensory signals coming from the same body area might be evaluated negatively, with stronger displeasure. Similarly, if a patient believes that a certain medication is effective, his/her symptoms (interoceptive signals) might become less unpleasant after taking that medication. Consistent with this, placebo analgesia and subjective relief from pain unpleasantness has been linked to changes in pgACC activation, and its functional connectivity with the amygdala and PAG (Bingel et al., 2006).

The anterior midcingulate cortex (aMCC), also often referred to as the dorsal anterior cingulate cortex (dACC), is involved in monitoring and appraisal of current actions, preparation of future actions based on anticipated outcomes, and in adaptive adjustment of behaviour based on the actual outcomes, current context, tasks, and long-term goals (Alexander and Brown, 2011; Ullsperger et al., 2014). The aMCC also evaluates the effort cost of actions, i.e., the number and difficulty of

actions needed to be performed in order to achieve the desired goal (Kurniawan et al., 2013; Rushworth et al., 2007). Various types of experiments with different designs and stimuli can elicit activation of the aMCC, in each case it may represent the appraisal of the congruence of performed actions with goals and context, evaluation of their effort cost, and planning of future actions if there is a mismatch between anticipated and actual outcomes (Alexander and Brown, 2011; Ullsperger et al., 2014). For example, activation of the aMCC in response to painful or threatful stimuli may reflect the process of appraisal and selection of action tendencies, such as approach or avoidance, preparation of defensive action plans and calculation of their effort costs (Dixon et al., 2017).

The dorsomedial PFC (dmPFC) is involved in appraisal of other people's unobservable intentions, thoughts, desires, and feelings depending on the situational context and one's own personal experience. Such appraisals help to understand the motives of other people and to determine whether their motives are likely to interfere with, or facilitate the goals of the observer (Brosch and Sander, 2013). The dmPFC is a part of the "mentalizing network" that also includes the angular gyrus and temporopolar cortex. Using abstract conceptual and social knowledge stored in these regions, the dmPFC enables a person to take the perspective of another person in a given situation and to infer their goals or intentions (Kestemont et al., 2015).

Although activity in the rostromedial prefrontal cortex (rmPFC) is frequently observed in studies of emotion (Lindquist et al., 2016), its specific role has remained poorly understood. However, there is evidence suggesting that the rmPFC plays an important role in explicit self-reflection (Murray et al., 2012; van der Meer et al., 2010). For example, when participants are asked to judge whether personality traits presented to them actually describe them, activity of the rmPFC positively correlates with the degree to which the traits are rated as self-descriptive (D'Argembeau et al., 2012). Thus, it might be involved in appraisal of the self-image, generation of self-concepts, and evaluation of the impact certain events have on the self-image. This has important implications for emotion regulation. For example, if fear is appraised by the rmPFC as contradicting to the self-image of a brave,

strong person, such appraisal could contribute to the initiation of emotion regulation processes to inhibit the fear (Dixon et al., 2017). Also, the rmPFC might be involved in appraisal of one's ability to control negative events based on contextual information or episodic memories of similar situations in the past. For example, in a study by Kerr et al. (2012) video clips of snakes were presented to people with snake phobia. In some trials, participants were able to control the presentation of a clip – a visual cue before the trial indicated that the following video of a snake can be avoided if participants press a button quick enough at the beginning of the trial. In other trials participants had no control over the presentation. The authors observed increased activation of the rmPFC that negatively correlated with activity of the amygdala only during the anticipation period of controllable trials (Kerr et al., 2012). These findings are consistent with the idea that the rmPFC is involved in evaluation of one's ability to control aversive events.

Finally, the lateral PFC, consisting of the rostrolateral, ventrolateral, and dorsolateral subregions, has a well-established role in cognitive control of behaviour based on rules, abstract concepts, context, and goals (Bunge et al., 2003; Miller and Cohen, 2001; Stokes et al., 2013). In relation to emotion regulation, the lateral PFC is thought to evaluate the relevance of current emotional state based on context, goals and to trigger emotion regulation processes if there is a mismatch between the goal and emotion (Dixon et al., 2017). Emotion regulation refers to implementation of different strategies (acceptance, avoidance, reappraisal, rumination, suppression, problem-solving) in order to start, stop, or modulate a certain emotion (Buhle et al., 2014; Ochsner et al., 2012). During emotion regulation the emotional reaction itself but not the emotion-provoking stimulus becomes the target of processing and modulation (Etkin et al., 2015). The dlPFC and vlPFC along with other regions of the frontoparietal network are thought to be involved in implementation and monitoring of the effectiveness of a chosen emotion regulation strategy (Koch et al., 2018). However, the outcome of an emotional control strategy may vary in different contexts. For example, reappraisal is more efficient in regulating low-intensity emotions, whereas distraction performs

better during high-intensity emotions. Successful emotion regulation requires the ability to flexibly switch between different strategies to meet contextual demands (Sheppes et al., 2014, 2011). It is suggested that the rostrolateral PFC, also known as anterolateral PFC, provides such flexibility by evaluating and accumulating evidence in favour of alternative strategies. In case the ongoing behaviour does not result in a desirable outcome, the rlPFC initiates switching to the best alternative course of action (Koch et al., 2018). New emotional control strategies may be created by the rlPFC based on internal models of previously learned behaviour that were successful in similar situations in the past (Koechlin, 2016). Thus, from the appraisal theory perspective, the lateral PFC as a whole evaluates the relevance, congruence, or obstructiveness of the current emotional state for personal goals, implements certain emotion regulation strategies if the emotion is unwanted and appraises possible alternative strategies when chosen strategies do not change the emotion (Dixon et al., 2017).

4.3 Summary

According to the appraisal theory (Brosch, 2013; Brosch and Sander, 2013; Sander et al., 2018), elicitation and regulation of the emotional response to a given event depends on comprehensive appraisal of many aspects of that event (Fig.3). Appraisal occurs at multiple levels of complexity, from simple conditioned associations to high-level contextual and conceptual appraisals (Cunningham et al., 2007). According to Dixon et al. (2017), initial low-level appraisals of the stimulus and early emotional responses initiated by such structures as sensory cortices, amygdala, or brainstem nuclei are reappraised from multiple perspectives and contexts simultaneously in various PFC regions allowing multifaceted evaluation of current event based on past experience, current context, and conceptual knowledge. Different subregions of the PFC are selectively involved in evaluation of specific types of information. Interacting with each other and with other cortical and subcortical structures, they contribute to different types of appraisal. For example, the rmPFC together with other regions of the default mode network, such

as PCC, is preferentially involved in appraisal of one's ability to control the event and the impact of the event on the self-image. The dmPFC together with the "mentalizing network" (angular gyrus, temporal pole) participates in appraisal of others' intentions, and compliance of personal goals with social norms. The vmPFC and regions of the memory systems (e.g., hippocampus) support the appraisal of expectedness. The lOFC evaluates the relevance of external stimuli for goals and physiological needs. The pgACC assigns value for interoceptive signals, such as pain, based on personal and conceptual knowledge. The sgACC evaluates the appropriateness of low-level autonomic and physiological reactions generated by the hypothalamus and medullary nuclei. The aMCC might be involved in appraisal of initial action tendencies based on context and memory. Whereas, the lateral PFC and frontoparietal network evaluate goal relevance of ongoing emotions and select appropriate emotion regulation strategies (Dixon et al., 2017). The appraisal model of emotion and the model of pain processing described previously are very similar in design (Fig.2 and Fig.3). In both models initial processing of the nociceptive and emotional signals is carried out in sensory areas and amygdala, whereas higher level appraisals and modulation are mainly performed by various prefrontal regions.

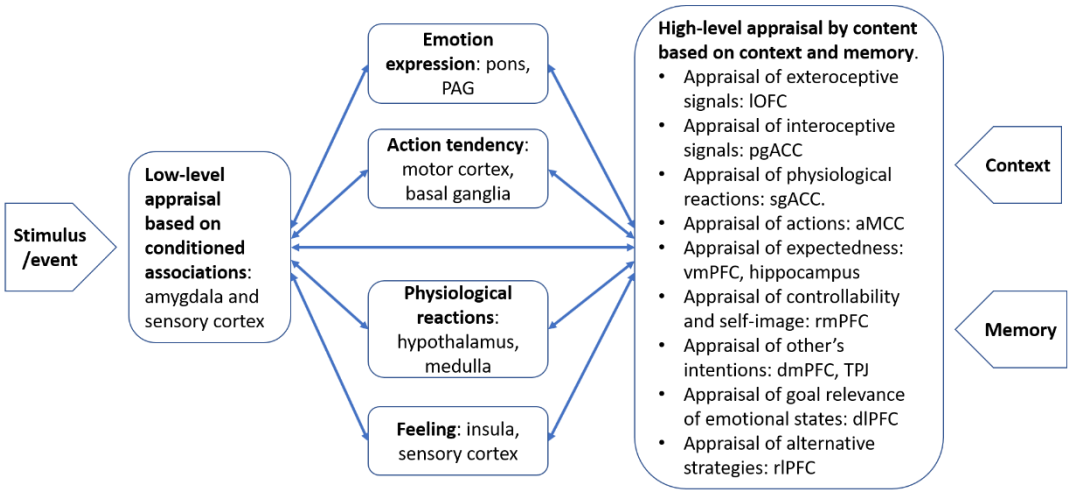


Figure 3. Schematic model of emotional processing. PAG – periaqueductal grey; lOFC – lateral orbitofrontal cortex; pgACC – perigenual anterior cingulate cortex; sgACC – subgenual anterior cingulate cortex; aMCC - anterior midcingulate cortex; vmPFC – ventromedial prefrontal cortex; rmPFC – rostromedial prefrontal cortex, dmPFC – dorsomedial prefrontal cortex; TPJ – temporoparietal junction; dlPFC – dorsolateral prefrontal cortex; rlPFC – rostrolateral prefrontal cortex.

5.0 Overview and general hypothesis

Chronic pain is a major public health problem that negatively affects almost every aspect of human life – from financial security to personal relationships (Turk et al., 2011). Patients with chronic pain are at high risk of developing psychiatric disorders, such as major depression and multiple anxiety disorders (Fine, 2011). Growing awareness of the harmful impact that chronic pain makes on health, society, and economy has urged a rigorous research of the problem.

There are still substantial gaps in understanding of the nature of chronic pain. However, accumulated evidence suggests that chronic pain conditions can be divided into two major groups that have supposedly different mechanisms of development (Treede et al., 2019). The first group, called chronic primary pain disorders, is mainly represented by chronic pain conditions with relatively unknown cause, such as FM, CLBP, CRPS. These disorders are thought to have a nociplastic mechanism of development (Kosek et al., 2016) characterized by pathological processing of pain leading to hyperalgesia. Another defining feature of primary pain is a significant emotional distress. The second group, called chronic secondary pain disorders, includes diseases with known etiology, such as OA, RA, cancer, trauma. These disorders may have either nociceptive or neuropathic mechanism of development. In either case, a causative agent of pain can be identified. Hyperalgesia and emotional distress are not characteristic to secondary pain disorders, however, prolonged duration of a secondary pain and aggregation of functional as well as structural changes in the brain may alter pain processing mechanisms leading to dissociation between the level of pain and the degree of tissue damage, in other words, a secondary pain disorder may transform into primary pain disorder (Kosek et al., 2016; Nicholas et al., 2019; Treede et al., 2019).

A large number of studies have confirmed a significant role of emotions in pain processing (Bushnell et al., 2013). In general, negative emotions exacerbate experience of pain, whereas positive emotions have opposite effect. Unfortunately, chronic pain disorders frequently coexist with various emotional disorders, such as MDD, DYS, GAD, SAD, SP, PD, PTSD, and OCD (Arnow et al., 2006; Bair et al., 2003;

Demyttenaere et al., 2007). Prevalence of emotional comorbidities in primary pain disorders is higher than in secondary pain disorders, however, in secondary pain disorders the prevalence is higher than in general population. Comorbidity can significantly aggravate severity of chronic pain and substantially worsen socioeconomic consequences (Engel et al., 1996; Tseli et al., 2019). The relationship between chronic pain and emotional disorders seems to be bidirectional, i.e., chronic pain may precede the onset of an emotional disorder and vice versa (Bair et al., 2003).

The problem of comorbidity poses serious challenges for conceptualization, classification, modelling, and treatment of coexisting disorders (Norton and Paulus, 2017). A growing number of researchers are now suggesting that rather than viewing emotional disorders as distinct entities, they better fit a transdiagnostic model (Barlow et al., 2014b; Harris and Norton, 2018; Nolen-Hoeksema and Watkins, 2011). Considering high comorbidity between chronic pain and emotional disorders (Arnow et al., 2006; Bair et al., 2003; Demyttenaere et al., 2007), several authors have also introduced transdiagnostic models of chronic pain and emotional disorders (Asmundson and Katz, 2009; Linton, 2013). Transdiagnostic models suggests that coexistence of different disorders occurs due to common factors and pathological processes shared by these disorders. However, most of the transdiagnostic models do not fully address the problem of divergent trajectories - why some people with the same transdiagnostic factors may develop different disorders. Considering these issues, Nolen-Hoeksema and Watkins (2011) have proposed a heuristic for developing transdiagnostic models of comorbid disorders.

Application of their heuristic to chronic pain and emotional disorders shows that these conditions, indeed, share many distal and proximal risk factors and mechanisms that may underlie their comorbidity. Common distal transdiagnostic factors include genetic predisposition and chronic uncontrollable stress, such as sexual, physical, and emotional abuse in childhood or adulthood. These distal factors via several mechanisms (e.g., conditioning, modelling, and cognitive schemas) may induce development of common proximal risk factors, such as neuroticism/negative affectivity, helplessness, dysregulated stress response,

cognitive deficits, and altered pain processing. These factors, in turn, are more directly involved in the pathogenesis of both emotional and chronic pain disorders. Occurrence of a specific disorder depends on the nature of the moderators (environmental or biological factors) that act upon existing proximal risk factors and shift the trajectory towards a specific disorder. Threatening and uncertain circumstances increase the likelihood of anxiety disorders, experiences of loss and failure promote depressive disorders, medical conditions with acute pain predispose to chronic pain disorders. High rates of current and lifetime comorbidity between chronic pain, depression, or anxiety might be due to the influence of different moderators on the same risk factors simultaneously or at different points in time. For example, recurrent physical or emotional abuse during childhood may lead to helplessness (a belief that one has little control over aversive events). If a person with such trait experiences a painful medical condition, he/she may later develop a chronic pain disorder. If, instead of the medical condition, one experiences social stress, he or she may develop social phobia. Simultaneous existence of chronic pain and social phobia may occur if both types of stressors act at the same time.

Thus, transdiagnostic factors play a pivotal role in the pathogenesis of both emotional and chronic pain disorders. Having a "pure" chronic pain disorder without any comorbid emotional disorder means that appropriate moderators that could have induced development of emotional disorders have not been encountered yet, but distal and proximal risk factors that predispose to mood and anxiety disorders are already present. Targeting such transdiagnostic factors and mechanisms of their development may be an effective strategy for treatment and prevention of chronic pain as well as emotional disorders. Therefore, it is important to identify neural mechanisms of nociceptive and emotional processing that could also be involved in development of transdiagnostic factors.

Pain is a complex phenomenon consisting of sensory, motivational, cognitive/attentional, and emotional components. According to Garcia-Larrea and Peyron (2013), noxious stimulation undergoes several levels of processing. During the first level, sensory-discriminative aspects (location, intensity) are processed by

the pIC, operculum, and S1-S2 regions. These regions store memories of previous painful experiences and by comparing current stimulus with previous experiences contribute to evaluation of the relevance of the stimulus. In parallel, early emotional and motivational appraisals of pain are performed by the amygdala and MCC respectively. The amygdala detects the relevance of the stimulation, whereas MCC initiates reflexive body orientation towards stimulation. During the next level, sensory-discriminative and emotional aspects converge in the anterior insular cortex, which is thought to be involved in conscious perception and attentional modulation of pain. Preparation of avoidance or withdrawal tendencies are represented by the activity of the aMCC. At the highest level, initial sensory, motivational, and emotional aspects of pain are reappraised and regulated by different subregions of the medial and lateral PFC based on contextual, conceptual knowledge, and past experiences.

In general, this model of pain processing is consistent with the appraisal theory of emotions (Brosch, 2013; Dixon et al., 2017; Brosch and Sander, 2013; Sander et al., 2018) which suggests that an event may produce an emotional response if it is considered as relevant to one's well-being, goals, expectations, self-image, and other aspects. According to the theory, there are two levels of appraisal (Brosch, 2013). Low-level appraisal based on conditioned associations is executed by sensory regions and subcortical structures, such as the amygdala. Initial appraisal of a stimulus as relevant triggers stereotypical physiological, endocrine, and behavioural responses that are modulated by the regions involved in the high-level appraisal (Cunningham et al., 2007). High-level appraisal based on context, memory, and semantic knowledge is performed mainly by the association areas, such as the PFC (Cunningham et al., 2007). Different subregions of the PFC evaluate different types of information and provide comprehensive analysis of the event from multiple perspectives (Dixon et al., 2017).

General hypothesis. Multiple lines of evidence emphasize the role of uncontrollability. Uncontrollable stress is a fundamental distal risk factor (Nolen-Hoeksema and Watkins, 2011) for both chronic pain (Sachs-Ericsson et al., 2017) and emotional disorders (Monroe, 2008). Uncontrollable stress is associated with

development of proximal transdiagnostic factors, such as dysregulated stress response (Doane et al., 2013), altered pain processing (Olango and Finn, 2014), cognitive deficits (Shansky and Lipps, 2013), neuroticism (Barlow et al., 2014a), and helplessness (Maier and Seligman, 2016).

Chronic uncontrollable stress, multiple unsuccessful attempts to control negative events may result in formation of helplessness, which is a cognitive schema characterized by a belief that one cannot control adversities. Importantly, such belief once developed under the influence of a certain type of uncontrollable stress effects appraisals of all types of stressors (Maier and Seligman, 2016). If a person experiencing, for example, chronic uncontrollable pain becomes helpless, he or she when faced, for example, with social stress may appraise it as unescapable too, even though it is objectively possible to avoid. This suggests that helplessness becomes independent of the stressor that caused it and, instead, becomes a part of the self-image. There is evidence suggesting that appraisal of one's ability to control negative events (Kerr et al., 2012) as well as appraisal of self-related information (Dixon et al., 2017), and generation of self-concepts, such as self-esteem is performed by the rmPFC (Somerville et al., 2010). Therefore, this region might play a crucial role in mediating the effects of uncontrollability and development of various transdiagnostic risk factors associated with it.

The rostrolateral PFC might be involved in the pathogenesis of chronic pain and emotional disorders too. It is implicated in preparation of alternative emotion regulation strategies and contributes to flexible switching between them depending on the context (Koch et al., 2018). Such ability is impaired in patients with chronic pain and emotional disorders (Coifman and Summers, 2019; Meesters et al., 2019). Both conditions are characterized by maladaptive persistence of certain strategies such as experiential avoidance or rumination (Aldao et al., 2010; Hayes et al., 2004; Linton, 2013). Reduced cognitive flexibility is partly responsible for persistence of affective and pain symptoms (Linton, 2013). Inability to implement more adaptive coping mechanisms might be due to dysfunction of the rlPFC. Individuals with impaired cognitive flexibility may continue to evaluate some stressful situation as uncontrollable even when it has become objectively controllable. Thus, dysfunction

of the rlPFC might also contribute to persistence of pain and emotional distress via impaired cognitive flexibility.

The rmPFC and rlPFC are implicated in the model of pain processing (Fig.2) as well as in the appraisal model of emotion (Fig.3). Considering that both regions are involved in higher-level (re)appraisal of initial nociceptive and emotional reactions, the general hypothesis of the thesis is that chronic pain disorders are characterized by impaired interaction of the rmPFC and rlPFC with regions associated with initial low-level nociceptive and emotional reactions, such as posterior insula, sensory cortices, amygdala, MCC, brainstem nuclei, hypothalamus, and others. To empirically test this hypothesis, the following questions will be addressed in the following study chapters:

1) Do patients with chronic pain disorders display signs of altered functioning of the rmPFC and rlPFC in comparison with healthy controls?
2) Does the interaction of the rmPFC and rlPFC with regions implicated in initial low-level nociceptive and emotional responses is impaired in chronic pain patients?
3) If so, how does this impairment correlate with clinical characteristics, such as pain intensity, pain duration, and emotional distress?

These questions will be addressed using functional magnetic resonance imaging (fMRI). In the following chapter basic principles of MRI and fMRI methods will be briefly described.

II. Basics of MRI and functional MRI analysis

1.0 Origin of the MR signal

Magnetic resonance imaging (MRI) has played an important role in recent advances in understanding of neurobiological foundations of pain (Martucci et al., 2014; Tracey and Bushnell, 2009) and emotional disorders (Huang et al., 2019; Lui et al., 2016). MRI is a technique that uses strong magnetic fields and low-energy radiofrequency signals to generate images of the body organs. Physics of MRI have been extensively described in several textbooks and papers (Heiken et al., 1986; Rinck et al., 1990; Stark et al., 1985; van Geuns et al., 1999). Only basic concepts and principles will be outlined below.

Magnetism is a fundamental property of matter associated with magnetic moments of elementary particles, such as protons, neutrons, or electrons. Body tissues contain large amounts of water molecules. Each water molecule has two hydrogen atoms or protons. Each proton has a small magnetic field and under normal circumstances vectors of magnetic fields of hydrogen atoms are randomly distributed in space, cancelling out magnetic moments of each other. Thus, the overall magnetic vector of all hydrogen atoms equals zero (Fig.4A). However, when subjected to a powerful magnetic field (measured in units of gauss (G) and Tesla (T)) of the MRI scanner, magnetic vectors of hydrogen nuclei adopt either parallel or antiparallel orientation relative to the external field (Fig.4B).

Hydrogen nuclei placed into external magnetic field do not precisely line up with the field but wobble or precess around its direction. The frequency of this precession may be described by the equation: $F = \gamma B_0/2\pi$ where *F* is the frequency of precession, γ is the gyromagnetic ratio of the nucleus, and B_0 is the strength of the external magnetic field. This frequency is also called the Larmor frequency. For example, in a 3-tesla magnetic field, the Larmor frequency for hydrogen will be 127.6 MHz.

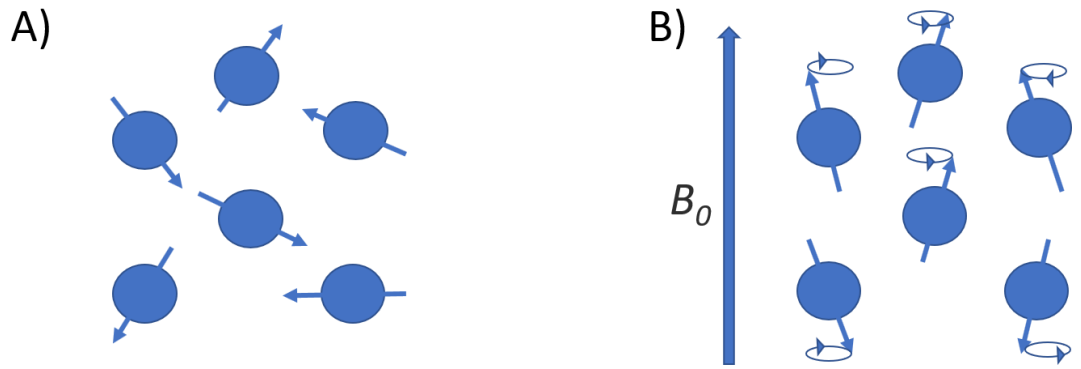


Figure 4. A) Magnetic moments of hydrogen nuclei without external magnetic field. B) When placed into strong external magnetic field (B_0) magnetic moments of hydrogen nuclei align with the field and precess around its direction at Larmor frequency.

Excitation. The overall magnetic vector from all hydrogen nuclei inside the scanner is static and cannot be measured. To obtain a signal, the direction of the vector must be altered by applying radiofrequency (RF) energy pulses of exactly the same Larmor frequency (resonance frequency) at which proton nuclei precess. When such RF signal is given (127.6 MHz in 3-tesla field), protons absorb the energy and change their orientation from the parallel lower energy state to the higher energy antiparallel state. In addition, the protons start to precess in phase (in synchrony). As a result, the net magnetization (Mz) flips 90° from the positive z-axis to transverse plane and rotates around the external magnetic field (B_0) at the Larmor frequency (Fig.5A). This rotating transverse magnetization can be measured because it will induce an alternating current (AC) in the receiver coil placed around the subject.

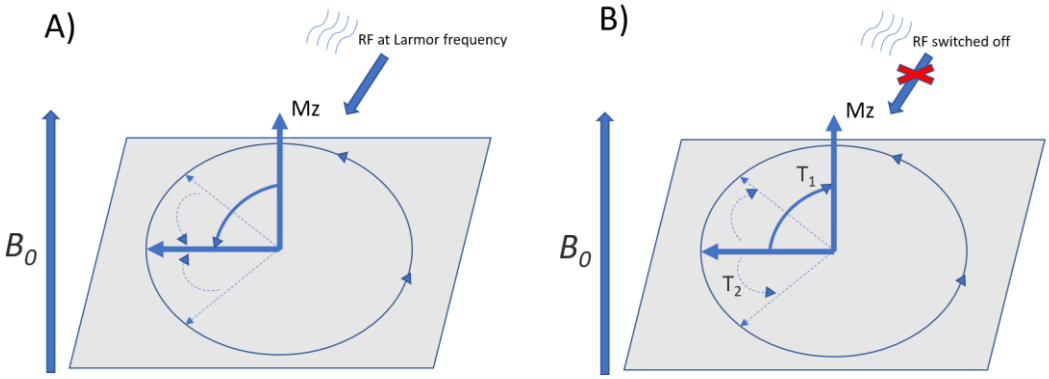


Figure 5. A) Application of a RF equal to the frequency of precession flips the net magnetization (Mz) of hydrogen nuclei to transverse plane (solid arrows) relative to the direction of the external

magnetic field (B_0) and forces the nuclei to precess around the B_0 in phase (dotted arrows). B) Switching off the RF pulse results in return of the net magnetization (Mz) to alignment with the B_0 (T_1 relaxation) and dephasing of precession (T_2 relaxation).

Relaxation. When the RF pulse is switched off, the nuclei start to return from high energy antiparallel to low energy parallel state and their precession starts to dephase (Fig. 5B). The process of realignment with the B_0 is called the longitudinal relaxation process. Different human tissues have different times of longitudinal relaxation (T_1). Dephasing of precession is called the transverse relaxation or spin-spin relaxation. It occurs due to interactions between individual nuclei (spin-spin interaction) and inhomogeneities of the main magnetic field. Again, time of transverse relaxation (T_2) is different in various tissues. The energy absorbed and subsequently emitted by the nuclei during two relaxation processes induces a current that can be detected by the scanner and translated into an image.

Spatial encoding. Excitation and relaxation processes occur simultaneously in the whole tissue placed inside the scanner. Without spatial localization, the output of the scanning would be a single signal from the entire scanned body part. To create an image, the signal emitted from the protons must contain information about where these protons are located. In order to differentiate signals from different locations, the strength of the magnetic field is deliberately altered in different directions. Changes in the magnetic field consequently change frequencies of precession allowing to use different radiofrequencies to selectively excite protons within certain slices of the body. Such spatial encoding allows creation of a matrix (K-space) in which each pixel has unique combination of phase and frequency codes.

2.0 Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging (fMRI) is a type of MRI used to measure activity of neuronal populations and connectivity between distant brain regions (Soares et al., 2016). fMRI is most commonly performed using the blood oxygenation level-dependent (BOLD) signal, which is an indirect measure of

neuronal activity (Buxton, 2013; Ogawa, 2012). Neuronal activity is a metabolically demanding process that requires an increased flow of oxygenated blood. However, the influx of oxygenated blood (oxyhemoglobin) into activated area exceeds actual consumption of the oxygen by the neuronal population. This process results in increased oxy-/deoxyhemoglobin ratio (Soares et al., 2016). Oxyhemoglobin is weakly diamagnetic (not attracted to a magnetic field) as it has no unpaired electrons. After oxygen molecule is released, the oxyhemoglobin transforms into deoxyhemoglobin with 4 unpaired electrons and becomes strongly paramagnetic (attracted to a magnetic field). The BOLD effect is directly related to the concentration of deoxyhemoglobin because regional relaxation times of brain tissues decrease as the fraction of deoxyhemoglobin increases. Brain areas with more oxyhemoglobin will have higher signal (and appear brighter) than those containing deoxyhemoglobin (Uludağ et al., 2009). Functional MRI data are usually acquired in sequential volumes (time-points), each one covering the entire brain and composed of a set of slices. Data from each voxel are organized into time-series, i.e., series of numerical data points from each scanned volume ordered in time.

In a typical fMRI experiment periods of brain activation during performance of a task are compared with periods of "rest" condition. Statistical analysis of the time series from each image voxel aims to determine if the BOLD signal is significantly correlated with the stimulus, i.e., increases when the stimulus is presented and decreases when the stimulus is removed (Soares et al., 2016). Voxels that do show such correlation are then displayed in colour as the areas activated by the stimulus.

3.0 Functional and effective connectivity

Brain areas do not process information in isolation. Performance of certain types of tasks activate certain sets of spatially distributed brain regions that together form functionally connected networks. Within these networks brain regions share the outputs of their own activity. For example, memory retrieval,

mind wandering, prospective and retrospective self-reflection tasks are associated with co-activation of the mPFC, PCC, anterior temporal lobe, superior frontal cortex, and inferior parietal cortex that collectively comprise the so-called "default-mode network" (DMN) (Cole et al., 2010). A broad range of different cognitive functions, including aspects of perception, response selection, executive control, working memory, episodic memory, and problem solving is associated with co-activation of the DLPFC, ACC, dorsal premotor area, anterior insular cortex, inferior frontal junction, posterior parietal cortex. These brain regions constitute the "cognitive control network" (CCN) (Cole and Schneider, 2007). Each network can be divided into smaller subnetworks which have more specific functions. For example, the CCN can be divided into cingulo-opercular and frontoparietal control networks. The cingulo-opercular network is thought to be preferentially involved in stable implementation of task sets, in other words in maintenance of control. Whereas the frontoparietal network is responsible for adjustment of control in response to feedback thereby providing flexibility of goal-directed behaviour (Marek and Dosenbach, 2018).

It has also been found that regions co-activated during performance of tasks remain functionally connected even in a resting state, i.e., when a person does not perform any particular task (S. M. Smith et al., 2009). Supposedly, such functional connectivity at rest occurs because frequent co-activation of regions during execution of certain functions many times results in enhancement of anatomical connections between the parts of the network. Anatomical connections cannot be completely "turned off" during the rest (Cole and Schneider, 2007). Consequently, any spontaneous neural firing in one area will likely cause an increase in neural firing in another connected area. Thus, resting-state functional networks could reflect the routes by which activity flows during task performance (Cole et al., 2016). Moreover, individual differences in resting-state FC can predict individual differences in cognitive task activations (Tavor et al., 2016). Thus, impaired resting state FC within a network may result in impaired performance of the tasks associated with that network.

One of the advantages of using resting state data over task-evoked activations is that analysis of resting state FC is less susceptible to "performance

confounds". For example, if some pathological condition is associated with cognitive impairments, then patients with such conditions may perform cognitive tasks differently than healthy controls. In this case, group differences in brain activation observed during performance of a task could be either a cause or a consequence of impaired task performance. Resting sate FC analysis helps to understand individual differences in cognitive task activations independently of task performance (Cole et al., 2016). Due to these findings, resting state FC analysis has recently become the dominant method of studying brain functions in health and disease.

However, although FC analysis is a useful tool to identify networks and the routes of activity flow, it is not very suitable for estimation of the directionality of the flow and causal interactions between connected regions (Friston, 2011). Such inferences are usually made using effective connectivity (EC) methods. If FC analysis is based on identification of statistical dependencies (mostly correlation coefficients) between BOLD signals from spatially distributed brain areas, EC measures the causal effect that the activity of one region exerts on the activity of another region. Several methods of effective connectivity analysis have been proposed so far including structural equation modelling, multivariate autoregressive modelling, dynamic Bayesian models, bilinear dynamic systems, switching linear dynamic systems, Granger causality analysis, and dynamic causal modelling (Smith et al., 2012). There is evidence suggesting that dynamic causal modelling (DCM) is more reliable and neurophysiologically plausible than other methods (Soares et al., 2016). Therefore, in recent years, DCM has become the most popular method of studying causal interactions (Daunizeau et al., 2011; Friston et al., 2019; Razi and Friston, 2016). Causality in DCM is based on Friston's control theory (Friston, 2009) in which causal interactions are expressed by differential equations that describe how activity in one neuronal population causes dynamics (i.e., rate of change) in another population via synaptic connections (Stephan et al., 2010). Initially, it was developed for task-based fMRI studies to estimate the influence of experimental conditions on EC between regions. More recently, spectral DCM (spDCM) was developed specifically for studying EC in resting state (Friston et al., 2014).

In spDCM original timeseries are replaced by their second-order statistics, i.e., instead of estimating time varying fluctuations in neuronal states, spDCM

estimates the parameters of their cross-spectra (or cross-correlation). The reason to use cross-spectrum is that this statistic indicates how much linear information is transferred from one signal to the other (and vice-versa) allowing to make inferences about the directionality of causal interactions between activity of separate neural populations (Friston et al., 2014).

In summary, MRI is a powerful non-invasive method to investigate structural and functional changes associated with pathological conditions. Considering that most (if not all) functions, including pain processing, emotion regulation, and cognitive appraisal, depend on integrated and coordinated activity of many brain regions, functional integration of the rostromedial and rostrolateral PFC in chronic pain conditions will be assessed using the resting state FC technique. In addition, causal interactions of the rmPFC and rlPFC with other relevant regions will be evaluated using spDCM.

III. Functional connectivity of the rmPFC and rlPFC in CLBP

1.0 Introduction

Chronic low back pain (CLBP) is one of the greatest problems for public health systems. It is a leading source of disability in the world that forces more people out of the workplace than heart diseases, diabetes, hypertension, neoplasm, respiratory diseases, and asthma pooled together (Maher et al., 2017). The prevalence of CLBP and costs associated with its management have been increasing in recent decades (Wu et al., 2020). Therefore, a lot of effort has been put to understand its nature and develop more effective treatments.

Effective treatment of pain often depends on correct identification of its origin. However, precise anatomical localisation of the tissue damage that triggers LBP can be difficult because many pathological processes in a range of structures within and beyond the lumbar spine may manifest with pain in this area (Allegri et al., 2016). It has been estimated that in approximately 90% of patients the exact pathoanatomical origin of pain cannot be identified (Maher et al., 2017). Although several specific structural abnormalities within the spine such as disc protrusion, disc degeneration, spinal stenosis, facet joint osteoarthritis, and nerve root compression are often found in LBP patients (Vagaska et al., 2019), pain cannot be fully attributable to them because many people with such abnormalities do not experience back pain (Endean et al., 2011). Moreover, presence of structural pathology does not predict occurrence of LBP in the future (Steffens et al., 2014) nor does it strongly correlate with the intensity of ongoing pain (Vagaska et al., 2019). Considering that spinal pathology is insufficient to explain occurrence and persistence of LBP and invasive interventions addressing putative structural pathology are usually not very effective (van Tulder et al., 2006), abnormalities in the central nervous system have been suggested to play a central role in the pathogenesis of CLBP (Wand and O'Connell, 2008).

Multiple structural and functional changes in the brain have been found in CLBP (Kregel et al., 2015). Pathological changes in pain processing areas (pain matrix) can clinically manifest in increased sensitivity to pain, which is a

fundamental symptom of chronic pain disorders. In a sensitized state, pain may occur even in the absence of detectable peripheral tissue damage (Wand and O'Connell, 2008) suggesting that altered functioning of the pain matrix is the main source of pain in patients without apparent structural pathology (Kosek et al., 2016). As described in Chapter I, Section 3.3, perception of pain is a complex process that consists of three phases with each phase carried out by a certain set of brain regions. The first (nociceptive) stage is characterized by activation of the spinothalamocortical system that analyses sensory (intensity, location) and early affective aspects of pain. Many studies of CLBP have reported functional and structural impairments in the dorsal horn (Thomas Cheng, 2010), brainstem (Henderson and Keay, 2017), thalamus, pIC, SII, and pMCC that together comprise the spinothalamocortical circuit (Garcia-larrea et al., 2013). As it mainly processes sensory characteristics of pain, increased reactivity of the system to noxious stimulation may underlie the phenomenon of sensitization. However, although activation of this circuit seems to be a prerequisite for experience of pain, processing of pain also includes subsequent cognitive and emotional modulations of initial sensory aspects during the second (perceptive-attentional) and third (reappraisal-emotional) phases (Chapter I, Section 3.4, Fig.2). There is evidence indicating that in CLBP such modulations are dysfunctional too (Garcia-larrea et al., 2013; Kregel et al., 2015). Because the pain matrix forms a fluid interacting system, disturbed processing of emotional or cognitive aspects of pain can alter sensory characteristics and vice versa. Thus, increased pain sensitivity may occur not only due to pathological changes in the spinothalamocortical circuit, but also due to impaired cognitive and emotional modulation of the spinothalamocortical circuit during the second and third phases of pain processing (Garcia-larrea et al., 2013).

Greater involvement of regions implicated in emotional processing during perception of pain has been noted in CLBP (Hashmi et al., 2013). CLBP patients often suffer from comorbid substance abuse, depression, and anxiety disorders (Fernandez et al., 2017), which can significantly reduce chances of recovery, worsen the clinical picture, quality of life, and socioeconomic consequences of the disease (Tseli et al., 2019). Frequent comorbidity suggests overlapping paths of

development. Therefore, identification of the neural mechanisms of comorbidity with emotional disorders may improve our understanding of both conditions.

Although pain is a well-known predictor of anxiety and depression, emotional disorders also often precede the onset of LBP (Fishbain et al., 1997). Several twin studies have concluded that CLBP and emotional disorders do not necessarily derive from each other, but rather share some common transdiagnostic risk factors, such as genetic predisposition, dysregulation of the HPA axis, dysfunction of the autonomic nervous system, and other factors, that equally predispose individuals to both types of disorders (Fernandez et al., 2017). Targeting such transdiagnostic factors in treatment may prevent development of emotional disorders in chronic pain patients and vice versa.

One of the most fundamental transdiagnostic risk factor is perceived uncontrollability of stress, which is associated with helplessness, low self-esteem, and low self-efficacy (see Chapter I, Section 2.3 for detailed description of the transdiagnostic model). Patients with CLBP (de Moraes Vieira et al., 2014) as well as patients with emotional disorders (Tarlow and Haaga, 1996) often have negative beliefs about their abilities to control adverse events. It has been shown that those acute LBP patients who have weak beliefs about controllability of their pain are more likely to develop chronic debilitating pain disorder and at higher risk of developing depression (Ferrari et al., 2019). On the contrary, higher self-efficacy (a belief that one is able to deal with any upcoming challenges) plays protective role against chronification of acute LBP (Puschmann et al., 2020) as well as against depression (Tahmassian and Jalali Moghadam, 2011). In addition, uncontrollability of pain and subjective helplessness positively correlate with perceived pain intensity (Müller, 2013, 2011) suggesting that these factors can modulate processing of sensory aspects of pain in the spinothalamocortical system. As mentioned in Chapter I, Section 4.2, one of the key brain regions associated with encoding, retrieval, evaluation of self-related information, and generation of self-concepts is the rostromedial prefrontal cortex (rmPFC) (D'Argembeau, 2013). Therefore, this area might play a crucial role in mediating protective effects of positive self-concepts against the effects of uncontrollable stress.

Self-concepts are created through the process of generalization and abstraction of multiple past experiences (Bowman and Zeithamova, 2018; Gilboa and Marlatte, 2017). Formation of positive self-concepts and their maintenance during challenging times depends on the ability to call to mind corresponding positive episodic memories that would reinstate and consolidate the concept (Pruessner et al., 2005). Thus, integrity of the connectivity between the rmPFC and memory systems is very important. For example, it has been shown that people with low self-esteem have weaker functional connectivity of the rmPFC with hippocampal formation (Pan et al., 2016). Reduced FC of the rmPFC with memory systems may obstruct recollection of episodic memories of successful coping that would negatively impact the sense of self-efficacy, increase perceived uncontrollability, and predispose individuals to development of emotional disorders. At the same time, increased perceived uncontrollability may alter pain processing in the spinothalamocortical system and contribute to pain sensitization.

Another important transdiagnostic risk factor linking chronic pain and emotional disorders that may result from experiencing uncontrollable stress is a cognitive deficit (Chapter I, Section 2.3). CLBP patients and patients with emotional disorders often display impairments in cognitive control of behaviour (Cáceda et al., 2014; Tamburin et al., 2014). For example, Tamburin et al. (2014) found that CLBP patients have difficulties with utilizing previous experiences to quickly adapt their decisions in changing environment. Similar pattern of impaired decision making has been observed in MDD patients (Must et al., 2013). The lateral part of the BA10 or the rostrolateral prefrontal cortex (rlPFC) in conjunction with the dorsolateral prefrontal cortex (dlPFC) and other parts of the frontoparietal network (FPN) plays an important role in adaptive decision-making (Dixon et al., 2017). More specifically, the rlPFC searches external and internal environments, collects, and holds in short-term memory evidence in favour of one or another strategy, which is then used by the dlPFC to make the most appropriate goal-directed decision in a given situation (Koch et al., 2018). Therefore, diminished ability to use previous experience during decision-making may occur due to dysfunction and impaired coordination of the rlPFC with the rest of the FPN.

Considering all the above, the main aim of this study was to investigate possible roles of the rostromedial and rostrolateral PFC in the pathogenesis of CLBP. Given that functions of these regions largely depend on their collaboration with other brain areas, resting-state FC analysis was chosen as the main method of research. The first hypothesis was that CLBP patients compared to healthy people would demonstrate impaired FC of the rmPFC with regions involved in episodic memory retrieval and with the spinothalamocortical system. The second hypothesis was that FC of the rlPFC with the FPN would also be compromised.

2.0 Methods

Participants

Data used in this work were obtained from the OpenPain Project (https://www.openpain.org, Principal Investigator: A. Vania Apkarian, Ph.D. at Northwestern University), which is supported by the National Institute of Neurological Disorders and Stroke and National Institute of Drug Abuse, USA. The dataset initially consisted of structural and functional MRI images from 68 participants, 34 chronic low back pain (CLBP) and 34 pain-free healthy participants from the study by Mansour et al (2016). As described in the original manuscript, all participants were provided with a written consent form, and all experimental protocols were approved and conducted according to the Northwestern University's Institutional Review Board committee. Clinical assessment of pain included the Short-Form of the McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987), where the visual analogue scale (VAS) (0 = no pain, 10 = worst pain imaginable) was used to evaluate pain intensity. Depression was measured with the Beck's Depression Inventory (BDI) (Beck et al., 1988). Participants were given the questionnaires 1 hour before scanning.

MRI data acquisition

Functional brain images were acquired using a 3T Siemens Trio whole-body scanner, with an 8-channel head coil, during rest, as follows: TR = 2.5 seconds; TE = 30 ms; flip angle = 90°; in-plane matrix resolution = 64 × 64; number of slices = 40; slice thickness = 3 mm; field of view = 256 × 256 mm; and number of volumes = 244, 300, or 305. In addition, for realignment purposes, structural brain images for each participant were acquired using the same scanner with the following parameters: isotropic resolution 1 mm; TR = 2.5 seconds; TE = 3.36 ms; flip angle = 9°; in-plane matrix resolution = 256 × 256; number of slices = 160; and field of view = 256 × 256 mm (Mansour et al., 2016).

Quality control

Signal dropout. The rmPFC and rlPFC are located in the most anterior part of the brain, which is close to frontal sinuses. Frontal sinuses contain air, bone, and soft tissues that all interact with the applied magnetic field in different ways. Depending on anatomical peculiarities, such as geometry and composition of the frontal sinuses and their orientation in relation to the main magnetic field, some individuals may have local magnetic field inhomogeneities that can cause signal dropout in this area (Cordes et al., 2000; Devlin et al., 2000). After careful inspection of the images 5 participants were excluded from the analysis due to significant signal loss in the frontopolar area.

Head motion. Another source of artifacts that can disturb fMRI signal is head movement during scanning (Satterthwaite et al., 2012; Van Dijk et al., 2012). Depending on the timing, duration, and trajectory of motion it can increase fMRI signal in some voxels, decrease it in others, or result in wavelike disruptions where signal increases and decreases over time (Power et al., 2015). Studies on functional connectivity are particularly susceptible to motion-induced artifacts (Power et al., 2012). Estimation of FC between two separate regions is based on the measurement of correlation between signal fluctuations in these regions. Due to head movement, two areas may have: 1) similar changes in signal fluctuations that

would increase statistical correlations or 2) different changes that would decrease correlations or cause anticorrelations (Power et al., 2015). Clinical populations tend to move more during scanning than healthy individuals. Thus, group differences in FC between patients and healthy controls can be partially or fully explained by differences in head motion (Power et al., 2014).

Many methods to resolve the issue of movement have been presented so far including regressing out variance associated with head movement in individual datasets as well as at the group level, deleting volumes contaminated with motion (censoring), their multiple variations and combinations (Parkes et al., 2018). Unfortunately, neither of the existing methods can eliminate the effects of motion completely. There is no consensus on which methods are better, or how to measure the effectiveness of motion correction (Power et al., 2015). There is also evidence suggesting that changes in FC associated with head motion are not entirely caused by physical effects of movement on fMRI signal but may represent a neurobiological trait that predisposes some individuals to excessive movement. For example, in a study by Zeng et al. (2014), group differences in FC between high and low head motion groups remained the same even when high motion group had identical motion parameters as low motion group on another scanning session. Furthermore, individual differences in head movement appear to be genetically mediated (Hodgson et al., 2017). Motion also correlates with various clinical, behavioural, and demographic factors, such as impulsivity, intelligence quotient (IQ), fluid intelligence, body mass, and other important variables (Siegel et al., 2017). Therefore, it is difficult to separate the artifactual effects of motion from the effects of clinical, neurobiological, or psychological factors (Geerligs et al., 2017). Aggressive motion-correction can be detrimental to accurate estimation of FC because true signal fluctuations can be erroneously attributed to head movement and removed (Bright and Murphy, 2015). Thus, the topic of motion-correction is controversial and research on developing more precise methods is still ongoing. Meanwhile, the most conventional approach is to minimize the effects of movement as much as possible at both individual and group-level analyses (Hlinka et al., 2010; Maknojia et al., 2019; Yan et al., 2013).

In a recent study by Parkes et al. (2018) the authors compared 19 different ways of reducing motion artifacts and concluded that a combination of some sort of censoring (exclusion of either motion contaminated volumes or the whole data from high motion participants) with ICA-AROMA (Independent Component Analysis based Automatic Removal of Motion Artifacts) performs better than other techniques. ICA-AROMA is a method that separates the BOLD data into spatially independent components, automatically identifies and removes components of non-neural origin including motion-related noise (Pruim et al., 2015). Parkes et al. (2018) also recommended exclusion of participants with mean framewise displacement (which is a metric used to measure head motion) of more than 0.2 mm. The mean framewise displacement (FD) in their study was calculated using the root mean squared volume-to-volume displacement of all brain voxels measured from the six head motion parameters. This metric was suggested by Jenkinson et al. (2002) and has been proved to be more accurate than other similar metrics (Yan et al., 2013).

Following these recommendations, participants with FD>0.2 mm were excluded from the present study. Data from all remaining participants (29 CLBP patients and 30 healthy controls) were denoised using ICA-AROMA. However, even small between group differences in residual head motion can introduce artifactual group differences in FC (Yan et al., 2013). For that reason, individual FD estimates were also entered as a nuisance covariate at the group level analysis in order to regress out correlations that are attributable to motion as was suggested by Yan et.al (2013), Maknojia et al. (2019), and Hlinka et al. (2010).

Image preprocessing

Image preprocessing was carried out using FSL (FMRIB Software Library) v.5.0.10 (Jenkinson et al., 2012). FSL is a software for processing of fMRI data created by the FMRIB (Functional Magnetic Resonance Imaging of the Brain) Analysis Group, Oxford University, UK. Preprocessing steps included removal of the first 5 volumes with unstable signal, high-pass temporal filtering (0.01-Hz cutoff),

interleaved slice-timing correction, motion correction, brain extraction, and spatial smoothing using an isotropic gaussian filter kernel with full width at half maximum (FWHM) size of 5 mm. Registration of the images was performed using FMRIB's Linear Image Registration Tool (FLIRT). Functional images were first registered to the T1-weighted structural images using the Boundary-Based Registration (BBR) method and then to the Montreal Neurological Institute (MNI) standard space with 12 degrees of freedom (Jenkinson et al., 2002; Jenkinson and Smith, 2001). As mentioned above, all functional images were denoised using ICA-AROMA (Pruim et al., 2015). To additionally control for physiological noise, time series data from the cerebrospinal fluid (CSF) and white matter (WM) were extracted for each participant. To achieve this, each participant's T1-weighted images were segmented into the grey matter, white matter, and cerebrospinal fluid using FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001). To avoid overlapping with the grey matter, the CSF and WM masks were eroded to retain only the top 20 and 198 cm^3, respectively (Chai et al., 2012). The CSF and WM maps were then transformed to fMRI space. Mean CSF and WM time series were then extracted per subject using these masks and regressed out of the data as part of the subsequent GLM analysis.

Regions of interest (ROI) selection

The rmPFC and rlPFC together comprise a Brodmann Area 10 (BA10) that occupies the frontal pole of the brain (Bludau et al., 2014). Several studies have delineated the borders of the BA10 and its subdivisions using functional connectivity (Schaefer et al., 2018), structural connectivity methods (Fan et al., 2016; Orr et al., 2015), and their combination (Glasser et al., 2016). However, they yielded inconsistent results, perhaps, because surrounding prefrontal areas have relatively similar to the frontal pole connectivity and architecture. There is no sufficient tissue contrast to detect subtle differences with MRI methods. Hence, histological methods of parcellation might be more reliable in that regard (Bludau et al., 2014). The latest histology-based parcellation of the frontopolar area was performed by Bludau et al. (2014). Probabilistic maps of the lateral and medial BA10

made by the authors were used as regions of interest in this study (Fig. 6). ROI masks were created using the SPM Anatomy toolbox v.2.2c. There is evidence suggesting bilateral involvement of the BA10 during pain processing (Peng et al., 2018), that is why the lateral BA10 masks from the right and left hemispheres were combined into a single lateral BA10 mask. Same procedure was performed for the right and left medial BA10. Both masks were additionally eroded with 3mm cube kernel to prevent overlapping.

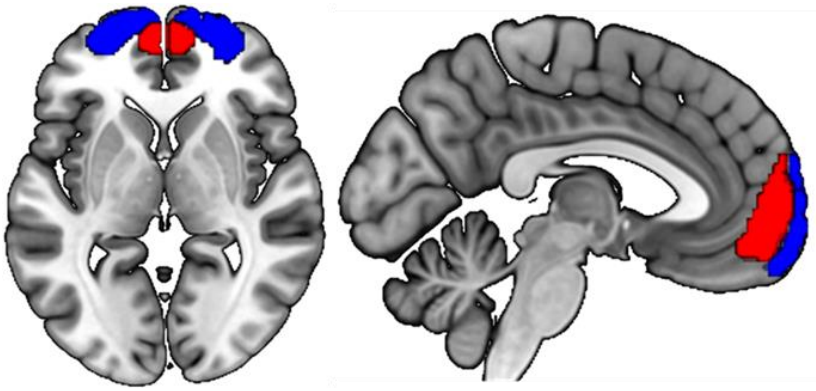


Figure 6. ROI masks of the rostromedial prefrontal cortex (red) and rostrolateral prefrontal cortex (blue) based on probabilistic maps created by Bludau et.al (2014).

Statistical analyses

First-level and group-level analyses of FC between the rmPFC and rlPFC and the rest of the grey matter of the brain were carried out using FMRI Expert Analysis Tool (FEAT, v6.00) (Woolrich et al., 2004, 2001). In the subject-level analyses, time series data extracted from each of the ROIs were used to identify voxels in the rest of the grey matter that showed correlated or anticorrelated activity with the data from the ROIs. Individual CSF and WM time series were also included in the General Linear Model (GLM) as nuisance covariates. Resulting statistical images were then analysed at the group-level GLM using FMRIB's Local Analysis of Mixed Effects (FLAME 1) method. Statistical contrasts were designed to identify: 1) regions with greater FC for patients compared to controls (CLBP>HC), and 2) regions with greater FC for controls compared to patients (HC>CLBP). All contrasts were thresholded at the whole-brain FWE-corrected level ($Z > 2.3$; cluster $p < 0.0125$). P-values were

corrected using the Bonferroni method (0.05/number of tests). Head motion estimates (FD) of each participant were included in the GLM as covariates of no interest to control for residual effects of head-movement. A group-covariate interaction analysis was also performed in order to test whether the linear relationship between FC and head movement differs between the two groups. Other potential confounds, such as sex and age, were not included into the GLM because every additional covariate reduces degrees of freedom (DOF) and, thus, may reduce statistical power (Jenkinson et al., 2018; Kahan et al., 2014). Considering that sample sizes were small in this study only head motion parameters were included.

In addition to the analyses of group differences, a mixed-effects group-level GLM of the correlation between FC of each ROI with pain intensity, pain duration, and BDI scores was performed in the patient group only. For these analyses, results were also thresholded at the whole-brain FWE-corrected level ($Z > 2.3$; cluster $p < 0.0125$). FD parameters were also entered as covariates of no interest. Statistical analyses of group differences in demographic data, depression, and head movement were performed using GraphPad Prism version 8.4.3 for Windows, GraphPad Software, La Jolla California, USA (www.graphpad.com).

3.0 Results

Independent samples t-tests did not reveal significant differences in age, sex, and head movement parameters between the CLBP and HC groups (Table 1 and Supplementary Table S1). CLBP patients had higher depression scores than healthy controls ($p<0.0001$). Also, the CLBP and HC groups did not significantly differ from each other with regards to interaction between FC of both ROIs with head movement parameters.

Table 1. *Demographics and questionnaire scores of CLBP patients and healthy controls*

Data	**CLBP patients**	**Healthy Controls**	**P-value**
N.	29	30	-
Mean age (min-max) in years	49.52 (21 - 62)	48.27 (21-64)	0.59
Males/Females	16/13	16/14	-
N. Right-handed	29	30	-
Mean pain duration (min-max) in years	15.55 (1 - 41)	-	-
Mean pain intensity (min-max)	6.47 (2.6 – 8.7)	-	-
Mean BDI (min-max)	6.7 (0-19)	1.4 (0-10)	<0.0001
Mean FD	0.08	0.06	0.08
Displayed are the mean (min-max) values and p-values from independent samples t-tests. CLBP - chronic low back pain, BDI – Beck Depression Inventory.			

Functional connectivity of the rmPFC

Group differences in FC of the rmPFC between CLBP and HC groups are presented in Fig.7 and Table 2.

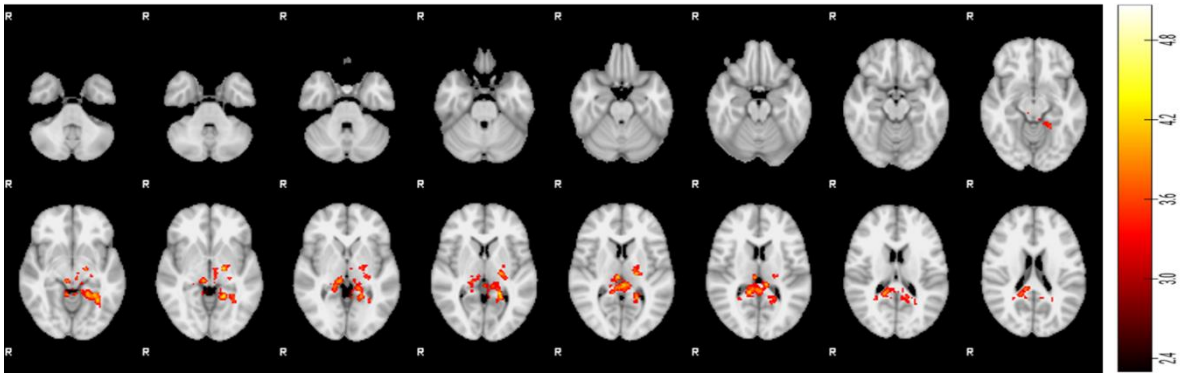


Figure 7. Statistical map showing the difference in FC of the rmPFC between the CLBP and HC groups (HC>CLBP contrast). The CLBP group showed reduced FC of the rmPFC with a single cluster of brain regions encompassing the posterior medial cortex, thalamus, pallidum, and midbrain structures. The map is displayed in radiological format. All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. R-right.

Table 2. *Peak MNI coordinates of regions with stronger rmPFC FC in HC group compared to CLBP patients.*

Anatomical regions	**Cluster extent**	**X**	**Y**	**Z**	**Z-score**
HC>CLBP					
R. mediodorsal thalamus	1956	6	-24	10	3.82
L. lingual gyrus		-18	-48	-4	3.62
L. ventral pallidum		-18	-12	-4	3.57
L. parahippocampal gyrus		-20	-44	4	3.53
R. retrosplenial cortex		12	-42	14	3.47
Results are FWE-corrected (Z>2.3, cluster-based threshold of p<0.0125) and reported in MNI152 standard space. L. – Left, R. – Right.					

Within the posterior medial cortex, the cluster consisted of the retrosplenial cortex (RSC), the transition zone between the RSC, posterior portion of the parahippocamapal cortex (PH), and anterior region of the lingual gyrus. It then extended inferiorly towards the posterior part of the ventral pallidum (VP), mediodorsal and pulvinar nuclei of the thalamus. In the midbrain area, it partially overlapped with the midbrain reticular formation (MRF) and ventrolateral periaqueductal grey (vlPAG). Main structures constituting the cluster and coordinates of the regions with strongest FC in HC group compared to CLBP are shown in Fig.8a and Table 2. Comparison of the mean FC values between the two groups (Fig.8b) shows that in the CLBP group FC of the rmPFC with the above-mentioned regions is reduced, not anticorrelated.

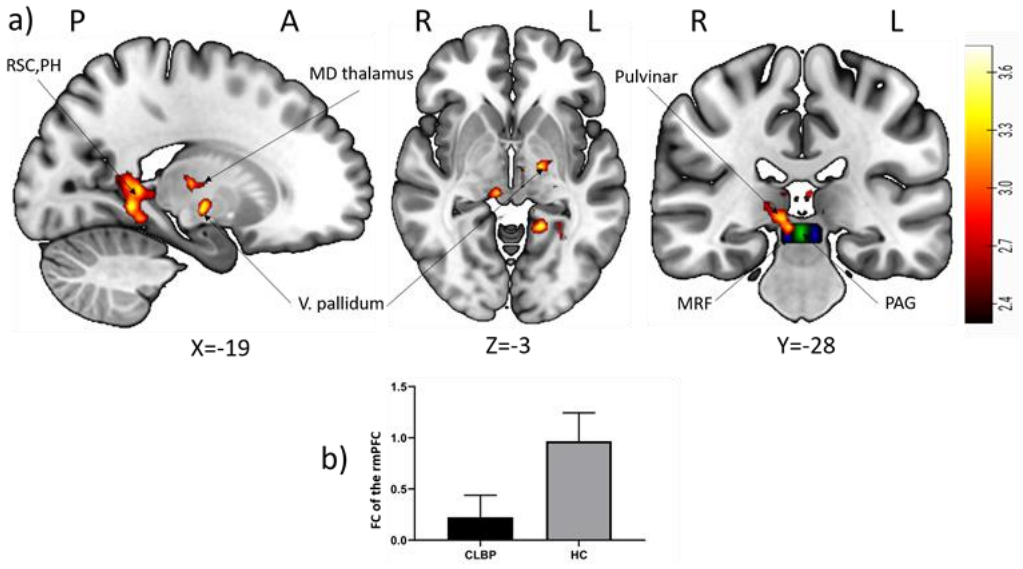


Figure 8. A) Structures showing reduced FC with the rmPFC in CLBP. Labelling of the structures was made according to the Harvard-Oxford subcortical and cortical atlases preinstalled in FSL, Vogt et al. (2001), Bzdok et al. (2015), Pergola et al. (2013), and Edlow et al. (2012). On the coronal slice the masks of the MRF (blue) and PAG (green) were taken from the Harvard Ascending Arousal Network atlas. B) Mean values of FC between the rmPFC seed and the cluster from the HC>CLBP contrast. All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. RSC – retrosplenial cortex; PH – parahippocampal cortex; MD thalamus – mediodorsal thalamus; V. pallidum – ventral pallidum; MRF – midbrain reticular formation; PAG – periaqueductal grey; P - posterior; A – anterior; L – Left; R - Right; CLBP – chronic low back pain; HC – healthy controls.

Correlation of the rmPFC FC with clinical scores

There was a negative correlation between pain intensity (r = -0.47, p<0.006) and FC of the medial BA10 with posterior insular cortex (pIC) and secondary somatosensory cortex (SII) (Fig. 9). Pain duration and depression did not correlate with FC of the rmPFC.

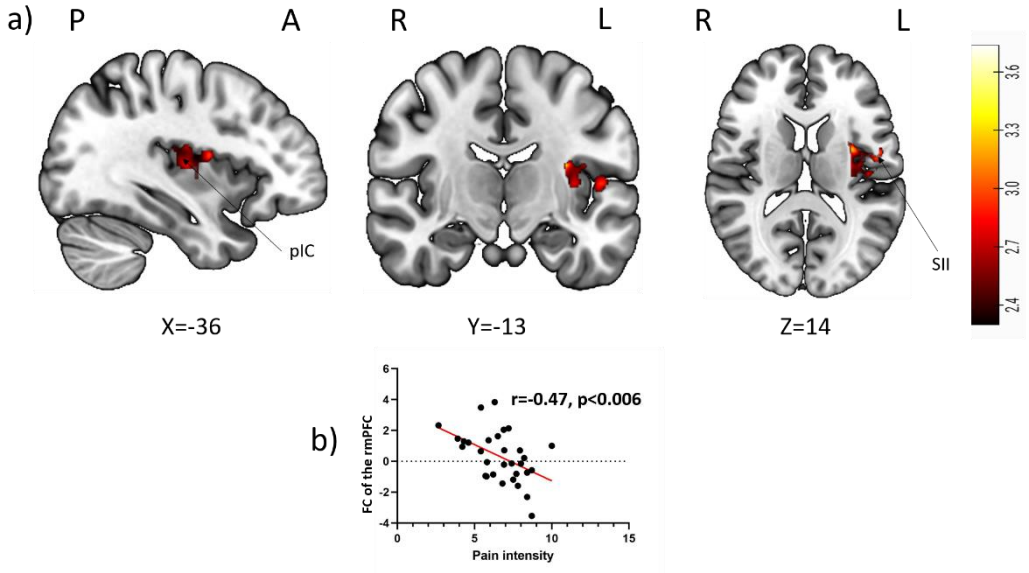


Figure 9. A,B) Negative correlation of pain intensity (VAS scores) with FC between the rmPFC and pIC/SII in the CLBP group. All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. P – posterior; A – anterior; L – Left; R - Right; pIC – posterior insular cortex; SII – secondary sensory cortex.

Functional connectivity of the rlPFC

There was no statistically significant difference in FC of the rlPFC between the CLBP and HC groups. FC of the rlPFC also did not correlate with any of the clinical scores.

4.0 Discussion

Compared to HC, CLBP patients demonstrated reduced FC of the rmPFC with retrosplenial and parahippocampal cortices, subcortical structures such as the mediodorsal thalamus and ventral pallidum, and brainstem nuclei including the midbrain reticular formation and periaqueductal grey (Fig.8). Also, pain intensity scores negatively correlated with FC between the rmPFC and posterior insular cortex (Fig.9). A possible role of such pattern of connectivity in the development of comorbidity between chronic pain and emotional disorders will be discussed below.

Perceived uncontrollability is associated with increased risk of emotional disorders, chronification of pain, and higher pain sensitivity. On the other hand, a strong sense of self-efficacy or a belief that one is able to control aversive events (Ferrari et al., 2019) buffers these negative effects of stress (Tahmassian and Jalali Moghadam, 2011). Formation of such belief requires recollection and generalization of multiple past episodes of successful control into a single abstract concept of self-efficacy (Bowman and Zeithamova, 2018; Gilboa and Marlatte, 2017). The key region implicated in retrieval of autobiographical memories and generation of self-concepts is the rmPFC (D'Argembeau, 2013). Chronic pain patients often demonstrate weak sense of self-efficacy (de Moraes Vieira et al., 2014) as well as other negative self-concepts, such as incompetence, defectiveness (Saariaho et al., 2012), and worthlessness (Jacobi et al., 2003; Kowal et al., 2012), that significantly increase chances of developing a comorbid emotional disorder (Turner et al., 2005). Development of such negative self-concepts suggests dysfunction of the rmPFC, perhaps, due to impaired interaction of the rmPFC with memory systems (Pan et al., 2016).

In general, results of the present study support this hypothesis. The CLBP group showed reduced FC of the rmPFC with the retrosplenial cortex (RSC), posterior part of the ventral pallidum (VP) and mediodorsal (MD) thalamus (Fig.8). Reduced connectivity with these regions may impair retrieval of positive autobiographical memories that, in turn, may hinder formation and maintenance of positive self-concepts.

The RSC is consistently activated in tasks associated with autobiographical memory, spatial navigation, imagination, and future planning (Vann et al., 2009). Exact functions of this region are poorly understood, however there is evidence suggesting that the RSC plays a crucial role in the process of mentally generating and maintaining complex scenes or events (scene construction), which is necessary for performance of all of the above-mentioned tasks (Vann et al., 2009). During retrieval of autobiographical memories the RSC is usually coactivated with the mPFC including its rostral part (Svoboda et al., 2006). Hence, reduced FC of the rmPFC with RSC found in CLBP patients may obstruct this process. This is in agreement with behavioural studies reporting poorer performance of patients with chronic pain (Liu et al., 2014) and emotional disorders (Köhler et al., 2015) in tasks on autobiographical memory retrieval.

However, disturbed episodic memory retrieval alone cannot explain why patients tend to better memorize and recall negative but not positive autobiographical events (Kim et al., 2018; Meyer et al., 2015). A possible reason for such negativity bias is reduced reinforcement of positive memories. It is well established that the strength of episodic memories is strongly influenced by reward (Calderon et al., 2020). Compared to unrewarded stimuli, items memorized within rewarding contexts are associated with better recognition (Shneyer and Mendelsohn, 2018). Therefore, impaired ability of patients with chronic pain and emotional disorders to call to mind positive but not negative episodic memories might to some extent be explained by dysfunction of the reward circuitry. The CLBP group in the present study demonstrated reduced FC of the rmPFC with the posterior portion of the ventral pallidum (VP) (Fig.8). The VP is one of the central structures in the reward system (K. S. Smith et al., 2009). It has reciprocal

connections with many brain regions associated with reward processing, such as the OFC, mPFC, nucleus accumbens, amygdala, lateral hypothalamus, ventral tegmental area, parabrachial nucleus, and subthalamic nucleus. Such widespread anatomical connectivity allows it to actively participate in reward and motivation functions. The VP consists of anterior and posterior parts that have antagonistic functions. The former is associated with aversion whereas the posterior VP is linked with hedonic processes (K. S. Smith et al., 2009). Posterior VP is more active, for example, during the presentation of images of appetizing food (Beaver et al., 2006). Conversely, pictures of rotten food increase activity in more anterior regions (Calder et al., 2007). Inhibition or lesion to the posterior VP results in reduced hedonic reactions and even aversion to previously highly rewarding stimuli. In contrast, stimulation of the posterior VP during presentation of some neutral stimuli leads to increased 'liking' and 'wanting' of the stimuli, their anticipation, enhanced encoding, and associative learning (K. S. Smith et al., 2009). Chronic pain (Borsook et al., 2016) and emotional disorders (Cooper et al., 2018) are characterized by reduced hedonic and increased aversive behaviours suggesting possible involvement of the VP. Pathological changes in the posterior portion of the VP may result in relative dominance of the anterior VP functions and consequent imbalance between hedonic and aversive processes. Diminished processing of rewards by the posterior VP may weaken the strength of positive episodic memories because such memories would be less reinforced than negative memories. Reduced FC between the rmPFC and posterior VP in CLBP suggests that the rmPFC could be deprived of reward related information associated with positive events leading to their poorer retrieval. In contrast, relatively stronger reinforcement of negative autobiographical memories can facilitate their recollection and subsequent generation of negative self-concepts.

The VP exchanges information with the rmPFC directly and via the mediodorsal (MD) thalamus (K. S. Smith et al., 2009). In the present study, FC of the rmPFC with mediodorsal thalamus was also reduced in CLBP patients (Fig.8). The MD thalamus plays a key role in rapid integration of object/reward/response information (Mitchell and Chakraborty, 2013). For example, in a study by

Chakraborty et al. (2016), lesion to the MD thalamus in monkeys impaired attribution of reward to the most recent action of the animal and impeded selection of the beneficial option once it has been found. In light of this findings, reduced FC of the rmPFC with MD thalamus and posterior VP may impair attribution of positive outcomes or rewards to personal actions and undermine the sense of self-efficacy, which is essentially a belief that one's own actions can lead to desirable outcomes.

In turn, a weak belief in one's own ability to cope with adversities can bias processing of incoming sensory information and increase attention towards threatening signals (hypervigilance) (Clark and Beck, 2010). Hypervigilance is a common feature of anxiety and chronic pain disorders (He et al., 2014; Kimble et al., 2014; Peters et al., 2002). In the present study CLBP patients showed reduced FC of the rmPFC with the medial pulvinar nucleus of the thalamus, midbrain reticular formation, and periaqueductal grey (Fig.8). These structures are involved in early subconscious processing of threat and facilitate rapid defensive fight-flight responses (Terpou et al., 2019). Hyperactivity of these brainstem regions has been identified as a key contributor to the development and maintenance of symptoms of anxiety disorders, e.g., PTSD (Rabellino et al., 2016). A possible mechanism whereby they facilitate anxiety is hyperarousal. PAG and MRF are parts of the ascending reticular activating system (ARAS) that regulates the level of general arousal in the CNS (Edlow et al., 2012). High levels of arousal in the CNS can amplify reactivity of neural systems that perform evaluation of threat or nociceptive signals (Venkatraman et al., 2017). Activity of these subcortical regions is controlled and modulated by higher order cortices, such as the mPFC (Brosch and Sander, 2013; Cunningham et al., 2007; Sander et al., 2018). Thus, reduced FC of the rmPFC with these structures suggests reduced regulation of arousal that may contribute to negative affectivity.

Negative self-concepts, such as low self-efficacy, worthlessness, helplessness, and resultant increased perceived uncontrollability, may also influence processing of pain. For example, studies by Muller (2013, 2011) found a direct relationship between uncontrollability, perceived pain intensity, and cortisol levels. Moreover, the effects of uncontrollability on pain intensity were mediated by

subjective helplessness. Sensory aspects of pain are processed by the spinothalamocortical system. Specifically, intensity of pain is strongly associated with activity of the posterior insular cortex (pIC). This is the only region in the brain where electrical stimulation of the area can elicit painful sensation (Garcia-larrea et al., 2013). Salomons et al. (2004) reported attenuated activation in the pIC and S2 when pain was perceived as controllable. In the present study, pain intensity scores negatively correlated ($r=-0.47$, $p<0.006$) with FC between the rmPFC and pIC (Fig. 9). Higher pain intensity was associated with weaker FC between the rmPFC and pIC. The pIC and S2 are activated during the first nociceptive phase of pain processing, whereas the rmPFC is engaged during the third reappraisal phase when initial low-level nociceptive reactions are modulated based on context and memory (Chapter I, Section 3.4, Fig.2) (Garcia-larrea et al., 2013). Results of the correlation analysis suggest that reduced FC between the rmPFC and pIC, i.e., weaker modulation of the spinothalamocortical system by the higher-order prefrontal regions may lead to hyperactivation of the spinothalamocortical system and increased pain intensity.

Overall, results of the FC analysis support the general hypothesis that dysfunction of the rmPFC in CLBP might predispose to emotional disorders and chronic pain. There is growing body of evidence suggesting that the mPFC including the rmPFC mediates resilience to stress (Holz et al., 2020; Maier and Watkins, 2010; Sinha et al., 2016). In a series of experiments Maier and Seligman (2016) subjected animals to either controllable or uncontrollable stress. The authors found that uncontrollable stress leads to helpless behaviour often accompanied by anxiety- or depression-like symptoms, such as reduced aggression, reduced social dominance, reduced food and water intake, exaggerated attention to external cues, reduced preference for sweet tastes, potentiated fear conditioning, slowed fear extinction, neophobia, and many other behavioural symptoms of emotional distress. However, if animals subjected to uncontrollable stress had a history of successful control in the past, none of the above-listed symptoms would occur. Importantly, the specific type of the current uncontrollable stress and previous controllable stress did not have to be the same. For example, experience of control over social stress would immunize against developing emotional distress in response to uncontrollable pain.

Such generalization and abstraction of controllability suggests involvement of higher order structures such as the rmPFC. Indeed, in subsequent experiments the authors found that it is the prelimbic cortex in mice that retrieves past episodes of control from memory and reward systems, generalizes them, and uses them to downregulate activity of the stress-responsive subcortical and midbrain structures. Although there is no prelimbic area in humans, similar experiment in human fMRI study showed that controllability of the stressor was associated with elevated activity of the rmPFC that inhibited amygdalar reactions to stress (Kerr et al., 2012).

Chronic pain disorder is a condition very similar to the uncontrollable stress condition in Maier and Seligman's (2016) experiments. Reduced FC of the rmPFC with memory systems and reward circuitry displayed by the CLBP patients suggests that their ability to retrieve episodes of control from the past and utilize them to cope with current stressful situations might be compromised. Consequently, downregulation of the stress-related structures by the rmPFC might be also deficient in CLBP putting patients at high risk of developing emotional disorders. However, this group of CLBP patients did not suffer from comorbid depression. Mean BDI score of 6.7 would characterize them as having no or minimal depression and BDI scores did not show any significant correlation with FC values. As described in Chapter I, Section 2.3, uncontrollable stress is a distal risk factor that only produces proximal risk factors, such as helplessness, dysregulated HPA axis activity, cognitive deficits, and many others. Development of a specific anxiety disorder or depression requires participation of additional moderators such as increased uncertainty, experience of loss, or failure. Thus, impaired FC of the rmPFC found in the present study can be considered as a proximal risk factor resulting from uncontrollable stress. Specific moderators acting upon this proximal risk factor may later transform it into a specific emotional disorder.

5.0 Conclusions

The rmPFC is involved in modulation of nociceptive (Chapter I, Section 3.4, Fig.2) (Garcia-larrea et al., 2013) as well as non-pain related emotional reactions (Chapter I, Section 4.3, Fig.3) (Dixon et al., 2017). It is associated with processing of self-referential information (D'Argembeau, 2013) and formation of self-concepts, such as self-efficacy (ability to cope with adversities) (Kerr et al., 2012; Ono et al., 2018) and self-esteem (overall sense of personal worth) (Somerville et al., 2010). Positive self-concepts are known to play protective roles against chronification of pain, disability (Saariaho et al., 2012), and emotional disorders (Greenberg et al., 1992; Tahmassian and Jalali Moghadam, 2011). Results of this study suggest that functions of the rmPFC might be impaired in CLBP. Disturbed FC of this regions with structures responsible for episodic memory retrieval and reward processing may promote generation of negative self-concepts, thereby contributing to increased sense of uncontrollability leading to increased pain sensitivity, negative affectivity, and possible development of comorbid emotional disorders.

6.0 Limitations

First limitation is a relatively small sample size. In seed-to-whole-brain FC analyses activity in the ROI is compared with activity in each of the remaining voxels from the rest of the brain. This raises the problem of multiple comparisons and limited statistical power due to small sample sizes that increases the risks of false-positive as well as false-negative results (Grady et al., 2021). However, there is no agreement in the literature with regards to sufficient number of participants required for obtaining reliable 'true' results. Recommendations on optimal sample sizes for fMRI studies range from 25 to 400 participants per group depending on the specific method, duration of the resting-state, and location of the regions of interest (Grady et al., 2021). Thus, optimal sample size calculation remains a critical issue. However, the sizes of each group (29 CLBP and 31 HC) used in the present

study were higher than the median sample size of all fMRI studies published in 2015 (Poldrack et al., 2017). Nevertheless, replication of the results using larger sample sizes is needed to validate the findings. Also, the study lacked behavioural data on perceived controllability, self-efficacy, helplessness, and other self-concepts that could be used to investigate the role of the rmPFC in mediating the effects of these factors in chronic pain.

Another limitation is that measurement of FC between two voxels is based on statistical correlation between activity in these voxels. Such dependencies cannot give information about causal relationships, i.e., how activity in one voxel influences activity in another voxel (Friston, 2011). Considering that the rmPFC is thought to regulate activity of stress-responsive subcortical regions, FC is not the most informative method to assess this role of the rmPFC. Effective connectivity (EC) analyses, such as dynamic causal modelling (DCM), are better suited for making inferences about causal interactions. Additionally, DCM estimates effective connectivity between relatively small number of ROIs unlike seed-to-brain FC analysis that looks for correlations with data from every voxel in the brain. Therefore, DCM is less vulnerable to the issue of multiple comparisons and less likely to produce false-positive or false-negative results (Friston et al., 2014). Considering these limitations, in the next study DCM was used to assess EC of the rmPFC.

IV. Effective connectivity analysis in CLBP

1.0 Introduction.

As already discussed in previous chapters uncontrollable stress is a significant risk factor of emotional disorders. The neural mechanisms that mediate between uncontrollable stress and emotional disorders are not well understood. However, some progress in understanding of these processes was achieved in recent decades by the authors and advocates of the Learned Helplessness theory (Maier and Seligman, 2016).

As the name suggests the theory aims to explain a phenomenon of helplessness, which occurs in animals and humans when they are subjected to uncontrollable stress. Typical animal experiment on learned helplessness is carried out on rodents, consists of two stages, and requires three comparison groups. On the first day of the experiment, two groups are subjected to exactly equal amounts of moderately painful electric shock, but in one of the groups animals are allowed to control it by, for example, pressing a lever that would terminate the shock, whereas animals from the other group do not have such opportunity. The third group is not subjected to any kind of shock at all. The next day, all three groups are tested in a shuttle-box apparatus, which is a chamber divided into two compartments where electric shock delivered through the grid floor in one of the compartments can be escaped by jumping over a barrier to another compartment. The main behavioural result of these experiments is that the animals who had experienced uncontrollable stress on the first day often fail to learn how to escape the shock on the next day. They do not try to escape and passively wait until the shock stops itself. Such passivity also accompanied by anxiety- and depression-like symptoms can last for several weeks after the experiment. When these animals are later subjected to another type of stress (e.g., social defeat stress instead of electric shock) in a different environment, they demonstrate the same passivity and emotional distress, i.e., they act as if they already know that their responses will not stop the stress. That is why such behavior was called “learned” helplessness. On the contrary, animals that had experienced controllable stress or no stress on the first

day of the experiment quickly learn how to escape the shock in a shuttle-box on the next day. Moreover, animals from the controllable group later behave as if they know that they are able to control any type of aversive events even when these events are objectively uncontrollable and occur in a different environment. Such resilience to uncontrollable stress is not permanent, animals will eventually become helpless, nevertheless it is quite long-lasting (Maier and Seligman, 2016).

In subsequent studies, the authors of the theory focused on the neural correlates of the helplessness phenomenon (Maier and Seligman, 2016). They identified that two main effects of uncontrollability, i.e., passivity and emotional distress (anxiety/depression), are mediated by the influence of the dorsal raphe nucleus (DRN) on dorsal periaqueductal grey (dPAG) and basolateral amygdala. The dPAG is associated with expression of active coping mechanisms, such as fight/flight reactions (Bandler et al., 2000). It was found that in animals subjected to uncontrollable stress excessive serotonin released by the DRN neurons inhibits the dPAG, thereby inhibiting active behaviour. In parallel, serotoninergic projections from the DRN activate the amygdala and facilitate fear and anxiety reactions. Besides the DRN, activity of other stress-related brain structures, such as the locus coeruleus (LC), bed nucleus of the stria terminalis (BNST), and habenula, is also heightened during stress, but only the DRN is sensitive to controllability - it is much more active in uncontrollable conditions than in controllable. Artificial stimulation of the DRN is sufficient to induce helplessness, whereas blockade of the DRN neurons prevents helpless behaviour and emotional distress even in uncontrollable conditions. Thus, the DRN was identified as a key node in the helplessness circuitry (Maier and Seligman, 2016).

According to the theory, helplessness is a default behavioural response to stress. It was preserved by the natural selection process because it can be useful for survival. Passivity in objectively inescapable situations can prevent greater damage that useless attempts to escape may cause. It also saves energy for maintenance of vital physiological functions (Bandler et al., 2000). In objectively uncontrollable stress conditions, the best strategy is to passively wait until the situation resolves itself. However, when an opportunity to escape or control the stressor presents

itself, the default helpless behaviour has to be overruled and replaced by active coping behaviour. It was later discovered that in controllable stress situations, the prelimbic (PL) cortex (in rodents) inhibits the DRN, thereby preventing passive behaviour. Artificial activation of the PL cortex during uncontrollable stress inhibits the DRN and abolishes helplessness. Conversely, inactivation of the PL cortex in controllable conditions results in the same default hyperactivation of the DRN, passivity and anxiety as in uncontrollable conditions. Thus, the PL cortex plays important role in mediating protective effects of controllability (Maier and Seligman, 2016). Human PFC anatomically differs from the rodent PFC and it is not clear what PFC region in humans corresponds to the PL cortex in rodents (Myers-Schulz and Koenigs, 2012). However, an fMRI study that investigated neural correlates of controllable and uncontrollable stress in humans found that activation of the rmPFC was significantly higher during controllable stress (Kerr et al., 2012). Also, activity of the rmPFC negatively correlated with activity of the amygdala suggesting that inhibitory functions of the rodent PL cortex might be carried out by the rmPFC in humans.

The rmPFC (PL cortex in rodents) estimates the probability of control based on the analysis of contingencies between previous actions and their outcomes. According to the helplessness theory, such information is provided to the rmPFC by the dorsomedial striatum (DMS), which is involved in processing of action-outcome associations and flexible feedback-based instrumental learning (Maier and Seligman, 2016).

In summary, helpless behaviour and emotional distress in uncontrollable stress conditions are associated with hyperactivation of the DRN, subsequent inhibition of the dPAG, and activation of the amygdala. Activity of the DRN can be inhibited by the PL (the rmPFC in humans) if the DMS-PL circuit determines that the probability of control is high. These are the main brain regions and networks that mediate effects of uncontrollability and controllability according to the learned helplessness theory and model (Maier and Seligman, 2016).

However, there is evidence suggesting that other brain areas could also be involved. For example, passive coping reactions such as freezing and immobility are

associated with ventral PAG (vPAG) activation (Bandler et al., 2000; Depaulis et al., 1994). The vPAG has strong anatomical connections with the DRN (Vianna and Brandão, 2003). Perhaps, passivity in uncontrollable stress may develop not only because of inhibitory influence of the DRN on dPAG but also due to increased excitatory inputs from the DRN to vPAG.

Also, estimation of controllability in the helplessness theory was ascribed to the DMS-PL network. However, the DMS (caudate) is a part of the striatal memory system that also includes the dorsolateral striatum (putamen) and ventral striatum (accumbens). Precise functions of each component of the striatal system have not been established yet, but it has been suggested that the DMS plays more downstream role than the ventral striatum in instrumental learning and memory (Humphries and Prescott, 2010). The ventral striatum is associated with offline replay of past action-outcome memories during periods of rest and sleep, selection of actions that were associated with greater than expected outcome, and generation of a strategic plan of actions necessary for achievement of a specific goal. Whereas the dorsal parts of the striatum are implicated in execution, updating (dorsomedial striatum), and automatization (dorsolateral striatum) of the plans that were initially created by the ventral striatum (Humphries and Prescott, 2010).

Besides the striatal system that encodes action related associations, there is also the hippocampal and amygdalar memory systems that process contextual and biologically salient information respectively (McDonald and White, 1993). The amygdala has already been implicated in the helplessness model. The other two memory systems might be involved as well. Animals subjected to uncontrollable stress often demonstrate changes in the hippocampus (Song et al., 2006), such as inhibition of long-term potentiation (Ryan et al., 2010), loss of spine synapses (Hajszan et al., 2009), and reduced neurogenesis (Ho and Wang, 2010), that can be reversed by antidepressant treatment (Malberg and Duman, 2003). Ventral striatum also shows morphological (Bessa et al., 2013) and neurochemical (Muneoka et al., 2020) alterations. Thus, dysfunction of these memory systems or impaired interaction of the rmPFC with any of them, not only with the DMS, might negatively impact correct estimation of controllability.

Chronic pain conditions, such as CLBP, can be considered as uncontrollable stress situations, because very often patients' actions to escape pain have no or little influence on the outcomes. The aim of the present study was to test whether the neural processes described in the learned helplessness theory and additional mechanisms that were outlined above are relevant in CLBP. The hypotheses were that CLBP would be characterized by hyperactivity of the DRN, increased inhibition of the dPAG by the DRN, increased activation of the vPAG and amygdala by the DRN, reduced inhibitory influence of the rmPFC on DRN, and reduced interaction between the rmPFC and memory systems (hippocampus, amygdala, and ventral striatum). FC analysis is not suitable for making inferences on excitatory or inhibitory influences that one region may exert on another region. Therefore, spectral dynamic causal modelling (spDCM) method (Friston et al., 2014) that was specifically developed for assessment of effective connectivity between brain regions in resting state was chosen to test the hypotheses.

2.0 Materials and methods

Data used in this study were the same as in the previous study on FC in CLBP. After exclusion of participants with FD > 0.2 mm and signal dropout in the regions of interest, 27 CLBP patients and 27 HC were available for analysis (Table 3). Preprocessing of resting state fMRI data required for spDCM analysis is the same as for FC analysis. Hence, images were already preprocessed and denoised with ICA-AROMA (see Section 2 of Chapter 3).

Table 3. *Demographics and questionnaire scores of CLBP patients and healthy controls*

Data	CLBP patients	Healthy Controls	P-value
N.	27	27	-
Mean age (min-max) in years	49.52 (21 - 62)	48.59 (21-60)	0.71
N. Males	15	14	-
N. Right-handed	27	27	-
Mean pain duration (min-max) in years	15.41 (1 - 41)	-	-
Mean pain intensity (min-max)	6.6 (2.6 – 8.7)	-	-
Mean BDI (min-max)	6.8 (0 - 19)	1.7 (0 - 10)	0.0002
Mean FD	0.08	0.05	0.02
Displayed are the mean (min-max) values and p-values from independent samples t-tests. CLBP: chronic low back pain, BDI – Beck's Depression Inventory, FD – framewise displacement.			

Regions of interest. Spherical ROI masks with 3 mm radii were created using Statistical Parametric Mapping 12 (SPM12) software (version 7771). ROIs included the DRN (MNI coordinates: x=0, y=-34, z=-18), dPAG (x=-2, y=-32, z=-5), vPAG (x=-3, y=-32, z=-12), amygdala (x=-24, y=-6, z=-18), rmPFC (x=-6, y=64, z=-2), anterior (ventral) hippocampus (x=-22, y=-12, z=-20), and ventral striatum, i.e., the nucleus accumbens shell (x=-10, y=14, z=-9). Selection of ROIs was restricted to the left hemisphere only because there is evidence indicating that reduced structural connectivity between left prefrontal and limbic structures plays an important role in the pathogenesis of depression. It has been suggested that heightened activity of the left amygdala often observed in depression is a result of reduced regulatory input from the left medial PFC via the left uncinate fasciculus (Taylor et al., 2007). Furthermore, it was found that severity and duration of depression, as well as number of previous depressive episodes, negatively correlate with structural aberrations in the left but not right rmPFC (Bludau et al., 2016). Also, encoding of episodic memories and binding of new events with contextual information is associated with the left hippocampus, whereas the right hippocampus is more active during navigational processes (Miller et al., 2018).

The DRN neurons that send projections to the PAG and receive inhibitory input from the prelimbic cortex are located in the caudal part of the DRN (Grahn et

al., 1999). Therefore, the ROI mask was located at the caudal lower third of the DRN, which was identified using the Harvard Ascending Arousal Network atlas (Edlow et al., 2012). Coordinates of the dorsal and ventral PAG were taken from the study on functional parcellation of the human PAG by Coulombe et al. (2016). Coordinates of the amygdala were identified using the Harvard-oxford subcortical atlas (part of FSL). The rmPFC mask was made by placing the ROI sphere in the centre of the probability map of the medial prefrontal pole created by Bludau et al. (2014). The human hippocampus is functionally divided into anterior and posterior regions (Adnan et al., 2016) that correspond to ventral and dorsal regions of the rodent hippocampus (Strange et al., 2014). Most of the hippocampal inputs to the nucleus accumbens come from the anterior (ventral) part of the hippocampal formation (Humphries and Prescott, 2010). In addition, the anterior (ventral) hippocampus receives most of its serotonergic projections from the DRN, whereas the posterior (dorsal) hippocampus is innervated by the median raphe nucleus (Adams et al., 2008). Also, connections with the mPFC are stronger for the anterior (ventral) hippocampus than for the posterior (dorsal) hippocampus (Abela et al., 2013). Therefore, the anterior (ventral) hippocampus was chosen as a region of interest. Coordinates of the anterior (ventral) hippocampus were taken from the study on functional parcellation of human hippocampus by Adnan et al. (2016). With regards to the striatal memory system, the nucleus accumbens shell (ventral striatum) instead of the DMS was selected as a region of interest because of its more upstream role in the system (Humphries and Prescott, 2010). Coordinates for this ROI were adopted from Wager et al. (2008).

Spectral Dynamic Causal Modelling. Effective connectivity between the ROIs was estimated using DCM 12 software implemented in SPM 12 (version 7771). DCM is a Bayesian framework used to infer how activity in one region effects activity in another region (Zeidman et al., 2019a). It is based on Friston's model of neural activity (Friston et al., 2003). According to this model, the fMRI signal is a haemodynamic convolution of underlying neural signal. Changes of the fMRI signal in a particular region reflect changes of the local neural activity that were caused by experimental inputs (e.g., performance of a task or presentation of a stimulus)

and/or by the influence of other brain regions. Changes in neural activity and corresponding haemodynamic responses can be mathematically modelled with non-linear differential equations (Friston et al., 2003). Using the mathematical model of neural activity, it is possible to predict haemodynamic responses, i.e., simulate fMRI timeseries. Altering certain parameters of the neural model, for example the strength or valence of connectivity between regions, will produce different simulated timeseries. By evaluating the fit between the original and simulated fMRI timeseries it is then possible to infer how activity in one area might be effected by activity of another region.

DCM estimates effective connectivity in two stages. During the first stage (model inversion or estimation), DCM identifies what parameter values (e.g., strength of a connection between certain regions) of the model generate timeseries that are closest to the actual data. As different combinations and values of parameters can potentially explain the actual fMRI data, during the second stage (model comparison), different models with different network architectures are compared with each other, either at individual or group level, to identify the best model that explains the data (Zeidman et al., 2019a, 2019b).

The fMRI data used in the present study were acquired in resting-state, therefore spectral DCM was used for the analysis (Friston et al.,2014). It uses the same mathematical model of neural activity as the standard DCM, but without modulatory parameters, as participants do not perform any tasks during the acquisition. Also, instead of fMRI timeseries per se, spDCM predicts cross-spectral characteristics of the timeseries, such as coherence, cross-power, and relative phase. This allows modelling of the resting state fMRI data in the frequency domain, rather than the time domain, which is more computationally efficient and sensitive to group differences (Friston et al.,2014).

First-level analysis. In the first-level analysis a bidirectional, two-state (excitatory and inhibitory), fully connected (each ROI connected to all other ROIs and to itself) model was specified for each participant to estimate effective connectivity between all the ROIs. The estimation procedure, called variational Laplace (Friston et al., 2007), was used to iteratively adjust the connectivity values

in order to identify an optimal model with the closest fit to the actual data. After estimation of connectivity parameters at the subject level, the next step was to test what within-subject effects are relevant at the between-subject level.

Second-level analysis. Group level analysis was performed using the Parametric Empirical Bayes (PEB) framework (Friston et al., 2016). First, the parameters of effective connectivity between each pair of ROIs from all participants (CLBP+HC) estimated at the first level were collated and specified in the second level GLM as a linear combination of a group mean, differences in connectivity due to CLBP, and unexplained between-subject variability. Residual head movement (FD) was also included as a covariate of no interest. After estimation (inversion) of group-level parameters, Bayesian model comparison (BMC), Bayesian model reduction (BMR), and Bayesian model averaging (BMA) were performed consecutively and automatically by the software to find the optimal group-level model of effective connectivity (out of all possible models) and differences in connectivity due to CLBP. Additional PEB analyses were conducted in the CLBP and HC groups separately in order to visually assess whether the two groups have similar or different models of effective connectivity (Zeidman et al., 2019a, 2019b).

3.0 Results

Analysis of effective connectivity using DCM and interpretation of results requires some a priori theoretical model that could explain the role of each region in the model (Stephan et al., 2010). Since DCM in the present study was inspired by the learned helplessness theory, only the mechanisms that were implicated in the learned helplessness theory will be described in this section and discussed in the following section.

Models of effective connectivity between all ROIs in CLBP and HC groups are presented in Figure 10. As spDCM estimates and predicts fMRI data in the frequency domain, connections between regions are measured in units of hertz (Hz). Excitatory connections displayed in red colour, inhibitory connections – in

blue. Final models were thresholded to only include parameters that had a 95% posterior probability of being present, i.e., parameters with strong evidence.

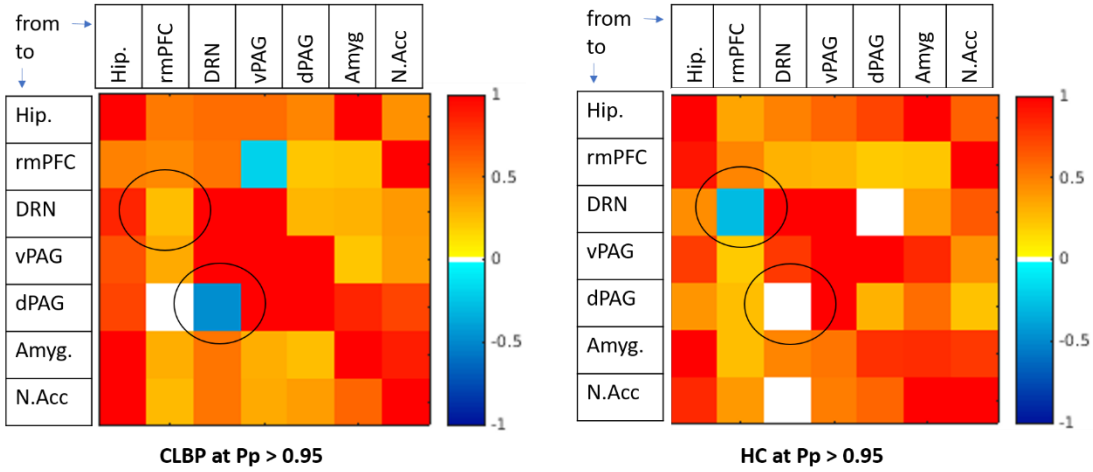


Figure 10. Models of effective connectivity in CLBP (left) and HC (right) groups thresholded at posterior probability >95%. CLBP – chronic low back pain; HC – healthy controls; Pp – posterior probability; Hip – hippocampus, rmPFC – rostromedial PFC; DRN – dorsal raphe nucleus; vPAG – ventral periaqueductal grey; dPAG – dorsal periaqueductal grey; Amyg – basolateral amygdala; N.Acc – nucleus accumbens shell (ventral striatum).

Visual comparison of the models suggests stronger inhibitory influence of the DRN on dPAG in the CLBP group. In the HC group, this connection was insignificant. However, lowering the threshold of posterior probability to >50%, which in Bayesian statistics is considered as a weak evidence (Kass and Raftery, 1995), in the HC group resulted in occurrence of a weak inhibitory connectivity between the DRN and dPAG (Fig. 11) suggesting that the DRN inhibits dPAG in the HC group too, but this effect is much weaker than in CLBP. This is in accordance with neurophysiological studies reporting that serotoninergic projections from the caudal DRN to dPAG are predominantly inhibitory (Lovick, 1994). It is also consistent with the learned helplessness model according to which inhibitory effect of the DRN on dPAG is higher in uncontrollable stress conditions, i.e., in CLBP patients (Maier and Seligman, 2016). CLBP patients also displayed stronger excitatory connection from the DRN to vPAG, but connectivity from the DRN to amygdala was similar in both groups. Effective connectivity from the rmPFC to DRN was inhibitory in the HC group indicating that the DRN is under inhibitory control. In contrast, this

connection was excitatory in the CLBP group. The HC group also showed stronger effective connectivity from the hippocampus to rmPFC.

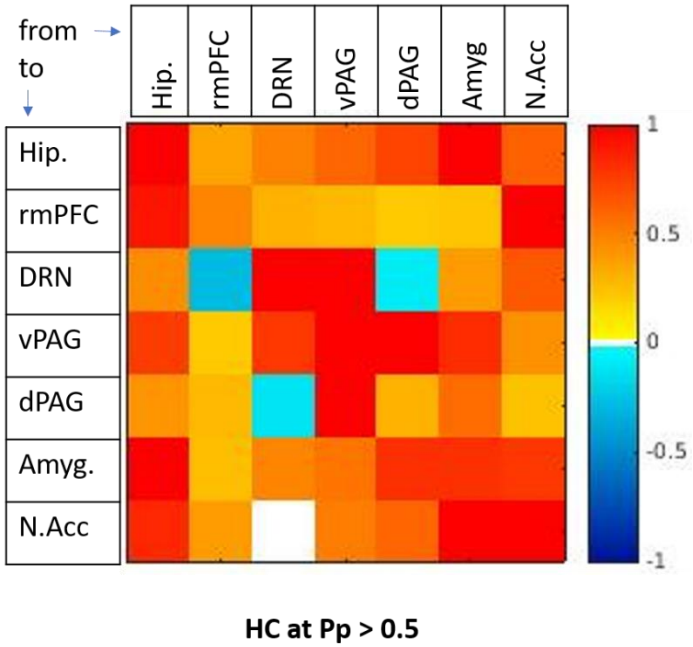


Figure 11. A model of effective connectivity in the HC group thresholded at posterior probability >50%. HC – healthy controls; Pp – posterior probability; Hip –hippocampus, rmPFC – rostromedial PFC; DRN – dorsal raphe nucleus; vPAG – ventral periaqueductal grey; dPAG – dorsal periaqueductal grey; Amyg – basolateral amygdala; N.Acc – nucleus accumbens shell (ventral striatum).

However, differences found with visual inspection of two models may be statistically insignificant. In DCM, strength of the connectivity between two regions is contingent on the overall model structure (Stephan et al., 2010). It is not reasonable to make statistical inferences about group differences in connectivity based on parameter values that were derived from the models with different structures. Therefore, group differences in DCM are inferred by, first, identification of an optimal model for all participants (CLBP patients and HC) and, second, evaluation of the influence that having CLBP or being healthy has on each parameter of that model. The single model for both groups is shown in Figure 12 and positive or negative effects of having CLBP are presented in Figure 13. Positive values (coloured in red) in Figure 13 mean more excitatory connections due to CLBP, whereas negative (coloured in blue) values mean more inhibitory influence of CLBP.

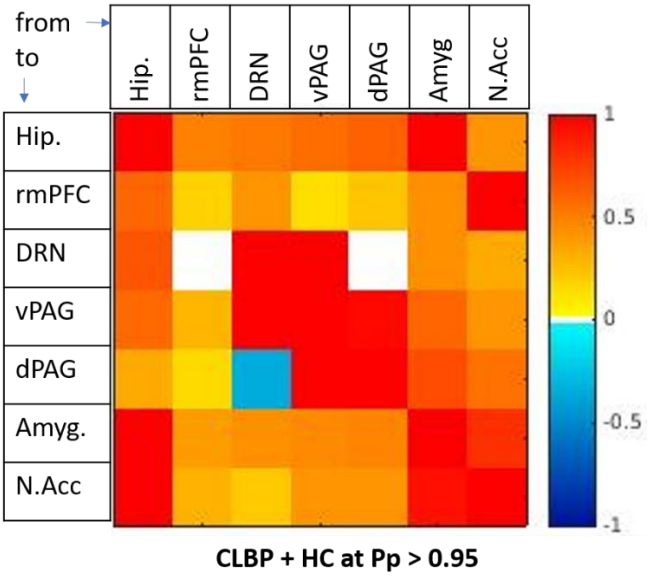


Figure 12. Single model of effective connectivity for both groups thresholded at posterior probability >95%. CLBP – chronic low back pain; HC – healthy controls; Pp – posterior probability; Hip – hippocampus, rmPFC – rostromedial PFC; DRN – dorsal raphe nucleus; vPAG – ventral periaqueductal grey; dPAG – dorsal periaqueductal grey; Amyg – basolateral amygdala; N.Acc – nucleus accumbens shell (ventral striatum).

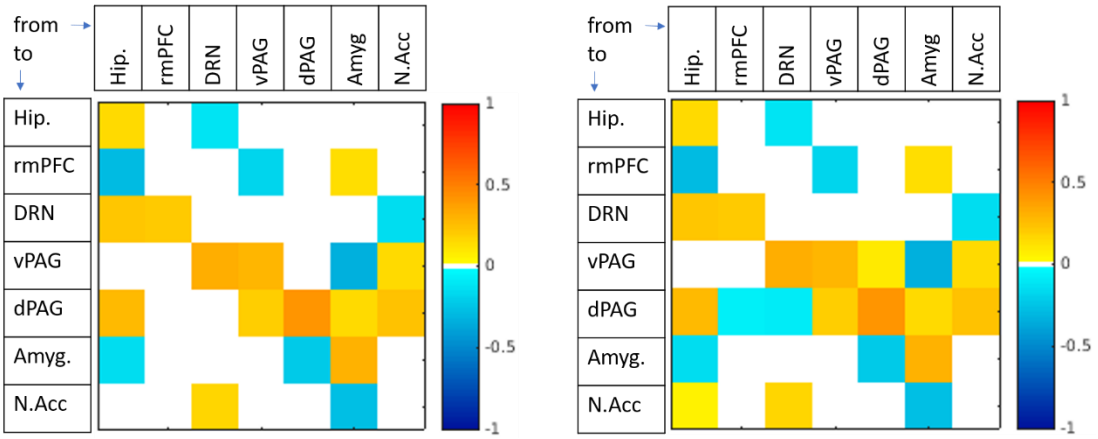


Figure 13. Group differences in effective connectivity thresholded at posterior probability >95% (strong evidence) (left) and >50% (weak evidence) (right). Positive values (red) represent more excitatory or less inhibitory connections in CLBP compared to HC. Negative values (blue) represent more inhibitory or less excitatory connections in CLBP compared to HC. Hip – hippocampus, rmPFC – rostromedial PFC; DRN – dorsal raphe nucleus; vPAG – ventral periaqueductal grey; dPAG – dorsal periaqueductal grey; Amyg – basolateral amygdala; N.Acc – nucleus accumbens shell (ventral striatum).

The connection from the DRN to dPAG in a single model for both groups is also inhibitory (Fig.12). It was hypothesized that CLBP patients would demonstrate increased inhibitory connectivity from the DRN to dPAG. However, comparison

between the groups did not reveal significantly higher inhibitory effect in the CLBP group (Fig.13) at posterior probability threshold > 95%. Lowering the threshold to >50% showed only weak evidence (Kass and Raftery, 1995) of increased inhibitory connectivity between the DRN and dPAG in CLBP (Fig.13). In contrast with another hypothesis, CLBP was not associated with increased excitatory connection from the DRN to amygdala. There was a positive association between CLBP and increased excitatory connection from the DRN to vPAG. Also, the CLBP group showed increased excitatory connection from the rmPFC to DRN and reduced excitatory connection from the hippocampus to the rmPFC.

4.0 Discussion

CLBP patients demonstrated increased excitatory connectivity from the DRN to vPAG and ventral striatum, but connectivity from the DRN to anterior hippocampus was more inhibitory (Fig.13). In turn, the DRN in CLBP patients was more activated by excitatory inputs from the rmPFC, whereas in HC the connectivity from the rmPFC to DRN was more inhibitory (Fig.10). The rmPFC in the patient group received less excitatory inputs from the hippocampus and more excitatory from the amygdala. Also, CLBP group displayed increased excitatory connections from the hippocampus, amygdala, vPAG, and nucleus accumbens to dPAG (Fig.13). In the following section these results will be discussed in more detail.

CLBP can be considered as an uncontrollable stress condition, because very often pain persists despite the actions that patients take in order to stop it. Uncontrollable stress is a major risk factor of emotional disorders. Therefore, neural processes associated with uncontrollable stress might play important role in the development of chronic pain and emotional disorders. The aim of this study was to test whether CLBP patients would demonstrate the same processes as described in the learned helplessness theory, which is considered as one of the strongest theories and animal models of emotional disorders (Vollmayr and Gass, 2013; Wang et al., 2017).

According to the theory (Maier and Seligman, 2016), there are three main brain networks that mediate the effects of uncontrollable stress. The first network consists of the DRN, dPAG, and amygdala. During uncontrollable stress, the DRN becomes hyperactivated by other stress-related regions, such as the locus coeruleus and bed nucleus of the stria terminalis (BNST). In turn, serotonergic inputs from the DRN inhibit activity of the dPAG, a region that mediates active coping, thereby causing passivity. At the same time, the DRN increases activity of the amygdala and facilitate emotional distress. The second network, the rmPFC-DRN pathway, inhibits activity of the first network when stress is perceived as controllable. Finally, the third network consisting of the rmPFC and memory systems, such as the DMS, evaluates probability of control (Maier and Seligman, 2016).

Results of this study are not entirely consistent with the learned helplessness model. In contrast to the helplessness model, DCM analysis found only weak evidence of increased inhibitory connectivity from the DRN to dPAG and no evidence of increased excitatory connectivity from the DRN to amygdala in CLBP patients. However, the results also suggest some alternative mechanisms how uncontrollable stress may cause passive behavior and emotional disturbances. DCM showed strong evidence of increased excitatory connectivity from the DRN to vPAG (Fig.13). Functions of the vPAG are opposite to the functions of the dPAG. If stimulation of the dPAG results in vigorous motor reactions, activity bursts in attempts to escape, hypervigilance, tachycardia, and tachypnea (Brandão et al., 2008), stimulation of the vPAG produces immobile behavior, reduction of spontaneous activity, quiescence, hyporeactivity to environment, bradycardia, and bradypnea (Depaulis et al., 1994). Perhaps, passivity can be explained not only by increased inhibitory influence of the DRN on dPAG, as was proposed in the learned helplessness model, but also by increased excitatory connectivity from the DRN to vPAG.

Moreover, the dPAG in CLBP patients was actually hyperactivated rather than inhibited. It received increased excitatory connections from the hippocampus, amygdala, vPAG, and nucleus accumbens (Fig.13). The dPAG is a fundamental part of the hierarchically organized fear system that also includes the mPFC,

hippocampus, amygdala, and medial hypothalamus. Higher-level regions of the circuitry process and integrate perceptual information, the hypothalamus controls autonomic and endocrine reactions, whereas the dPAG is responsible for behavioral expression of fear (Panksepp et al., 2011). Although induction of a fear response can be achieved by electrical stimulation of any part of the system, stimulation of the dPAG produces stronger and faster fear response than stimulation of, for example, the amygdala or hypothalamus. Additionally, lesion to the dPAG abolishes the negative affect produced by electrical stimulation of the amygdala or hypothalamus, but lesions to the amygdala or hypothalamus do not prevent the negative affect induced by dPAG stimulation (Davis and Montag, 2019). Furthermore, chronic stimulation of the dPAG in animals results in depression-like behaviour that manifests in decreased exploration, altered sucrose intake, and suppressed positive affect that can persist for a very long period (30 days) after the final stimulation (Wright and Panksepp, 2011). These behavioural effects are similar to the main symptoms of major depressive disorder, i.e., psychomotor retardation, anhedonia, and low mood (Lemke et al., 1999). Considering all the above-mentioned findings, results of this study suggest that passivity in uncontrollable stress conditions could be mediated by hyperactivation of the vPAG, rather than by inhibition of the dPAG, whereas emotional consequences (anxiety/depression) are probably caused by hyperactivity of the dPAG, rather than by hyperactivation of the amygdala. As described in Chapter I, Section 4.2, the amygdala plays an important role in conditioning, i.e., in establishing associations between neutral signals and rewards, punishments, and threats, that allows apprehension of biologically salient events before they actually happen. Therefore, the amygdala is more important for appraisal of the salience of incoming sensory information, but the experience of fear per se is more dependent on the dPAG activity (Panksepp et al., 2011).

Prolonged hyperactivation of the dPAG and vPAG can also explain hypersensitivity to pain, a hallmark of chronic pain disorders. Many animal models that use chronic stress to produce emotional disorders also report increased sensitivity to pain, referred to as stress-induced hyperalgesia (SIH) (Jennings et al., 2014). Lesion to the dPAG prevents and eliminates SIH (McLemore et al., 1999). On

the other hand, exposure to acute, intense stress reduces pain sensitivity, a phenomenon called stress-induced analgesia (SIA). SIA has been linked with activation of the descending pain inhibitory pathway and release of endogenous opioids, particularly in the vPAG (Jennings et al., 2014). However, prolonged stimulation of the vPAG during uncontrollable physical or psychological stress with excessive levels of opioids gradually lead to reduced sensitivity and expression of opioid receptors leading to reduced analgesic effect of endogenous or exogenous opioids (Suarez-Roca et al., 2006). This is one of the reasons why pain sensitivity thresholds become lower in chronic pain patients, especially in those treated with opioid analgesics (Le Roy et al., 2011). Another important negative consequence of increased opioid secretion is upregulated synthesis of cholecystokinin (CCK) which has strong anxiogenic, depressogenic (Netto and Guimarães, 2004), and pronociceptive effects (Jennings et al., 2014). Increased CCK levels may also facilitate hyperactivation of the dPAG because CCK receptors are abundantly expressed in this region (Lovick, 2008). Taken together, prolonged hyperactivity of the dorsal and ventral PAG might be responsible not only for behavioral and emotional consequences of uncontrollable stress but also contribute to altered pain processing.

With regards to the second network that inhibits activity of the DRN in controllable stress situations, visual comparison of effective connectivity models that were estimated separately for two groups showed that the rmPFC inhibits the DRN in healthy controls but excites it in CLBP (Fig.10). CLBP patients also demonstrated higher excitatory connectivity from the rmPFC to DRN (Fig.13). In the original learned helplessness model (Maier and Seligman, 2016), the PL cortex in rodents plays only inhibitory role and becomes active only when stress can be controlled. In the present study, however, results suggest that the rmPFC, which is far more developed in humans (Bludau et al., 2014), can exert both inhibitory and facilitatory influence on the DRN. As already discussed in previous chapters, the rmPFC is involved in processing of autobiographical memories and generation of self-concepts (D'Argembeau, 2013), such as self-efficacy, which is a belief that one is capable of coping with any adverse events. High self-efficacy and positive self-

concepts in general play protective role against emotional disorders and chronification of pain (Ferrari et al., 2019; Tahmassian and Jalali Moghadam, 2011). Opposite effects of the rmPFC on the DRN activity in the HC and CLBP groups probably reflect their differences in self-concepts. Healthy people usually have positive self-concepts and even tend to overestimate their abilities (Jones et al., 2019). A strong belief that one is capable of controlling any stressful situation might facilitate inhibition of the DRN activity even when stress is objectively uncontrollable. In contrast, CLBP patients are known to have negative, depreciating self-concepts (de Moraes Vieira et al., 2014). As described in Chapter I, Section 2.3, negative self-concepts, such as low self-esteem or self-efficacy, can be a premorbid personality feature that developed due to other non-pain related chronic uncontrollable stress (e.g., childhood abuse) experienced before the onset of a low back pain. Alternatively, they can also develop after the onset of CLBP as a result of generalization of multiple failed attempts to control pain itself and/or its socio-economic consequences. Regardless of the timeline, negative self-concepts may exaggerate perceived sense of uncontrollability and contribute to hyperactivation of the DRN. Importantly, as they are generalized beliefs, they may also incline patients to interpret controllable non-pain related stress situations as uncontrollable too, thereby increasing vulnerability to emotional disorders. Formation of concepts, including self-concepts, has been ascribed to the mPFC that interacts with memory systems, such as the hippocampus, extracts the commonalities across multiple episodic memories, and generalizes them (Bowman and Zeithamova, 2018; Gilboa and Marlatte, 2017). Thus, unimpaired interaction of the mPFC with memory systems is important for generation of accurate concepts including the concept about one's ability to control negative events.

Similarly, in the learned helplessness theory, determination of whether the situation is controllable or not is performed by the network consisting of the DMS and PL cortex that evaluates the probability of control by examining contingencies between previous actions and their outcomes (Maier and Seligman, 2016). However, the DMS is only a part of the striatal memory system. In turn, striatal system is only one of several memory systems. In addition to the striatal system

that specializes on action-reward associations, there is also the hippocampal system that memorizes stimulus-stimulus associations, and the amygdalar system that encodes stimulus-reward associations. All three systems operate independently of each other, but can also complement each other by encoding different aspects of the same event (White et al., 2013). For example, a neutral signal (conditioned stimulus) associated with pain (unconditioned stimulus) would be memorized by the amygdala. Actions that caused or terminated pain would be encoded by the striatum. Whereas context, e.g., a specific combination or a sequence of events that preceded the pairing of unconditioned and conditioned stimuli, or time and place, in which that neutral signal, painful stimulation, and action co-occurred would be encoded by the hippocampus. All three networks are reciprocally connected with the mPFC that probably integrates information from all three sources (White et al., 2013). Thus, altered interaction of the rmPFC (PL cortex in rodents) with any of these memory systems can potentially compromise accurate assessment of controllability. The CLBP group demonstrated reduced excitatory effective connectivity from the hippocampus to rmPFC (Fig.10, 13), which is consistent with the study by Ayoub et al. (2019) who found decreased FC between the same regions in CLBP. Reduced connectivity with the hippocampus indicates that the rmPFC might be deprived of contextual information. The lack of contextual information may hinder retrieval of previous episodes of successful control if control was dependent on a specific context, interfere with accurate evaluation of one's ability to control negative events, and lower the sense of self-efficacy.

Besides reduced connectivity from the hippocampus, the CLBP group was also characterized by heightened connectivity from the amygdala to rmPFC (Fig.13). This result is in line with animal studies that found stronger dopaminergic metabolic activation of the mPFC by amygdala during conditioned fear experiments (Davis et al., 1994; Goldstein et al., 1996). Weaker connectivity with the hippocampus and stronger connectivity with the amygdala suggests that the rmPFC is in short supply of contextual information but relatively overloaded with conditioned associations. Such imbalance may predispose patients to exaggerated fear reactions because contextual information serves as a natural restraint to conditioned fear. Expression

of fear in response to a neutral signal (e.g., tone) that was previously paired with unconditioned stimulus (e.g., pain) is normally limited by the context (e.g., environment) in which the association occurred. Without contextual restriction, presentation of the conditioned stimulus elicits fear reaction irrespective of the context leading to overgeneralization of fear. Such mechanism has been implicated in the pathophysiology of PTSD and other anxiety disorders (Kheirbek et al., 2012). There is also evidence showing that the hippocampus plays important role in extinction of previously learned conditioned fears (Qi et al., 2018) and that extinction is dependent on the strength of coupling between the hippocampus and mPFC (Meyer et al., 2019).

Reduced connectivity from the hippocampus to rmPFC could be partly due to inhibitory influence of the DRN (Fig.13). Enhanced inhibitory connectivity from the DRN to hippocampus is in line with studies reporting that serotonin inhibits pyramidal cells of the hippocampus (Varga et al., 2009; Yoshida et al., 2019). One of the functions associated with the anterior (ventral) hippocampus is exploratory locomotion (Bast and Feldon, 2003). During locomotion and other behaviors that involve active engagement with environment, such as navigating or exploration of novel objects, the hippocampal local field potentials oscillate in theta frequency (Drieu and Zugaro, 2019). It was found that activation of serotonin 5-HT2c receptors in the hippocampus inhibits, whereas blockade of 5-HT2c receptors facilitates hippocampal theta activity (Sörman et al., 2011). Hence, hyperactivation of the DRN in uncontrollable stress situations and consequent increased release of serotonin in target regions can suppress active behavior not only via activation of the vPAG, but also through inhibition of the exploratory drive that is mediated by the anterior hippocampus. As mentioned in the introduction, biological purpose of passivity is probably to prevent additional damage and save energy for more vital functions (Bandler et al., 2000; Maier and Seligman, 2016). Additionally, inhibition of exploratory behavior and disengagement from external environment allows an offline replay of spatially and temporally remote past experiences necessary for consolidation, relative association, simulation, imagination, and future planning processes (Pfeiffer, 2020). Replay of previous experiences is associated with a

pattern of local field potential oscillations called the sharp-wave ripples which spontaneously occur in quiescent behavioral states and during sleep (Drieu and Zugaro, 2019). There is evidence showing that serotonin can inhibit not only theta oscillations but also the sharp-wave ripples meaning that serotonin can interfere with reactivation and consolidation of hippocampal memories (Kubota et al., 2003; Wang et al., 2015). It appears that this effect of serotonin is dose dependent. Decrease in sharp wave ripples occurs when serotonin levels are very high, whereas low levels do not inhibit them (ul Haq et al., 2016). Hence, previously described consequences of impaired contextual processing, such as inaccurate estimation of controllability, overgeneralization of fears, and diminished fear extinction, could be mediated by amplified serotoninergic input from the DRN to hippocampus in uncontrollable stress conditions.

Similar spontaneous reactivations of neuronal firing in resting state were also found in the ventral striatum and amygdala (Cox et al., 2020; Lansink et al., 2008). Moreover, they normally appear at the same time as hippocampal reactivations. Simultaneous replay of hippocampal, amygdalar, and ventral striatal memories during rest is thought to represent consolidation and integration of contextual, action-related, and reward-related information (Cox et al., 2020; Lansink et al., 2008). The CLBP group in the present study displayed enhanced activation of the ventral striatum by the DRN (Fig.13). This is in line with the observation that electrical stimulation of the DRN results in heightened dopamine release in the nucleus accumbens, whereas serotonin depletion and serotonin receptor antagonists abolish the effects of DRN stimulation (De Deurwaerdère et al., 1998). In turn, increased dopamine release is associated with consolidation of striatal dependent memories (Managò et al., 2009). Therefore, enhanced excitatory connectivity from the DRN to nucleus accumbens and subsequent increase in ventral striatal dopamine levels might facilitate reactivation and consolidation of action-reward associations. In the context of CLBP, such increased striatal reactivation might contribute to the development and persistence of a fear of movement. Essentially, fear of movement is a manifestation of a learned action-reward or, in this case, action-punishment association where movement (action)

was conditioned to elicit fear response because it had been previously penalized by pain (punishment). Fear of movement plays important role in persistence of low back pain and predicts greater disability (Vlaeyen and Linton, 2000). Considering that the hippocampus was inhibited by the DRN, such fear will probably be less constrained by contextual information and more resistant to extinction.

5.0 Conclusions

This study aimed to assess causal interactions between brain regions that mediate negative effects of uncontrollability and protective effects of perceived control according to the learned helplessness theory. In general, results of the study are compatible with the theory; however, they suggest different mechanisms of passivity and negative affect. Passive coping behavior in chronic pain conditions could be mediated by hyperactivation of the vPAG and inhibition of the anterior hippocampus, whereas emotional distress is probably caused by increased activity of the dPAG. Also, besides the processes outlined in the learned helplessness theory, DCM analysis found evidence of additional mechanisms that could contribute to increased vulnerability of chronic pain patients to emotional disorders. Patients showed altered interaction of the rmPFC with the hippocampal and amygdalar memory systems that may contribute to inaccurate evaluation of controllability, overgeneralization, and impaired extinction of fears. Suppression of hippocampal functions probably occurs as a result of excessive inhibitory influence of the DRN.

6.0 Limitations

First limitation of this study is that effective connectivity cannot be measured directly, not by DCM nor by any other existing neuroimaging methods (Bielczyk et al., 2019). Estimation of causal interactions in DCM is based on

mathematical modelling of dynamic processes that occur in neuronal networks (Friston et al., 2003). Although the neural network model implemented in DCM is considered as biologically plausible (David et al., 2008), it is only an approximate depiction of complex processes and cannot account for all the intricacies that might exist. Some researchers even question fundamental validity of the DCM approach (Lohmann et al., 2012), some are cautious with regards to biophysical accuracy of the modelling and reliability of statistical methods used in DCM (Daunizeau et al., 2011). DCM evaluates thousands of possible models of effective connectivity and selection of the final model that fits the real fMRI data is based on a trade-off between model accuracy and complexity (Zeidman et al., 2019a, 2019b). It has been demonstrated with simulation studies that under certain conditions Bayesian model selection (BMS) algorithm utilized in DCM can select incorrect model, especially when evidence in favor of true and false models is very similar (van den Honert et al., 2017). However, some of the results of the present study (e.g., inhibitory effect of the DRN on dPAG activity) are consistent with the results of direct electrophysiological recordings (Lovick, 1994) suggesting that models of connectivity selected by DCM are likely to be correct but need validation in an independent cohort.

Another limitation is that Parametric Empirical Bayes (PEB) procedure used to make comparisons between groups requires identification of a single best model of effective connectivity for both groups (Zeidman et al., 2019a, 2019b). In other words, DCM assumes that patients and controls differ only in strength and/or valence (excitatory vs inhibitory) of connectivity parameters. However, it is theoretically possible that patients and healthy controls might also differ in model structure - certain connections might be relevant in one group and irrelevant in another group. For example, in the PEB models that were estimated separately for CLBP and HC groups, the connection from the DRN to dPAG was strongly inhibitory in the CLBP group and nearly absent in the HC group (Fig.10). After averaging across all participants (CLBP+HC) this connection became less inhibitory than it was in CLBP group and more inhibitory than it was in the HC group (Fig.12), probably because high parameter values of the CLBP patients were diluted by low values of the HC

group. Inferring group differences by comparing connectivity parameters of one group (e.g., CLBP) with the parameters of the overall group (CLBP+HC) could potentially underestimate some of the differences between groups and overestimate others.

Finally, the present study as well as the previous one lacks behavioral data to support some of the conclusions. For example, there was no data on self-efficacy and other self-concepts that could be used to see how individual differences in self-concepts correspond with the differences in rmPFC connectivity. Also, the sample of CLBP patients did not suffer from comorbid depression. Comparison of effective connectivity in depressed vs non-depressed CLBP patients could confirm or reject some of the conclusions described above.

V. Functional connectivity of the rmPFC and rlPFC in patients with osteoarthritis

1.0 Introduction

Results of functional and effective connectivity studies in CLBP described in two previous chapters showed altered connectivity of the rmPFC with memory and reward-related systems. Altered interaction with these systems may hamper accurate estimation of one's ability to cope with stress. This, in turn, may result in impaired regulation of brainstem regions implicated in early nociceptive and emotional reactions leading to hyperalgesia and negative affectivity. However, according to the latest classification, CLBP is a primary pain disorder (Nicholas et al., 2019; Treede et al., 2019) that has different mechanisms of development than secondary pain disorders (Kosek et al., 2016). In primary pain disorders, altered central processing of pain and its modulation by emotional or cognitive factors play more important role than peripheral structural pathology, whereas in secondary pain disorders, nociception is mainly driven by pathological changes in affected organs. Another characteristic feature of primary pain is a significant emotional distress (Nicholas et al., 2019; Treede et al., 2019), which makes patients with primary pain more susceptible to psychiatric comorbidities compared to patients with secondary pain disorders (Bair et al., 2003; Margaretten et al., 2011; Sale et al., 2008). Therefore, it is possible that impaired connectivity and dysfunction of the rmPFC observed in CLBP might be relevant only for primary but not secondary pain disorders. To test whether this assumption is true, the present study investigated FC of the rmPFC in patients with chronic osteoarthritis (OA).

OA is the most common form of joint diseases that affects approximately 15% of the population of the world (Johnson and Hunter, 2014). It is currently considered as a chronic secondary pain disorder (Treede et al., 2019). However, there is evidence contradicting such categorization. As mentioned above, the main defining feature of a secondary pain disorder is that it can be attributed to some underlying structural pathology. Indeed, OA is associated with multiple structural

abnormalities in affected joints, such as cartilage degeneration, subchondral bone remodelling, formation of osteophytes, synovial inflammation, and many others (Hunter et al., 2013). However, approximately 50% of individuals with such structural changes do not report pain (Hannan et al., 2000). In symptomatic OA patients, pain severity does not always correlate with the degree of structural pathology (Hunter et al., 2013). These findings suggest that experience of pain in OA cannot be fully explained by peripheral pathology and other factors might play an important role as well. A longitudinal study by Wise et al. (2010) found a strong relationship between negative affect and severity of OA pain. More negative affect at baseline was associated with more severe pain, conversely, improvement of the emotional state led to reduction of pain. Moreover, exacerbation of pain could be predicted by worsened mental health one week prior to the flare (Wise et al., 2010) indicating that altered emotional modulation of pain plays an important role not only in primary pain disorders but in OA too. Depression and anxiety are also common among patients with OA (Sharma et al., 2016). Epidemiological studies suggest that approximately 20% of patients have at least moderately severe depression (Rosemann et al., 2007; Sale et al., 2008). Albeit prevalence of depression in OA is lower than in primary pain disorders, for example in CLBP the point prevalence of depression is 60% (Andersson, 1999), it is still much higher than in general population (5-8%) (Bair et al., 2003). There is also evidence suggesting important role of cognitive factors. Reduced cognitive flexibility, i.e., the ability to appropriately adjust one's behaviour to a changing environment (Dajani and Uddin, 2015), has been found in OA patients. Moreover, it was strongly associated with persistence of pain 6 and 12 months after total knee arthroplasty (Attal et al., 2014). Finally, several studies reported altered central pain processing in OA (Imamura et al., 2008; Moss et al., 2016; Wylde et al., 2012). For example, Moss et al. (2016) found reduced pain thresholds for pressure and cold in patients with chronic knee OA in pain-free parts of their bodies indicating widespread hyperalgesia due to central sensitization.

Taken together, at first sight, these findings contradict the proposed distinction between primary and secondary pain disorders. It seems that altered

pain processing in the CNS and impaired modulation of pain by emotional or cognitive factors play important roles in secondary pain disorders too. However, the authors of the new classification noted that prolonged experience of secondary pain may cause structural and functional changes in the brain that, in turn, may result in altered processing and modulation of pain at the central level making the pathophysiology of a secondary pain disorder at later stages similar to the pathophysiology of a primary pain disorder (Kosek et al., 2016; Treede et al., 2019). Indeed, there is evidence suggesting that experience of chronic OA pain is associated with reduction of grey matter in areas involved in pain modulation including the rmPFC, rlPFC, dlPFC, ACC, and insula that reverses after endoprosthetic surgery (Rodriguez-Raecke et al., 2013). Another study found that cortical thickness of temporal, parietal, and frontal areas including the rmPFC and rlPFC negatively correlates with OA pain duration (Alshuft et al., 2016). It has been estimated that such structural changes appear in the brain after approximately 5 years of chronic pain (Baliki et al., 2011).

Structural changes in the rmPFC at later stages of OA may cause its dysfunction and altered interaction with memory systems. This may result in inaccurate estimation of controllability and consequent dysregulation of low level nociceptive and emotional responses leading to hyperalgesia and negative affectivity. Structural changes in the rlPFC may impair its interaction with other frontoparietal cortical regions implicated in cognitive flexibility (Mansouri et al., 2017; Varjacic et al., 2018). Patients with impaired cognitive flexibility may continue to use maladaptive behavioural strategies, e.g., avoidance, thereby contributing to chronification, emotional distress, and disability (Vlaeyen and Crombez, 2020).

Considering all the above, the OA group in the present study was divided into two subgroups depending on duration of their knee pain. The first hypothesis was that FC of the rmPFC in patients with shorter duration of pain would not differ from healthy controls. The second hypothesis was that patients with longer duration of pain would demonstrate reduced connectivity of the rmPFC with memory systems (e.g., the hippocampus, amygdala, ventral striatum) and stress-

related regions of the brainstem (e.g., the PAG, MRF, DRN) similar to CLBP patients in previous studies.

With regards to the rlPFC, the first hypothesis was that FC of the rlPFC in patients with shorter duration of OA would not differ from healthy controls. The second hypothesis was that patients with longer duration of OA pain would demonstrate reduced FC of the rlPFC with multiple frontoparietal regions implicated in cognitive control.

2.0 Methods

Participants

This was a sub-study of a larger project on multidimensional phenotyping of OA pain (INCOPE, Imaging Neural Correlates of Osteoarthritis Phenotypes). The dataset consisted of structural and functional MRI images from 86 community-dwelling patients with chronic OA of the knee and 41 healthy, pain-free participants. The OA group was further subdivided into two subgroups depending on duration of their knee pain using the median split method. Inclusion criteria for patients were a diagnosis of knee OA and reported chronic pain in the knee for more than 3 months with pain present for most of the day and more than 14 days per month. Also, knee pain had to be their most troublesome pain complaint. Healthy participants reported no current or past knee pain nor chronic pain elsewhere. Participants were excluded from the study if they had a past or current diagnosis of major neurological or psychiatric disease. The study was approved by the Nottingham Research Ethics Committee 2 (NREC reference: 10/H0408/115) and all participants provided written informed consent before enrolling in the study.

Psychometric data and quantitative sensory testing

All participants underwent psychometric testing before the MRI scanning session. Pain severity was measured approximately one hour prior to scanning using

a numerical rating scale (NRS) ranging from 0 (no pain) to 100 (worst imaginable pain). Questionnaires included the Beck's Depression Inventory II (BDI-II) (Beck et al., 1996), the Trait anxiety scale of the State-Trait Anxiety Inventory (STAI-T) (Spielberger et al., 1983), and the Pain Catastrophizing Scale (Sullivan et al., 1995) consisting of helplessness, magnification, and rumination subscales. The BDI-II was additionally divided into cognitive and somatic-affective subscales considering the recommendation to measure symptoms of depression in patients with somatic disorders using the cognitive subscale, because items of the somatic-affective subscale may reflect symptoms of a somatic disorder rather than depression per se (Steer et al., 1999).

Quantitative sensory testing (QST) was carried out using pressure algometer (Somedic AB, Sösdala, Sweden). Pressure pain thresholds (PPT) were measured on all participants in order to characterise their pain sensitivity. PPT were taken from the sternum and the most painful knee (or either knee in healthy participants).

MRI Data acquisition

Structural and functional MRI data were acquired using 3T Discovery MR750 (GE Healthcare) scanner, with a 32-channel head coil, during rest, as follows: TE = 30 ms; TR = 2000 ms; interleaved acquisition; slice thickness =3 mm; slice gap = 0.5 mm; 37 axial slices parallel to anterior-posterior commissure plane; flip angle = 77°; matrix resolution = 64 x 64; field of view = 192 mm; voxel resolution = 3 x 3 x 3.5 mm. fMRI resting state data consisted of 205 volumes acquired over 6 minutes 50 seconds whilst participants were asked to keep their eyes open looking at a fixation cross. High resolution anatomical images were acquired in the sagittal plane using a fast spoiled gradient echo (FSPGR) sequence with the following parameters: TE/TR=3.164/8.132 ms; TI = 450 ms; slice thickness = 1 mm; field of view = 256; matrix = 256 x 256; flip angle=12°; voxel resolution = 1 mm^3.

Quality control

Functional and structural images were assessed using the MRI Quality Control tool, v0.9.10 (Esteban et al., 2017). Images were excluded if they displayed visual artefacts, signal dropouts in regions of interest, and incomplete volume acquisitions. As in the previous studies, following the recommendations by Parkes et al. (2018), participants with mean FD > 0.2 mm were also discarded. After exclusion, 68 OA patients and 35 pain-free healthy participants were available for further analysis.

Image preprocessing and ROI selection

Image preprocessing and preparation of ROI masks were performed exactly the same way as in the Chapter 3 on FC of the rostral PFC in CLBP (see Section 2.0 of Chapter 3). Preprocessing steps included removal of the first 5 volumes in order to allow for signal equilibrium effects, high-pass temporal filtering (0.01-Hz cutoff), interleaved slice-timing correction, motion correction, brain extraction, and spatial smoothing using an isotropic gaussian filter kernel with full width at half maximum (FWHM) size of 5 mm. Registration of the images was performed using FMRIB's Linear Image Registration Tool (FLIRT). Functional images were first registered to the T1-weighted structural images using the Boundary-Based Registration (BBR) method and then to the Montreal Neurological Institute (MNI) standard space with 12 degrees of freedom (Jenkinson et al., 2002; Jenkinson and Smith, 2001). All functional images were denoised using ICA-AROMA (Pruim et al., 2015). To additionally control for physiological noise, time series data from the cerebrospinal fluid (CSF) and white matter (WM) were extracted for each participant. To achieve this, each participant's T1-weighted images were segmented into the grey matter, white matter, and cerebrospinal fluid using FMRIB's Automated Segmentation Tool (FAST) (Zhang et al., 2001). To avoid overlapping with the grey matter, the CSF and WM masks were eroded to retain only the top 20 and 198 cm^3, respectively (Chai et al., 2012). The CSF and WM maps were then transformed to fMRI space. Mean CSF and WM time series were then extracted per subject using these masks and

regressed out of the data as part of the subsequent GLM analysis. ROI masks (Fig.6) were created using probabilistic maps of the rmPFC and rlPFC made by Bludau et al. (2014).

Statistical analyses

First-level and group-level analyses of FC between the rmPFC and rlPFC and the rest of the grey matter were carried out using FMRI Expert Analysis Tool (FEAT, v6.00) (Woolrich et al., 2004, 2001). In the subject-level analyses, time series data extracted from each of the ROIs were used to identify voxels in the rest of the grey matter that showed correlated or anticorrelated activity with the data from the ROIs. Individual CSF and WM time series were also included in the General Linear Model (GLM) as nuisance covariates. Resulting statistical images were then analysed at the group-level GLM using FMRIB's Local Analysis of Mixed Effects (FLAME 1) method. The OA group was divided into two subgroups with shorter (OA1) and longer (OA2) duration of OA using the median split method. Statistical contrasts were designed to identify: 1) regions with greater FC for OA1 compared to OA2 (OA1>OA2), 2) regions with greater FC for OA2 compared to OA1 (OA2>OA1), 3) regions with greater FC for OA1 compared to HC (OA1>HC), 4) regions with greater FC for HC compared to OA1 (HC>OA1), 5) regions with greater FC for OA2 compared to HC (OA2>HC), and 6) regions with greater FC for HC compared to OA2 (HC>OA2). All contrasts were thresholded at the whole-brain FWE-corrected level ($Z > 2.3$; cluster $p < 0.0125$). P-values were corrected using the Bonferroni method (0.05/number of tests). FD estimates of each participant were included in the GLM as covariates of no interest to control for residual effects of head-movement. Also, prior to testing group differences in FC, group-covariate interaction analysis was conducted to investigate whether head movement had similar effects on FC of the ROIs in all three groups. Other potential confounds, such as sex and age, were not included into the GLM because every additional covariate reduces degrees of freedom (DOF) and, thus, may reduce statistical power (Jenkinson et al., 2018; Kahan et al., 2014). Considering that sample sizes were small in this study only head motion parameters were included.

Additional post-hoc multiple regression analyses (one-way ANOVA) were carried out to investigate the relationship between group differences in FC and behavioural data. *Z*-scores from the regions that showed significant differences in FC with the ROIs were entered as dependent variables, whereas measures of helplessness, cognitive symptoms of depression, trait anxiety, and pain sensitivity were entered as independent variables. Post-hoc Tukey test was used to correct for multiple comparisons. Statistical analyses of group differences in demographic, clinical, and behavioural data, as well as multiple regression were performed using GraphPad Prism version 8.4.3 for Windows, GraphPad Software, La Jolla California USA (www.graphpad.com).

3.0 Results

Median duration of OA was 7 years across all patients. Patients with duration of less than 7 years were included in the OA1 group, whereas patients with duration of more than or equal to 7 years were allocated to the OA2 group.

Results of between-group comparisons of demographic, clinical, and psychometric data are presented in Table 4 and Supplementary Table S2. All three groups did not differ in age, sex, magnification subscale of the pain catastrophizing scale, trait anxiety, and cognitive symptoms of depression. There was also no difference in pain severity and pain sensitivity between groups. The OA1 group had significantly higher scores on overall pain catastrophizing compared to the HC but not to OA2 group. Patients with shorter duration of OA also had higher scores on rumination in comparison with the OA2 and HC groups. Helplessness was significantly higher in both OA groups compared to HC, but the OA1 group did not significantly differ from the OA2 group. Overall, the PCS scores in both groups were below the suggested cut-off score of 30 for clinically meaningful level of catastrophizing (Sullivan et al., 1995). Both OA groups also demonstrated higher total BDI scores than HC. However, the difference was significant only in the somatic-affective subscale that may reflect somatic symptoms of OA rather than of

depression per se (Steer et al., 1999). Finally, the OA2 group had higher measures of head movement parameters relatively to the HC group. Taken together, psychometric evaluation showed that although some of the metrics were higher in OA groups than in healthy controls, the level of psychological distress was not clinically meaningful in either of OA groups.

Table 4. *Demographics and questionnaire scores of OA patients and healthy controls*

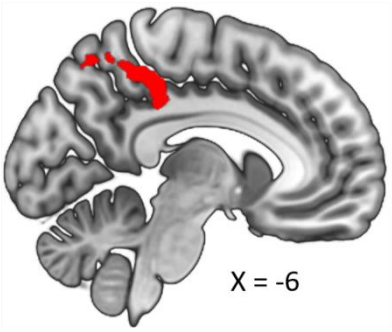
Data	**OA1 (PD<7years)**	**OA2 (PD>7years)**	**HC**	**P value**
N.	33	35	35	
Mean age (min-max) in years	60.4 (22-80)	63.37 (32-80)	64.8 (44-81)	ns
Males/Females	14/19	14/21	20/15	ns
PCS (min-max)	18.58 (1-52)	12.9 (0-48)	7.5 (0-28)	<0.0001 (OA1>HC)
• Rumination	7.5 (0-16)	4.5 (0-16)	3.3 (0-15)	0.009 (OA1>OA2), 0.0002 (OA1>HC)
• Helplessness	8.0 (0-24)	5.7 (0-22)	2.8 (0-11)	< 0.0001 (OA1>HC) 0.03 (OA2>HC)
• Magnification	3.0 (0-12)	2.6 (0-12)	1.6 (0-5)	ns
STAI-T (min-max)	36.6 (24-57)	37.2 (23-72)	31.8 (21-48)	ns
BDI-II total (min-max)	12.5 (2-40)	11.1 (2-31)	5.6 (0-27)	0.001 (OA1>HC), 0.01 (OA2>HC)
• BDIcog	2.8 (0-15)	2.5 (0-10)	1.6 (0-12)	ns
• BDIsom	9.6 (2-25)	8.2 (2-21)	3.9 (0-15)	<0.0001 (OA1>HC), 0.002 (OA2>HC)
PPT sternum (min-max) in kPa	230.9 (34-983)	281.9 (66-1291)	288.1 (101-657)	ns
PPT knee (min-max) in kPa	284.9 (19-1019)	313.6 (64-1374)	397.9 (161-894)	ns
Pain duration (min-max) in years	3.1 (0.5-6)	16 (7-48)	-	<0.0001
Pain severity (min-max)	34.2 (0-85)	33.1 (0-90)	-	ns
FD (min-max) in mm	0.09 (0.02-0.18)	0.11 (0.03-0.19)	0.07 (0.02 – 0.2)	0.002 (OA2>HC)

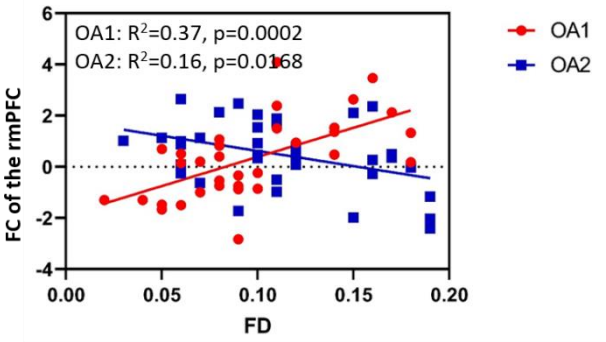
Psychometric, clinical, and demographical factors between three groups were tested using one-way ANOVA corrected for multiple comparisons with post-hoc Tukey test. Differences in sex were tested using chi-square method. Differences in clinical factors between two OA groups were examined using t-test. Only significant p values for each pair of compared groups are presented. OA1 – patients with shorter duration of osteoarthritis; OA2 – patients with longer duration of osteoarthritis; PD – pain duration; HC – healthy controls; ns – not significant; PCS – pain catastrophizing scale; STAI-T – state-trait anxiety inventory, trait version; BDI-II – Beck's depression inventory, second revision; BDIcog – cognitive subscale of the BDI-II; BDIsom – somatic-affective subscale of the BDI-II; FD – mean framewise displacement, PPT – pressure pain threshold; kPa – kilopascal.

Group-covariate interaction analysis.

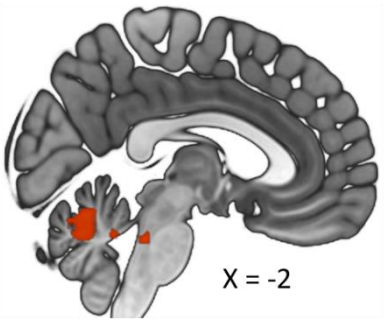
Exclusion of participants with FD>0.2 mm and denoising of movement related artifacts with ICA-AROMA did not prevent from significantly different effects of head motion on FC across groups (Fig.14-15). Specifically, FC between the rmPFC and precuneus/PCC correlated positively with FD in the OA1 group and negatively in the OA2 and HC groups (Fig.14a, 14c). The OA1 and OA2 groups demonstrated opposite effects of head motion on FC between the rmPFC and cerebellum, pedunculopontine region of the brainstem (Fig.14b). The relationship between head movement and FC was also different in the OA2 compared to the HC group. FC of the rmPFC with dmPFC increased with increasing FD in the OA2 group but decreased in the HC group (Fig.14d). Also, while FC with the basal ganglia decreased with increasing motion in the OA2 group, it increased in the HC group (Fig.14e).

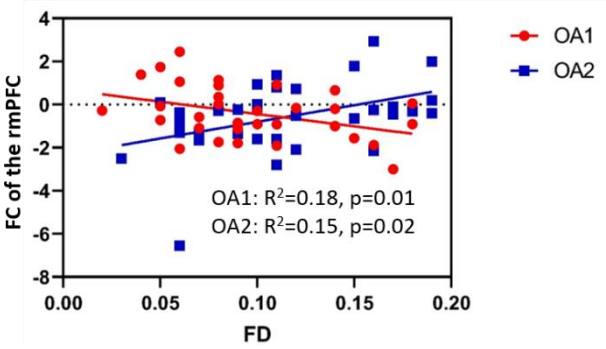
a)


X = -6

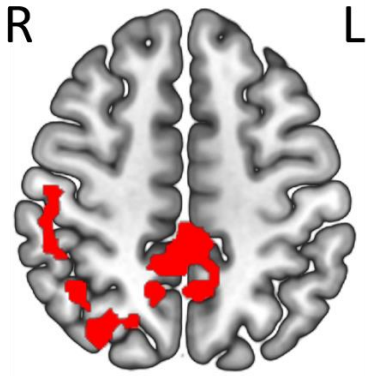

OA1: R²=0.37, p=0.0002
OA2: R²=0.16, p=0.0168
FC of the rmPFC
FD
OA1
OA2

b)

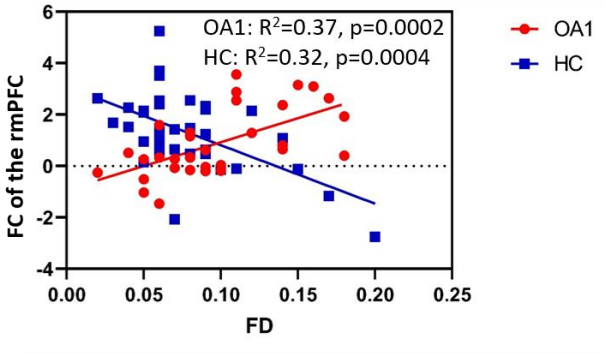

X = -2


OA1: R²=0.18, p=0.01
OA2: R²=0.15, p=0.02
FC of the rmPFC
FD
OA1
OA2

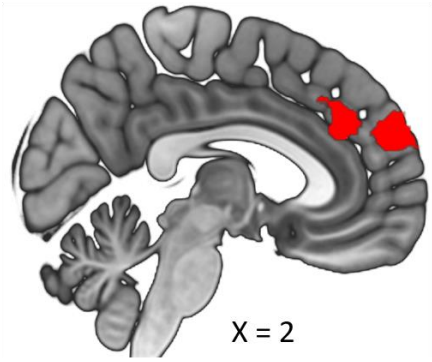
c)

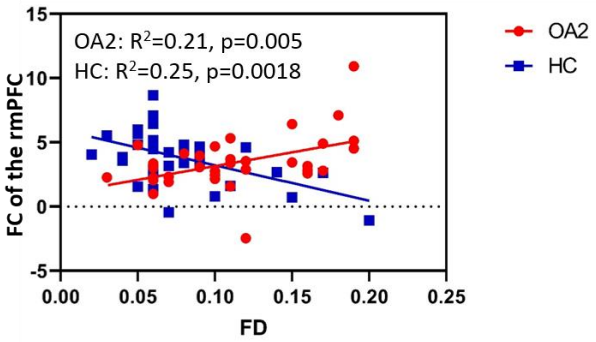

R
L

Z = 44


OA1: R²=0.37, p=0.0002
HC: R²=0.32, p=0.0004
FC of the rmPFC
FD
OA1
HC

d)


X = 2


OA2: R²=0.21, p=0.005
HC: R²=0.25, p=0.0018
FC of the rmPFC
FD
OA2
HC

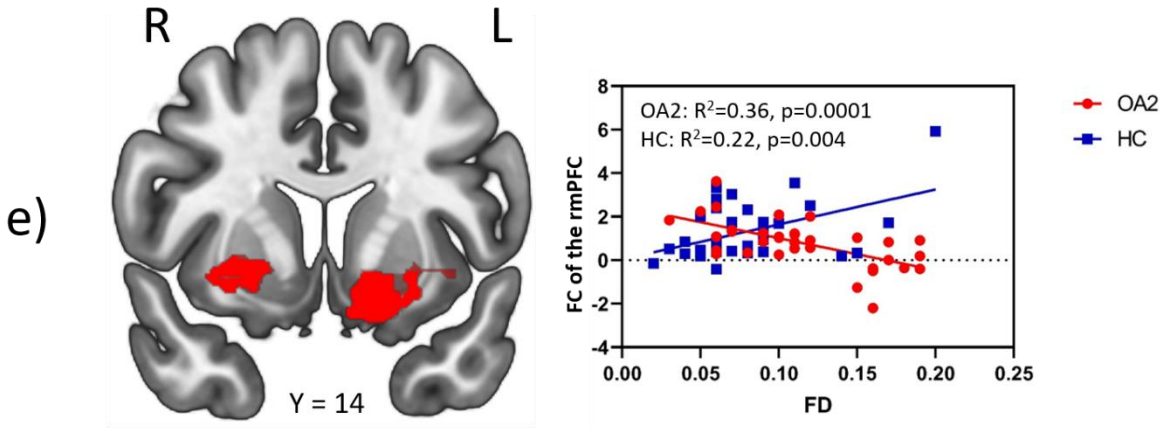
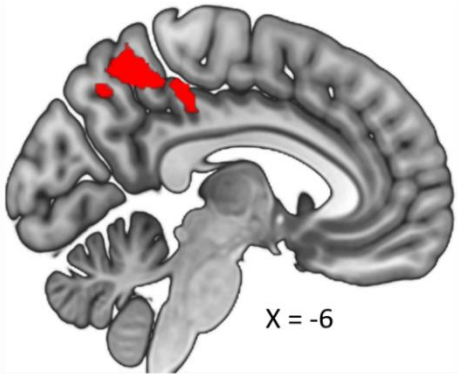
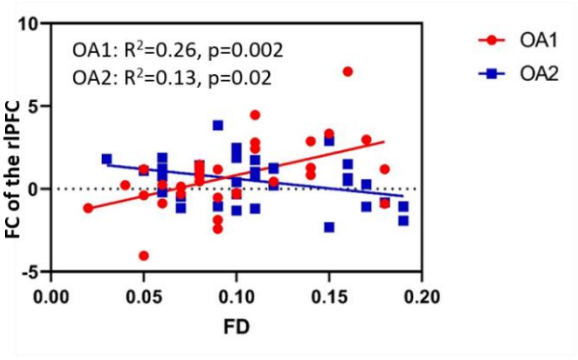


Figure 14. Different effects of head motion on FC of the rmPFC in the OA1, OA2, and HC groups compared to each other (FWE-corrected at z>2.3, cluster-based threshold of p<0.05). A) With increasing head motion (FD), negative FC between the rmPFC and precuneus/PCC decreases and becomes positive in the OA1 group (R^2=0.37, p=0.0002), whereas in the OA2 group positive FC of the rmPFC with the same regions becomes negative (R^2=0.16, p=0.0168). B) Positive FC with the cerebellum and pedunculopontine region becomes negative in the OA1 group (R^2=0.18, p=0.01), conversely, negative FC becomes positive in the OA2 group (R^2=0.15, p=0.02). C) FC of the rmPFC with precuneus, PCC, and posterior parietal cortex increases in the OA1 group (R^2=0.37, p=0.0002) and decreases in the HC group (R^2=0.32, p=0.0004). D) FC of the rmPFC with dorsomedial PFC and dorsal ACC increases in the OA2 group (R^2=0.21, p=0.005) and decreases in the HC group (R^2=0.25, p=0.0018). E) FC between the rmPFC and basal ganglia decreases in the OA2 group (R^2=0.36, p=0.0001) and increases in the HC group (R^2=0.22, p=0.004). R^2 – proportion of the variance in FC (dependent variable) explained by FD (independent variable); OA1 – patients with pain duration less than 7 years; OA2 – patients with pain duration more than 7 years; HC – healthy controls; FD – mean framewise displacement; R - right; L – left.

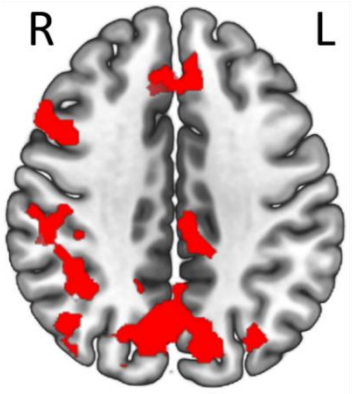
Head motion had also different effects on FC of the rlPFC in the OA1, OA2, and HC groups. Connectivity of the rlPFC with precuneus/PCC increased with greater FD in the OA1 group and decreased in the OA2 group (Fig.15a). The OA1 and HC groups demonstrated opposite effects of head motion on FC with the frontoparietal network (FPN) and left anterior insula (Fig.15b,c). Greater movement was associated with increased connectivity with the FPN in the OA1 group and reduced FC with the same networks in the HC group (Fig.15b), while FC with the anterior insula increased in HC but decreased in the OA1 group (Fig.15c). Interaction with head movement also differed in the OA2 compared to the HC group. FC with the lateral occipital cortex increased with increasing FD in the OA2 group but decreased in the HC group (Fig.15d). Finally, head movement was associated with decreased connectivity between the rlPFC and amygdala in the OA2 group but with increased connectivity in the HC group (Fig.15e).

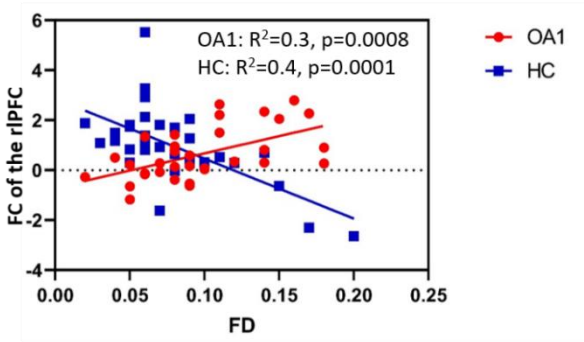
a)


X = -6

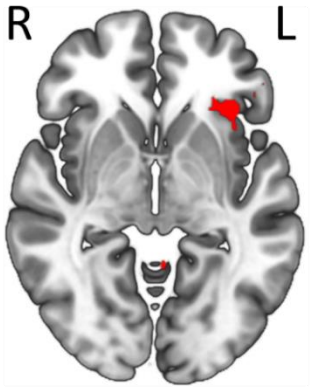

OA1: R²=0.26, p=0.002
OA2: R²=0.13, p=0.02
FC of the rlPFC
FD
OA1
OA2

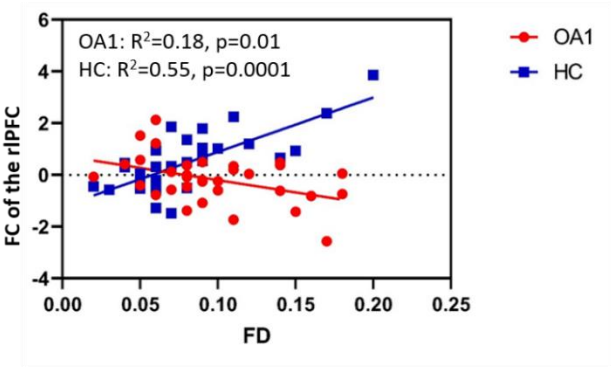
b)


R
L
Z = 38

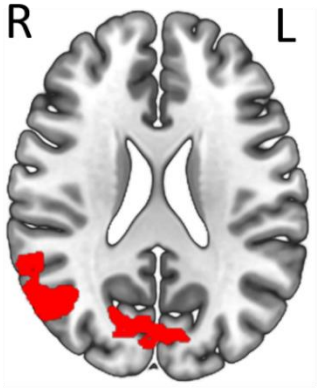

OA1: R²=0.3, p=0.0008
HC: R²=0.4, p=0.0001
FC of the rlPFC
FD
OA1
HC

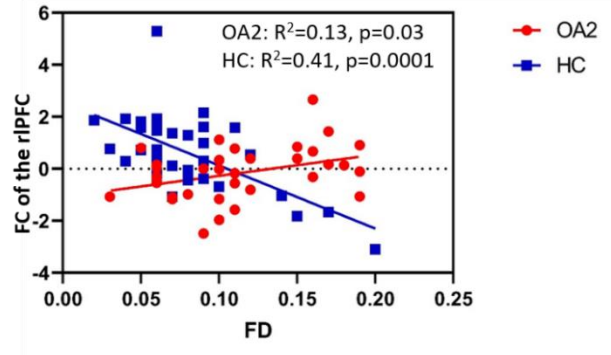
c)


R
L
Z = -2


OA1: R²=0.18, p=0.01
HC: R²=0.55, p=0.0001
FC of the rlPFC
FD
OA1
HC

d)


R
L
Z = 16


OA2: R²=0.13, p=0.03
HC: R²=0.41, p=0.0001
FC of the rlPFC
FD
OA2
HC

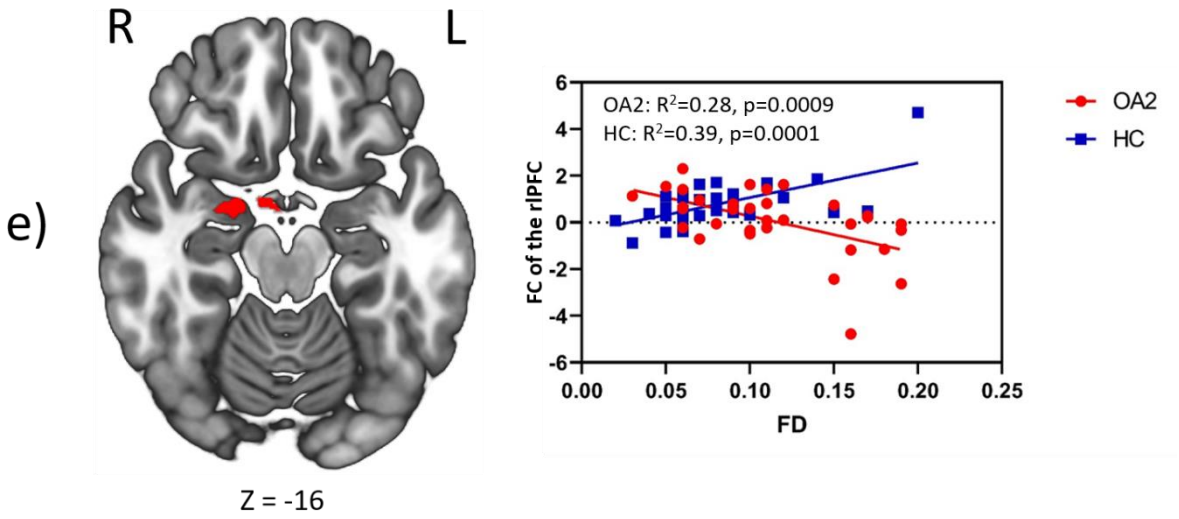


Figure 15. Different effects of head motion on FC of the rlPFC in the OA1, OA2, and HC groups compared to each other (FWE-corrected at z>2.3, cluster-based threshold of p<0.05). A) With increasing head motion (FD), negative FC of the rlPFC with precuneus/PCC increases and becomes positive in the OA1 group (R^2=0.26, p=0.002) and slightly decreases in the OA2 group (R^2=0.13, p=0.02). B) FC of the rlPFC with regions of the DMN and FPN increases in the OA1 group (R^2=0.3, p=0.0008) and decreases in the HC group (R^2=0.4, p=0.0001). C) Positive FC between the rlPFC and left anterior insula becomes negative in the OA1 group (R^2=0.18, p=0.01), conversely, negative FC changes to positive FC in the HC group (R^2=0.55, p=0.0001). D) Negative FC of the rlPFC with visual and lateral occipital cortex increases and becomes positive in the OA2 group (R^2=0.13, p=0.03) and shifts from positive to negative in the HC group (R^2=0.41, p=0.0001). E) FC between the rlPFC and amygdala decreases in the OA2 group (R^2=0.28, p=0.0009) and increases in the HC group (R^2=0.39, p=0.0001). R^2 – proportion of the variance in FC (dependent variable) explained by FD (independent variable); OA1 – patients with pain duration less than 7 years; OA2 – patients with pain duration more than 7 years; HC – healthy controls; FD – mean framewise displacement; R - right; L – left.

Group differences in FC of the rmPFC

Results of group-level comparisons in FC of the rmPFC are presented in Fig. 16-20 and Table 5. Differences between the OA1 and OA2 groups are shown in Fig.16. FC of the rmPFC with a cluster encompassing parts of the cerebellum and brainstem was closer to 0 in the OA1 group. In contrast, the OA2 group showed stronger negative FC (anticorrelation) of the rmPFC with the same cluster, i.e., increased activity of the rmPFC was associated with decreased activity of the brainstem structures and vice versa. The cluster included the caudal part of the DRN, parabrachial complex (PBC), and locus coeruleus (LC).

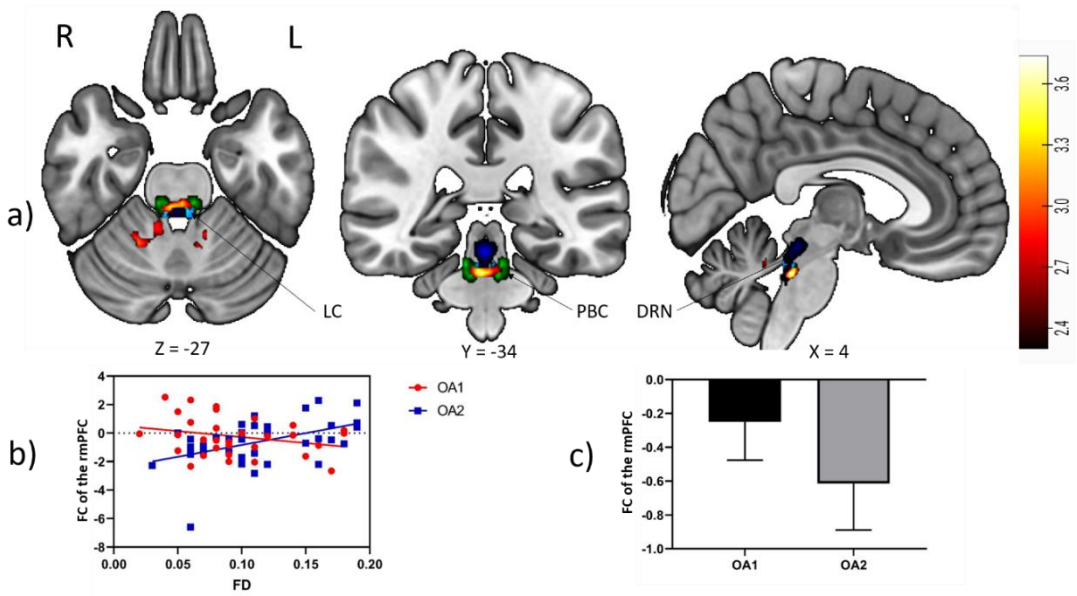


Figure 16. A) Statistical map showing the difference in FC of the rmPFC between the OA1 (duration of OA < 7 years) and OA2 (duration of OA > 7 years) groups. The groups displayed different FC of the rmPFC with brainstem and cerebellum. The cluster of voxels (yellow-red) showing different FC with the rmPFC is overlaid on anatomical masks of brainstem structures adopted from the Harvard Ascending Arousal Network atlas (Edlow et al., 2012). The cluster partially overlapped with the caudal DRN (dark blue), PBC (green), and LC (light blue). B) Interaction of FC between the rmPFC and the cluster with head motion parameters (FD) in two groups. C) Mean values of FC between the rmPFC and the cluster. Interaction plot (B) and mean FC values (C) suggest that FC between the rmPFC and brainstem areas is closer to 0 in the OA1 group and negative (anticorrelated) in the OA2 group. All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. R- right; L- left; LC – locus coeruleus; PBC – parabrachial complex; DRN – dorsal raphe nucleus; FD – framewise displacement; FC – functional connectivity; rmPFC – rostromedial prefrontal cortex; OA - osteoarthritis.

Compared to HC, patients from the OA1 group displayed reduced FC of the rmPFC with anterior precuneus, PCC, primary motor and sensory cortex, and premotor areas (Fig.17).

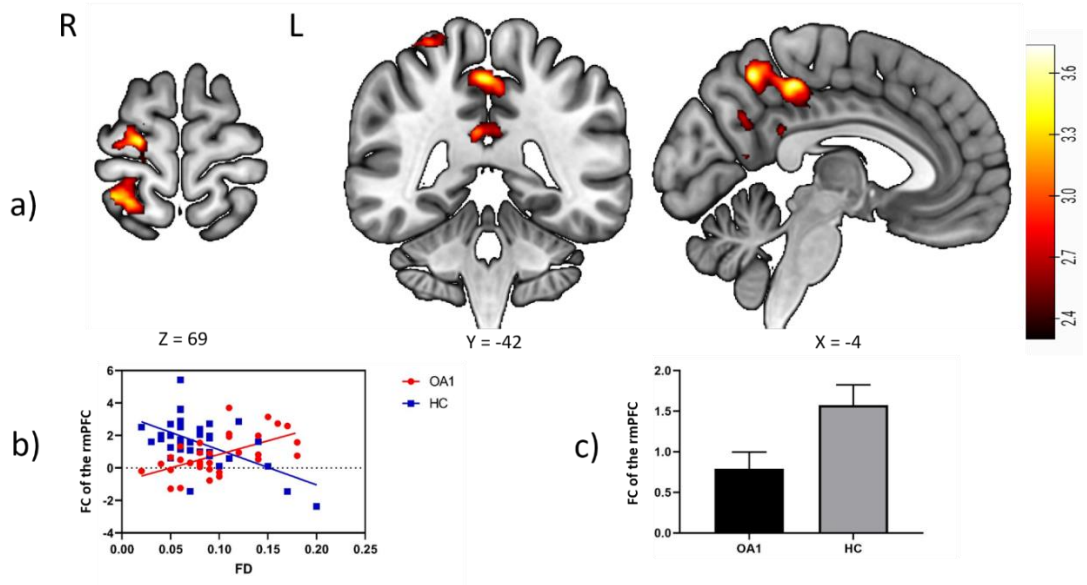


Figure 17. A) Statistical map showing the difference in FC of the rmPFC between the OA1 (duration of OA < 7 years) and HC groups. The groups displayed different connectivity of the rmPFC with precuneus, PCC, primary motor, sensory, and premotor cortex. B) Interaction of FC between the rmPFC and the cluster with head motion parameters (FD) in two groups. C) Mean values of FC between the rmPFC and the cluster. Interaction plot (B) and mean FC values (C) suggest that the OA1 group has reduced positive FC between the rmPFC and the regions constituting the cluster. All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. R-right; L- left; FD – framewise displacement; FC – functional connectivity; rmPFC – rostromedial prefrontal cortex; OA – osteoarthritis; HC – healthy controls.

The OA2 group compared to healthy controls was characterized by altered FC of the rmPFC with 3 separate clusters. The first cluster was located in the area of the ventral angular gyrus (Seghier, 2013). HC showed higher positive FC of the rmPFC with this region, whereas in the OA2 group FC was weaker (Fig.18).

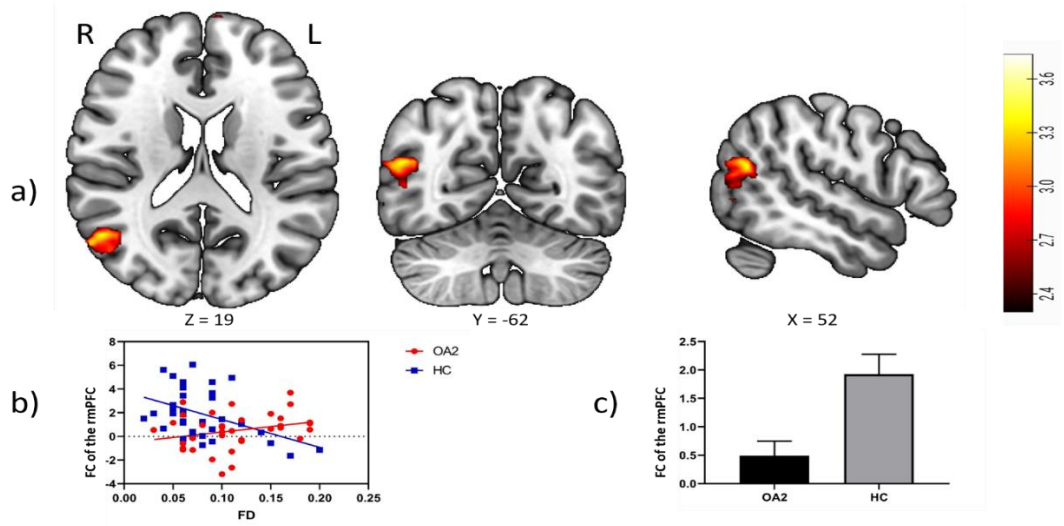


Figure 18. A) Statistical map showing the difference in FC of the rmPFC between the OA2 (duration of OA > 7 years) and HC groups. The groups displayed different connectivity of the rmPFC with the cluster of voxels in the ventral angular gyrus area. B) Interaction of FC between the rmPFC and the cluster with head motion parameters (FD) in two groups. C) Mean values of FC between the rmPFC and the cluster. Interaction plot (B) and mean FC values (C) suggest that the OA2 group has reduced positive FC between the rmPFC and the cluster. All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. R-right; L- left; FD – framewise displacement; FC – functional connectivity; rmPFC – rostromedial prefrontal cortex; OA – osteoarthritis; HC – healthy controls.

The second cluster included the rostrolateral PFC, dorsomedial PFC, and anterior paracingulate cortex. In both groups, FC with this cluster was positive, however in the HC group it was stronger than in the OA2 group (Fig.19).

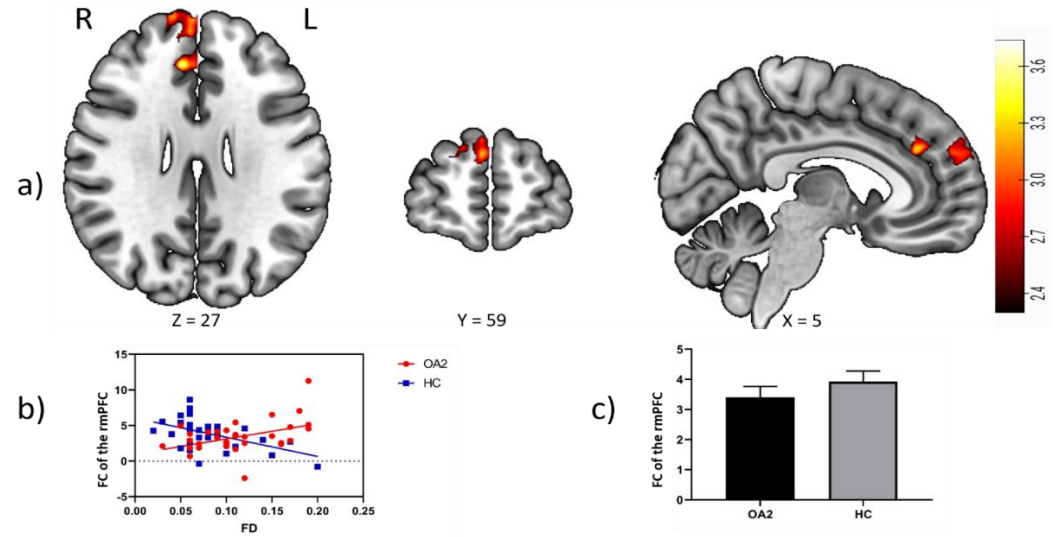


Figure 19. A) Statistical map showing the difference in FC of the rmPFC between the OA2 (duration of OA > 7 years) and HC groups. The groups displayed different connectivity of the rmPFC with the cluster of voxels in the dorsomedial PFC and anterior midcingulate cortex. B) Interaction of FC between the rmPFC and the cluster with head motion parameters (FD) in two groups. C) Mean values

of FC between the rmPFC and the cluster. Interaction plot (B) and mean FC values (C) suggest that the OA2 group has reduced positive FC between the rmPFC and the cluster. All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. R-right; L- left; FD – framewise displacement; FC – functional connectivity; rmPFC – rostromedial prefrontal cortex; OA – osteoarthritis; HC – healthy controls.

The third cluster overlapped with many brainstem structures such as the dPAG, midbrain reticular formation (MRF), caudal part of the DRN, median raphe nucleus (MRN), PBC, LC (Edlow et al., 2012), and tail of the ventral tegmental area (tVTA) (Sanchez-Catalan et al., 2014). In healthy controls, activity of the rmPFC weakly correlated with the activity of these regions. In contrast, patients from the OA2 group demonstrated negative FC with this cluster (Fig.20). Interestingly, almost the same pattern of stronger negative FC between the rmPFC and brainstem structures in the OA2 group was observed when the OA2 group was compared with the OA1 group (Fig.16) suggesting that the OA1 group is similar to HC in this regard. Measures of depression, anxiety, rumination, magnification, helplessness, pain severity, and pain sensitivity did not correlate with either of the differences in FC between the groups described above.

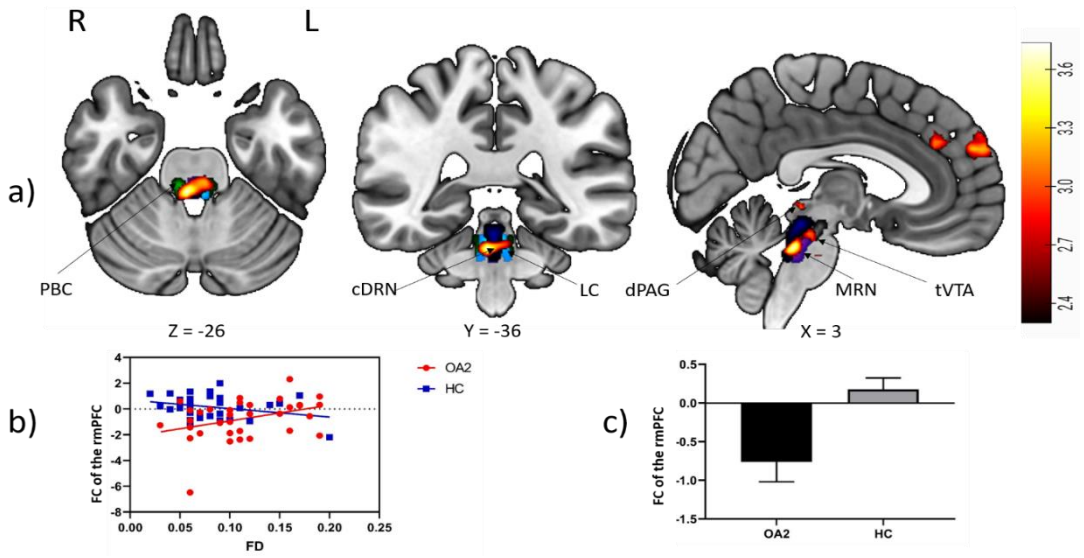


Figure 20. A) Statistical map showing the difference in FC of the rmPFC between the OA2 (duration of OA > 7 years) and HC groups. The cluster of voxels (yellow-red) showing different FC with the rmPFC is overlaid on anatomical masks of brainstem structures adopted from the Harvard Ascending Arousal Network atlas (Edlow et al., 2012). The cluster partially overlapped with the caudal DRN (dark blue), MRN (purple), PBC (green), LC (light blue), dorsal PAG, and VTA (greyscale). B) Interaction of FC between the rmPFC and the cluster with head motion parameters (FD) in two groups. C) Mean values of FC between the rmPFC and the cluster. Interaction plot (B) and mean FC values (C) suggest that the OA2 group has increased negative FC (anticorrelation) between the rmPFC and the cluster.

All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. R-right; L-left; LC – locus coeruleus; PBC – parabrachial complex; cDRN – caudal dorsal raphe nucleus; dPAG – dorsal periaqueductal grey; tVTA – tail of the ventral tegmental area; FD – framewise displacement; FC – functional connectivity; rmPFC – rostromedial prefrontal cortex; OA - osteoarthritis.

Table 5. *Peak MNI coordinates for regions with significantly different medial rmPFC FC between OA groups and HC*

Anatomical regions	**Cluster extent**	**X**	**Y**	**Z**	**Z-score**
OA1>OA2					
R. locus coeruleus	510	4	-36	-28	3.42
R. cerebellum		20	-52	-24	3.26
L. cerebellum		-12	-54	-30	3
L. cerebellum (I-IV)		-6	-48	-18	2.89
L. cerebellum (I-IV)		-2	-48	-22	2.83
R. cerebellum (I-IV)		8	-46	-26	2.8
HC>OA1					
L. precentral gyrus	2337	-2	-34	50	4.19
L. precuneus		-4	-56	54	4.15
R. precentral gyrus		20	-18	70	4.12
R. precuneus		2	-42	52	4
R. superior parietal lobule		32	-46	70	3.79
R. precuneus		12	-56	52	3.77
HC>OA2					
R. anterior midcingulate cortex	527	8	36	28	3.94
L. rostrolateral prefrontal cortex		-8	68	18	3.62
R. dorsomedial prefrontal cortex		4	56	26	3.56
R. rostrolateral prefrontal cortex		12	64	26	3.45
R. dorsomedial prefrontal cortex		4	60	34	3.15
R. rostrolateral prefrontal cortex		6	68	22	2.85
R. locus coeruleus	503	4	-36	-28	4.05
R. dorsal periaqueductal grey		4	-32	-6	3.47
L. brainstem		-4	-24	-32	3.42
L. midbrain reticular formation		-4	-30	-12	3
L. cerebellum (I-IV)		-10	-44	-22	2.88
L. dorsal periaqueductal grey		-2	-32	-4	2.86
R. ventral angular gyrus	492	52	-60	18	3.66
R. ventral angular gyrus		58	-66	18	3.62
R. ventral angular gyrus		50	-62	22	3.62
R. lateral occipital cortex		54	-68	14	3.52
R. lateral occipital cortex		48	-68	20	3.33
R. lateral occipital cortex		60	-66	-2	3.1
Results are FWE-corrected (Z>2.3, cluster-based threshold of p<0.0125) and reported in MNI152 standard space. L. – Left, R. – Right.					

Group differences in FC of the rlPFC

Compared to HC, patients from the OA1 group displayed reduced FC of the rlPFC with anterior midcingulate cortex, supplementary motor area, precuneus, PCC, superior parietal lobule, and dorsolateral prefrontal cortex (Fig.21, Table 6).

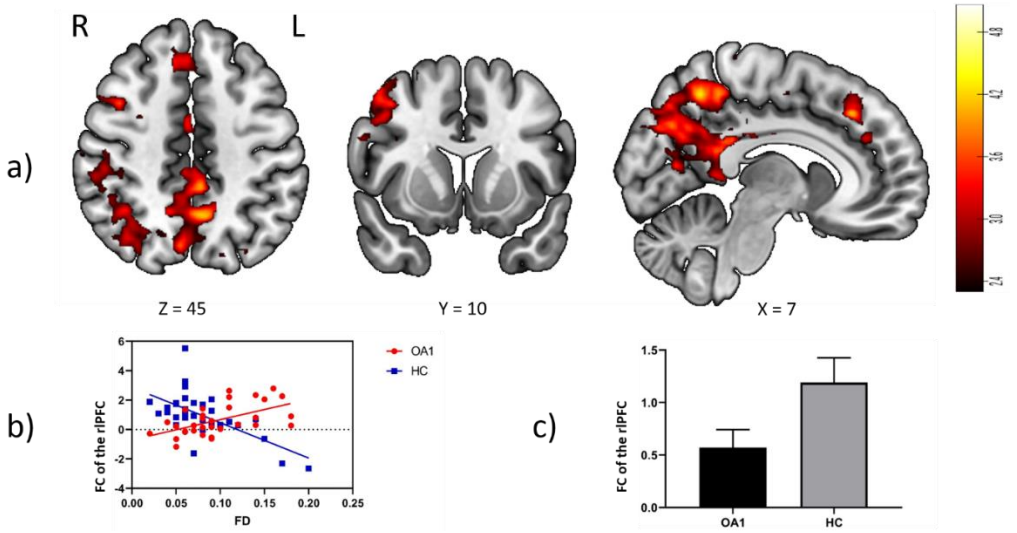


Figure 21. A) Statistical map showing the difference in FC of the rlPFC between the OA1 (duration of OA < 7 years) and HC groups. The groups displayed different connectivity of the rlPFC with the cluster of voxels in the supplementary motor area (Brodmann area 8), anterior midcingulate cortex, PCC, precuneus, dlPFC, and superior parietal lobule. B) Interaction of FC between the rlPFC and the cluster with head motion parameters (FD) in two groups. C) Mean values of FC between the rlPFC and the cluster. Interaction plot (B) and mean FC values (C) suggest that the OA1 group has reduced positive FC between the rlPFC and the cluster. All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. R-right; L- left; FD – framewise displacement; FC – functional connectivity; rlPFC – rostrolateral prefrontal cortex; OA – osteoarthritis; HC – healthy controls.

The OA2 group showed reduced FC of the rlPFC with supplementary motor area, precuneus, cuneus, PCC, lateral occipital cortex, and angular gyrus (Fig.22, Table 6). There were no significant differences between the OA1 and OA2 groups. Both patient groups showed a similar pattern of reduced FC with various regions of the so-called multiple demand network (MDN) (Fig.23) (Camilleri et al., 2018; Fedorenko et al., 2013). FC of the rlPFC with regions above did not correlate with depression, trait anxiety, rumination, magnification, helplessness, pain severity, and pain sensitivity.

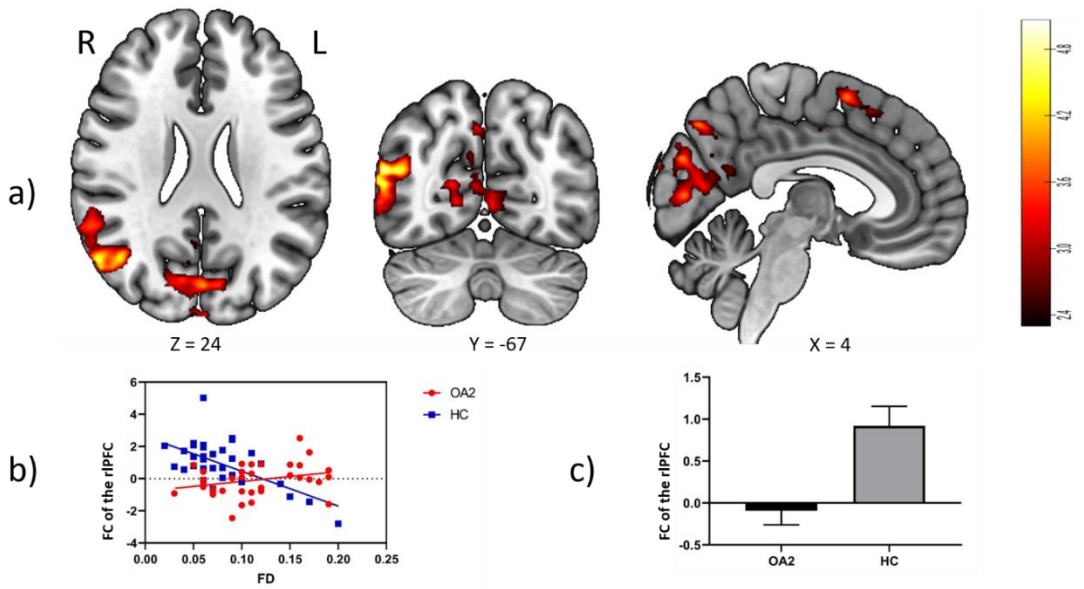


Figure 22. A) Statistical map showing the difference in FC of the rlPFC between the OA2 (duration of OA > 7 years) and HC groups. The groups displayed different connectivity of the rlPFC with the cluster of voxels in the supplementary motor area (Brodmann area 8), PCC, precuneus, cuneus, and ventral angular gyrus. B) Interaction of FC between the rlPFC and the cluster with head motion parameters (FD) in two groups. C) Mean values of FC between the rlPFC and the cluster. Interaction plot (B) and mean FC values (C) suggest that the OA2 group has reduced positive FC between the rlPFC and the cluster. All statistical images are FWE-corrected at Z > 2.3, cluster-based threshold of p < 0.0125. R-right; L- left; FD – framewise displacement; FC – functional connectivity; rlPFC – rostrolateral prefrontal cortex; OA – osteoarthritis; HC – healthy controls.

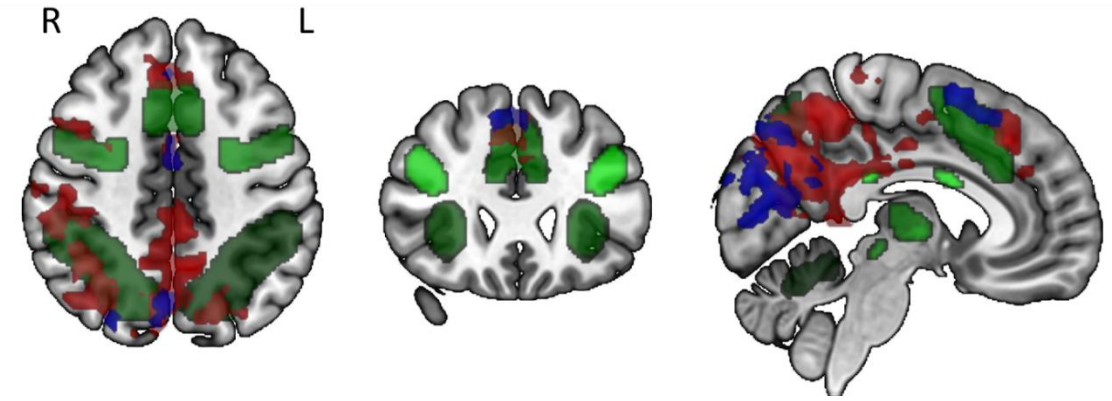


Figure 23. Statistical maps showing significant differences in functional connectivity of the rlPFC in the OA1 (red) and OA2 (blue) groups when compared with the HC group. Both groups demonstrated reduced FC with the multiple demand network (green). The map of the multiple demand network was adopted from Fedorenko et al. (2013). R-right, L-left.

Table 6. *Peak MNI coordinates for regions with significantly different medial rlPFC FC between OA groups and HC*

Anatomical regions	**Cluster extent**	**X**	**Y**	**Z**	**Z-score**
HC>OA1					
L. precuneus	11215	-6	-56	52	5.09
R. precuneus		12	-56	52	4.89
R. precentral gyrus		22	-20	70	4.49
R. precentral gyrus		30	-20	70	4.47
R. precentral gyrus		34	-22	70	4.42
R. ventral angular gyrus		42	-60	22	4.35
L. lateral occipital cortex	932	-58	-68	0	3.94
L. middle temporal gyrus		-64	-56	2	3.86
L. middle temporal gyrus		-58	-68	6	3.74
L. middle temporal gyrus		-56	-40	-8	3.59
L. ventral angular gyrus		-48	-72	20	3.47
L. middle temporal gyrus		-60	-64	12	3.44
R. superior frontal gyrus	522	4	32	42	4.36
L. superior frontal gyrus		-8	34	40	4.22
R. anterior midcingulate cortex		12	40	30	3.3
L. superior frontal gyrus		-4	24	52	3.29
R. anterior midcingulate cortex		8	38	28	3.23
R. superior frontal gyrus		10	38	44	3.1
HC>OA2					
L. cuneus	2554	0	-82	8	4.2
R. cuneus		12	-74	18	3.95
L. cuneus		0	-80	26	3.92
R. precuneus		4	-72	46	3.79
R. cuneus		16	-74	18	3.79
R. cuneus		16	-74	10	3.65
R. ventral angular gyrus	1619	44	-64	22	4.66
R. ventral angular gyrus		54	-66	22	4.59
R. lateral occipital cortex		54	-68	14	4.3
R. ventral angular gyrus		52	-60	18	4.11
R. ventral angular gyrus		62	-48	20	4.08
R. lateral occipital cortex		54	-70	6	3.94
R. supplementary motor cortex	491	4	8	60	3.67
R. superior frontal gyrus		10	28	50	3.35
R. superior frontal gyrus		12	30	54	3.32
R. superior frontal gyrus		6	20	52	3.16
Midcingulate cortex		0	-6	44	3.15
R. supplementary motor cortex		8	14	54	2.96
Results are FWE-corrected (Z>2.3, cluster-based threshold of p<0.0125) and reported in MNI152 standard space. L. – Left, R. – Right.					

4.0 Discussion

In contrast to patients with shorter duration of OA (< 7 years) and HC, patients with longer duration of OA (> 7 years) showed stronger negative functional connectivity between the rmPFC and cluster of brainstem regions consisting of the dorsal PAG, midbrain reticular formation (MRF), caudal part of the DRN, median raphe nucleus (MRN), parabrachial complex (PBC), locus coeruleus (LC), and tail of the ventral tegmental area (tVTA) (Fig.16,20). Compared to HC, patients with longer duration of OA also showed weaker FC of the rmPFC with ventral part of the angular gyrus and dorsomedial PFC (Fig.18,19). Patients with shorter duration of OA, relative to the HC group, showed reduced FC of the rmPFC with premotor cortex, primary motor cortex, primary somatosensory cortex, anterodorsal precuneus, and posterior cingulate cortex (Fig.17). Both OA groups, in comparison with HC, showed reduced connectivity of the rlPFC with several frontoparietal cortical regions that collectively comprise the multiple demand network (MDN) consisting of the dorsal and ventral portions of the lateral PFC, presupplementary motor cortex extending to dACC, anterior insula, and superior parietal cortex (Fig.23). Possible reasons for such differences between the groups and how these changes in connectivity might contribute to the development of chronic pain and emotional disorders will be discussed below.

Chronic primary and secondary pain disorders are considered as distinct nosological entities with different mechanisms of development (Treede et al., 2019). However, initial diagnosis of chronic secondary pain disorder may later change to chronic primary pain disorder if clinical characteristics of pain no longer correspond to the actual tissue damage, for example, if pain becomes disproportionate to the degree of tissue damage or occurs in body parts that are not affected by the underlying disease (Treede et al., 2019). Also, primary and secondary pain disorders can coexist. For instance, 11-30% of patients with rheumatic diseases suffer from comorbid fibromyalgia, while in general population its prevalence is 2-7% (Haliloglu et al., 2014; Yunus, 2012). Specific neural mechanisms that determine the transformation of secondary pain into primary pain

or their coexistence are poorly understood. However, results of connectivity analyses in CLBP discussed in previous chapters suggest that impaired connectivity of the rmPFC with memory systems (the hippocampus, amygdala, ventral striatum) and brainstem structures that regulate stress reactions (the PAG, DRN, MRF) might play an important role in mediating two main characteristic features of primary pain, i.e., hypersensitivity to pain and increased vulnerability to emotional disorders (Treede et al., 2019). The aim of this study was to investigate whether patients with a secondary pain disorder, such as osteoarthritis, would demonstrate a similar pattern of altered functional connectivity. Considering that the shift from secondary to primary pain mechanisms may occur mainly at later stages of the disease as a result of prolonged experience of pain (Kosek et al., 2016; Treede et al., 2019), patients with knee OA were divided into two subgroups depending on disease duration with the hypothesis that patients with longer OA duration would display altered FC of the rmPFC with memory systems and brainstem areas similar to CLBP patients.

FC of the rmPFC in patients with longer duration of OA (OA2 group). Patients with longer duration of OA pain (OA2 group), in contrast to patients with shorter duration (OA1 group) and healthy controls, showed increased negative connectivity with a widespread cluster of brainstem regions partially overlapping with the dorsal PAG, midbrain reticular formation (MRF), caudal part of the DRN, median raphe nucleus (MRN), parabrachial complex (PBC), locus coeruleus (LC), and tail of the ventral tegmental area (tVTA) (Fig.16,20).

Contributions of the dorsal PAG, MRF, and DRN to altered nociception and emotional distress have already been described in previous chapters. Briefly, activity of the dPAG is associated with hyperalgesia (McLemore et al., 1999), behavioral arousal (Brandão et al., 2008), and enhanced fear and panic reactions (Panksepp et al., 2011). The MRF is involved in subconscious early processing of threat. Activation of the MRF is associated with hyperarousal, hypervigilance, and anxiety (Terpou et al., 2019). The DRN via serotonin secretion regulates activity of many stress-related structures. Stimulation of this nucleus can induce helplessness and anxiety-like behavior, whereas inhibition of the caudal DRN by the rmPFC in

controllable stress conditions prevents these effects (Maier and Seligman, 2016). Functions of the MRN are similar to the functions of the DRN, the majority of neurons in the MRN are also serotonergic. Activation of the median raphe produces generalized anxiety, whereas its inhibition results in anxiolysis (Andrade et al., 2013). The PBC contains mainly glutamatergic cells that relay somatosensory including nociceptive information to limbic structures, such as the amygdala, and participates in associative learning and fear conditioning (Silva et al., 2016). Artificial stimulation of the PBC during presentation of a neutral stimulus is sufficient for acquisition of a conditioned fear response to that stimulus (Sato et al., 2015). Hyperactivation of the PBC has also been associated with increased sensitivity to pain (L. Sun et al., 2020). The LC is another major node implicated in regulation of stress response (Borodovitsyna et al., 2018). Activation of the LC during stress induces increased release of norepinephrine throughout the central nervous system (CNS) resulting in increased arousal, anxiety, attention towards threat, and enhanced threat-related learning and memory formation (Morris et al., 2020). Chronic long-term stress has been associated with sustained hyperactivity of the LC and its increased sensitivity to subsequent stressors. Hyperactivation of this nucleus has been reported in many anxiety disorders, such as PTSD, GAD, SAD, and panic disorder (Morris et al., 2020), as well as in chronic pain disorders where it contributes to hyperalgesia and allodynia (Taylor and Westlund, 2017). Regarding the tVTA, this recently discovered structure is mainly composed of GABAergic neurons. Its main function is best described as inhibitory control of dopaminergic neurons in the VTA and substantia nigra. Stimulation of the tVTA inhibits activity of the midbrain dopamine cells, while inhibition of the tVTA has opposite effects (Sanchez-Catalan et al., 2014). The tVTA receives projections from a variety of brain regions including the mPFC, nucleus accumbens, hippocampus, hypothalamus, ventral pallidum, lateral habenula, PAG, DRN, MRN, LC, and others, but its efferent projections mainly target dopamine neurons in the VTA and substantia nigra suggesting that this structure plays essential role in regulation of the functions associated with dopamine signaling in the midbrain (Fakhoury, 2018). Most of the inputs to this nucleus come from the lateral habenula, therefore tVTA is strongly involved in behavioral functions ascribed to the lateral habenula, such as processing

of aversive stimuli and negative rewards. For example, aversive painful stimulation increases excitatory glutamatergic transmission from the lateral habenula to the tVTA. Increased activity of the tVTA neurons, in turn, reduces dopamine release in the VTA and substantia nigra (Fakhoury, 2018). Participation in encoding of aversive stimuli indicates that the tVTA may also mediate defensive behaviors and play important role in emotional disorders. Supporting this idea, animal studies have demonstrated that inactivation or lesions to the tVTA reduce anxiety, passive behavior and facilitate active coping with adversities (Fakhoury, 2018). There is also evidence suggesting important role of the tVTA in pain processing and opioid analgesia. Opioid receptors are abundantly expressed in this nucleus. Both morphine and opioid agonists can inhibit the tVTA and consequently disinhibit dopamine release in the VTA (Sanchez-Catalan et al., 2014). Taylor et al. (2019) have demonstrated that local infusion of morphine into the tVTA or selective inhibition of its GABAergic neurons reproduces 87% of the maximal analgesic effect produced by systemic administration of morphine. The authors also showed that activation of the VTA dopamine neurons that receive inhibitory inputs from the tVTA significantly alleviates pain and reduces the dose of systemic morphine required for achievement of maximal analgesia by 75% (Taylor et al., 2019) suggesting that inhibition of the tVTA and consequent disinhibition of the VTA is a powerful antinociceptive mechanism.

Taken together, it seems that all these brainstem structures have overlapping functions. All of them are implicated in regulation of emotional reactions, nociception, and stress response in general. Due to small sizes, complex anatomy, intricate relationships with each other, and limitations of existing research methods, specific roles and contributions of each individual region are poorly understood (Venkatraman et al., 2017). However, one fundamental function that they share is involvement in generation, maintenance, and regulation of a general arousal state in the brain. The PBC, LC, DRN, MRN, VTA, MRF, and PAG together comprise the ascending reticular activating system (ARAS) (Edlow et al., 2012). Arousal serves as a foundation for many reflexive processes. Low or high levels of arousal in the CNS can respectively suppress or amplify reactivity of neural

systems including those that perform evaluation of threat or nociceptive signals (Venkatraman et al., 2017). Although transient increase in arousal is critical for normal stress response (Kyle and McNeil, 2014; Morris et al., 2020), excessive engagement of the ARAS during prolonged stress or chronic pain can cause permanent changes in this circuitry leading to pathological anxiety and hyperalgesia (Finan and Smith, 2013; Morris et al., 2020; Taylor and Westlund, 2017; Thome et al., 2019).

In the present study, patients with longer duration of pain showed increased negative connectivity (anticorrelation) of the rmPFC with the arousal system indicating increased neuronal inhibition (Devor et al., 2007; Shmuel et al., 2006). However, it is difficult to infer the direction of this inhibition. On the one hand, it is possible that prolonged hyperactivation of the ARAS and increased anxiety may impair functions of the rmPFC and reduce its activation. For example, it has been demonstrated that prolonged anxiety can reduce spontaneous activity of PFC neurons (Park et al., 2016). Excessive stimulation of the LC and very high levels of norepinephrine can also reduce activity of the PFC (Chandler, 2016). On the other hand, negative FC may represent increased inhibition of the ARAS by the rmPFC and suppression of pain-induced arousal and anxiety. In support of this interpretation, evaluation of psychometric data showed that despite longer duration of pain, patients did not display signs of significant emotional distress and hyperalgesia. Scores on depression, pain catastrophizing, anxiety, pain severity, and pain sensitivity in the OA2 group were not significantly elevated (Table 4) suggesting that the rmPFC successfully inhibits the ARAS and prevents negative consequences of hyperarousal such as hyperalgesia and emotional distress. The rmPFC is associated with processing of self-referential information (D'Argembeau, 2013) and formation of self-concepts, such as self-efficacy (ability to cope with adversities) (Kerr et al., 2012; Ono et al., 2018) and self-esteem (overall sense of personal worth) (Somerville et al., 2010). These closely related psychological constructs (Gardner and Pierce, 1998) are known to play protective roles against negative affect, anxiety, and depression (Greenberg et al., 1992; Tahmassian and Jalali Moghadam, 2011). In OA patients, higher self-efficacy has been associated with less pain, less

disability, less depressive symptoms, and better overall well-being (Marszalek et al., 2017; Somers et al., 2012). Perhaps, ability to counteract the negative effects of chronic pain and inhibit the arousal system reflects higher perceived control due to high self-efficacy and self-esteem in the OA2 group. Although these psychological factors were not investigated in this study, it is likely that patients would have demonstrated high levels of positive self-concepts considering that measures of negative affect were low.

Patients with shorter duration of OA did not differ from HC with regards to FC between the rmPFC and ARAS suggesting that hyperactivation of the arousal system and compensatory inhibition of the system by the rmPFC develops at more advanced stages of the disease. Interestingly, results of functional (Chapter III) and effective (Chapter IV) connectivity analyses in CLBP also imply increased activation of the arousal system. Thus, dysfunction of the ARAS seems to be a common feature of primary pain disorders and secondary pain disorders at later stages. Amplification of nociceptive and emotional responses in hyperarousal state may explain two main characteristic symptoms of primary pain, i.e., hyperalgesia and significant emotional distress. Therefore, occurrence of this mechanism in a secondary pain disorder may determine its transformation into primary pain disorder.

Patients with longer duration of OA compared to HC also showed reduced FC of the rmPFC with ventral part of the angular gyrus and dorsomedial PFC (Fig. 18, 19). These two regions are involved in processing of social stimuli and considered to be central hubs of the so-called “mentalizing network” that supports the ability to understand and predict feelings, thoughts, intentions, and actions of other people (Dixon et al., 2017). Within this network, the dmPFC evaluates possible implications of others’ intentions for one’s well-being or goals (Dixon et al., 2017) based on contextual information provided by the angular gyrus which integrates past personal social experiences with semantic and conceptual social knowledge (Carter and Huettel, 2013; Seghier, 2013). Reduced interaction between the rmPFC and mentalizing network suggests that patients with longer duration of OA might have difficulties with processing of social stimuli, empathizing (sharing feelings of other

people), perspective-taking (putting oneself in the other person's position), and understanding others' mental states. Although mentalizing ability has not been extensively investigated in chronic pain population, there is some evidence suggesting its impairment in chronic pain patients. For example, Shin et al. (2013) found that patients with complex regional pain syndrome have reduced ability to recognize emotional states of other people (Shin et al., 2013). Another study found impaired empathy in CLBP patients (Ma et al., 2020). It has been suggested that reduced empathy, social and emotional detachment from other people can be considered as a protective mechanism whereby people who might be overwhelmed by their own negative experiences distance themselves from sufferings, pain, and negative emotions of others (Carré et al., 2013; Singer and Klimecki, 2014). In addition, reduced reactivity to social stimuli can protect one's self-concepts from negative social evaluation that they might receive from other people (Somerville et al., 2010).

FC of the rmPFC in patients with shorter duration of OA (OA1 group). The rmPFC processes information related not only to personal psychological qualities, such as worthiness or ability to cope with adversities, but also to one's physical attributes. It has been implicated in formation of a body image, i.e., person's general perception of the body, appreciation, satisfaction or dissatisfaction with the look or functioning of the whole body or its different parts (Gao et al., 2016). Patients with shorter duration of OA showed reduced FC of the rmPFC with premotor, primary motor and sensory cortices, anterodorsal precuneus, and posterior cingulate cortex (Fig. 17). These regions are involved in construction of a body schema, which is a mental multisensory representation of the position and configuration of different parts of the body in space relative to each other and to the objects in the nearest space surrounding the body. Accurate body schema is essential for planning and controlling movements (Holmes and Spence, 2004). Although body schema and body image are thought to represent different types of body representation, they are closely related and can shape each other (Pitron et al., 2018; Pitron and de Vignemont, 2017). For example, negative appraisals of some body parts (i.e., negative body image) in patients with low self-esteem or anorexia

nervosa may contribute to development of body schema distortions, such as perception that certain parts of the body are oversized or too small (Dalhoff et al., 2019; Irvine et al., 2019). Distortions of the body schema may also result from pathological changes in somatosensory regions. For example, patients with lesions to the anterodorsal precuneus often feel drifting of limb position when it is not under visual control (fading limb symptom), or complain that some of their body parts are disproportionately larger (macrosomatognosia), or cannot be properly controlled (alien hand symptom) (Herbet et al., 2019). Distortions of the body schema can be found in chronic pain patients too (Lotze and Moseley, 2007; Viceconti et al., 2020). For example, it has been reported that 84% of patients with complex regional pain syndrome demonstrate neglect-like symptoms, e.g., patients perceive their painful limbs as foreign to them (Galer and Jensen, 1999). Another study found that patients with hand OA have abnormally small representation of the affected hand (Gilpin et al., 2015). Interactions between the rmPFC, that participates in formation of the body image, and sensorimotor areas, that are involved in generation of the body schema, might be implicated in development of such distortions. Perhaps, reduced connectivity between these areas observed in the OA1 group reflects patients' efforts to suppress or avoid pain-related negative emotions by rejecting representation of the affected knee in the body image that may result in distortions of the body schema and neglect-like symptoms. Interestingly, patients with longer duration of OA did not show impaired FC with the sensorimotor regions probably indicating that they have accepted their pain and learned more adaptive ways of coping with it. Acceptance of pain and acceptance-based psychological interventions have been associated with better body image and better coping with chronic pain disorders (Markey et al., 2020).

FC of the rlPFC in patients with shorter (OA1) and longer (OA2) duration of OA. Regarding the rlPFC, FC of this region did not significantly differ between the OA1 and OA2 groups. In comparison with HC, both groups showed reduced connectivity with several frontoparietal cortical regions that collectively comprise the multiple demand network (MDN) (Duncan, 2013) (Fig. 21-23). It was called "multiple demand" network because of the observation that the same set of

cortical regions is involved in a large variety of cognitive tasks including tasks on working memory, selective attention, set shifting, response inhibition, and fluid intelligence (Assem et al., 2020). Structurally, the MDN network is similar to the cognitive control network (Cole and Schneider, 2007), frontoparietal control system (Vincent et al., 2008), superordinate cognitive control network (Niendam et al., 2012), task-positive network (Fox et al., 2005), working memory network (Rottschy et al., 2012), inhibitory control network (Cieslik et al., 2015), and others. Although there are some variations in constituents, the main hubs of all these networks are the dorsal and ventral portions of the lateral PFC, presupplementary motor cortex extending to dACC, anterior insula, and superior parietal cortex (Camilleri et al., 2018). The MDN is sometimes further divided into, for example, cinguloopercular and frontoparietal subnetworks in attempts to characterize specific roles of different MDN components (Dosenbach et al., 2007). However, it is difficult to ascribe certain cognitive processes to specific areas of the MDN using fMRI because most of the regions coactivate in a very short temporal window (~ 500 ms), whereas the onset of the BOLD response occurs several seconds later (Cole and Schneider, 2007). The overarching role of the whole MDN in cognitive control of goal-directed behaviour is thought to be the elaboration of a structured plan of actions or sub-tasks that are needed for achievement of the main goal, execution of these sub-tasks in consecutive fashion, and controlling the process by separating task steps, orienting attention to current sub-task while inhibiting execution of previous or following steps (Duncan, 2010). The rlPFC is not a part of the typical MDN. Activity of the rlPFC seems to be unrelated to set shifting, working memory, selective attention to ongoing task, inhibition of previous tasks or subtasks, and other cognitive processes associated with the MDN (Mansouri et al., 2017). However, the rlPFC becomes engaged in cognitive control of behaviour when several goals are pursued simultaneously. The ability to perform several unrelated tasks in parallel is called cognitive branching or multitasking. The rlPFC keeps one of the tasks in a pending state in short-term memory and resumes it after the completion of another unrelated task. Cognitive branching is usually involved in planning, analogical thinking, abstract thinking, and prospective memory (i.e., memory for future intensions). Such ability is especially useful in uncertain environment when several

behavioural options with relatively equal expected reward values are available and it is too costly or risky to abandon one of them. By monitoring and comparing rewards or penalties associated with execution of each task, the rlPFC selects the most advantageous behaviour, which is then executed by the MDN. When ongoing behaviour becomes inefficient or less rewarding, the rlPFC switches behaviour toward some alternative goal that was kept pending or initiates exploration of alternative options if they have not been established yet (Mansouri et al., 2017). Animal studies show that even when ongoing behaviour is fully efficient and rewarding, animals still explore alternative courses of action at least 10% of the time (Charron and Collette, 2012; Kembro et al., 2019). Such spontaneous exploratory activity increases chances of finding more profitable resources and more efficient behavioural strategies (Charron and Collette, 2012). Switching from exploitation of current behaviour to exploration of new options has been associated with increased activity of the rlPFC (Daw et al., 2006).

Reduced FC between the rlPFC and MDN suggests that the ability to perform cognitive branching might be diminished in OA patients. This may contribute to deficits in planning, analogical reasoning, multitasking, prospective memory, and selection or identification of the most advantageous behavioural strategy. Cognitive branching has not been specifically investigated in chronic pain disorders, however, there is some evidence suggesting that it might be impaired. For example, several studies found that pain can interfere with multitasking (Moore and Law, 2017) and prospective memory (Pitães et al., 2018) in healthy people and in chronic pain patients (Ling et al., 2007; Miller et al., 2014). Altered connectivity and dysfunction of the rlPFC may also contribute to persistence of maladaptive coping strategies due to impaired exploration of alternative options beyond the ongoing behaviour (Koch et al., 2018). It has been suggested that chronic pain patients often tend to invariably exploit pain avoidance strategy instead of exploring other ways of coping. Although avoidance may be protective at early stages of the disease, it may also become detrimental as it does not allow disconfirmation of negative beliefs and fears thereby contributing to emotional disorders, disability, and chronification (Vlaeyen and Crombez, 2020).

The fact that FC of the rlPFC did not significantly differ between patients with shorter (OA1) and longer (OA2) duration of the disease suggests that dysfunction of the rlPFC may represent a premorbid risk factor that predisposes to development of chronic pain. In support of this interpretation, study by Attal et al. (2014) found that reduced cognitive flexibility can predict persistence of pain after total knee arthroplasty in OA patients as well as after mastectomy in patients that were pain-free before the surgery (Attal et al., 2014). In their study cognitive flexibility was measured by the Trail-Making Test, part B (TMT-B) which requires cognitive branching and has been associated with activation of the rlPFC and MDN (Varjacic et al., 2018).

Correlation of FC with behavioural data. Scores on BDI, STAI-T, PCS, as well as pain severity and PPT scores did not explain any of the group differences in FC of the rmPFC and rlPFC probably because of small sample sizes and low variation in the behavioral data which was mainly within the normal range (Table 4). Another possible explanation for the absence of correlation with behavioral measures is that FC values represented correlation coefficients between averaged activity in the ROIs and averaged activity of big clusters consisting of multiple distinct structures. For example, the brainstem cluster showing more negative FC with the rmPFC in the OA2 group included the dPAG, DRN, MRN, PBC, LC, MRF, and tVTA. Perhaps, a specific symptom such as pain severity cannot account for averaged variation in FC of the whole cluster. Behavioral data could potentially be better explained by FC between the rmPFC and more specific structures. Pain severity probably depends more on FC with the tVTA, helplessness on FC with the caudal DRN, and so on. Therefore, region-to-region, instead of region-to-whole-brain, connectivity analysis might be more suitable for detection of relationships between FC and behavioral data.

5.0 Limitations

The biggest limitation of this study is the impact of head motion. Existence of interaction between the grouping variable (OA1, OA2, HC) and movement variable (FD) means that the effects of both variables on FC (dependent variable) cannot be separated from each other. Motion only partially explained the variance in FC. For instance, only 16% of the variance (R^2=0.16) in FC between the rmPFC and precuneus was attributable to FD in the OA2 group (Fig.14a) suggesting that the rest of the variance might be related to other biological or psychological factors represented by the grouping variable. The fact that head movement had opposite influence on FC between same regions in different groups might also indicate that these effects are not entirely due to physical impact of motion, otherwise the effects of movement, probably, would have been the same across groups. As mentioned in Chapter III, Section 2, there is little agreement on the best approach to the problem of head motion. On the one hand, the most conventional approach, which is based on multiple reports showing that head motion can spuriously increase or decrease group differences in FC (Power et al., 2015, 2012; Satterthwaite et al., 2012; Van Dijk et al., 2012), emphasizes the importance of minimizing the effects of movement as much as possible at both individual and group-level analyses (Hlinka et al., 2010; Maknojia et al., 2019; Yan et al., 2013). On the other hand, it has also been suggested that aggressive motion-correction can be detrimental to accurate estimation of group differences too, because head motion is closely related to various clinical and behavioural factors, such as impulsivity, IQ, fluid intelligence, and other important variables (Siegel et al., 2017) making it difficult to separate physical effects of head motion on fMRI signal from the effects of neurobiological factors that predispose individuals to move more in the scanner (Geerligs et al., 2017). Removal of motion related effects can also reduce the effects of important variables (Bright and Murphy, 2015). While research on finding the most optimal strategy for dealing with head motion is still ongoing, in the present study the most conventional approach was utilized. However, results of the interaction analysis show that even after stringent exclusion of participants with

mean FD > 0.2 mm and denoising of individual data with ICA-AROMA, group differences in FC should still be interpreted with extra caution.

Another limitation is that results of this study could be confounded by medication. OA patients used various types of analgesics and other non-pain-related drugs including non-steroidal anti-inflammatory drugs, opioids, antidepressants, anticonvulsants, beta-blockers, hypolipidemic drugs, and others (Supplementary Table S3). Considering that even within a certain class of medications patients used different drugs with different mechanisms of actions (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors) it was not feasible to properly assess the effects of medication on performed analyses.

This study also lacked some important behavioral (self-concepts, cognitive tasks) and physiological data (e.g., skin conductance, heart rate variability) that could be used to support some of the interpretations. Future studies should aim to include these types of data.

6.0 Conclusions

It has been suggested that the pathophysiology of secondary pain disorders at more advanced stages of the disease may become similar to the pathophysiology of primary pain disorders which are mainly characterized by hyperalgesia and significant emotional distress (Treede et al., 2019). Consistent with this hypothesis results of the present study suggest that longer duration of OA is associated with hyperactivation of the brainstem arousal system that may contribute to enhanced nociception and negative affectivity. Importantly, these processes can be opposed by increased inhibitory control from the rmPFC. The rmPFC has been implicated in evaluation of self-efficacy and self-esteem (Somerville et al., 2010). Thus, pharmaceutical and psychological interventions that reduce physiological arousal and improve self-concepts might be helpful in preventing the transformation of secondary pain disorders into primary pain disorders. However, before making

strong conclusions about the role of the rmPFC in chronic pain it would be useful to evaluate its functioning in patients with more severe emotional distress, investigate its relationships with self-concepts, coping behaviors, and parameters of physiological arousal, such as heart rate variability or skin conductance.

Dysfunction of the rlPFC seems to be a premorbid risk factor that may predispose to chronification of pain. In patients with already developed pain disorder it may underlie deficits in functions requiring cognitive branching, such as planning, prospective memory, relational reasoning, and abstract thinking. It may also contribute to persistence of maladaptive coping behaviors, negative beliefs, and fears. Considering that existing literature on cognitive branching in chronic pain disorders is limited, more studies investigating this cognitive ability are needed.

VI. General discussion

1.0 Summary

Epidemiological studies report that approximately 20% of the population worldwide is affected by chronic pain (Goldberg and McGee, 2011). Growing awareness of the harmful impact on health, society, and economy was one of the reasons for inclusion of chronic pain disorders into the International Classification of Diseases (ICD). According to the ICD-11, chronic pain conditions are divided into chronic primary and chronic secondary pain disorders (Treede et al., 2019). Chronic primary pain disorder is considered as a disease in its own right characterized by pathological processing of pain and significantly increased modulation of pain by emotional factors. In contrast, chronic secondary pain is thought to be a symptom of some underlying structural pathology with either nociceptive or neuropathic mechanism of development. The role of emotional modulation and altered nociceptive processing in secondary pain disorders is not as prominent as in primary pain disorders. However, at later stages, secondary pain may lose its association with the underlying disease and become similar to primary pain (Kosek et al., 2016; Nicholas et al., 2019; Treede et al., 2019).

Both types of chronic pain are associated with increased risk of developing comorbid mood and anxiety disorders, however the risk is higher for patients with primary pain disorders (Bair et al., 2003; Demyttenaere et al., 2007). For example, comorbid depression occurs in 13–42% of patients with rheumatoid arthritis (secondary pain disorder) (Margaretten et al., 2011) and in 62–86% of patients with fibromyalgia (primary pain disorder) (Gracely et al., 2012). Comorbidity with emotional disorders has been associated with more intense pain and greater functional limitations (Bair et al., 2003; Berrahal et al., 2017; Sharma et al., 2016; Steiner et al., 2017). Therefore, the overarching aim of the thesis was to improve our understanding of the mechanisms that may underlie development of such comorbidity.

A growing body of evidence indicates that coexistence of nosologically distinct disorders occurs due to common transdiagnostic risk factors (Barlow et al., 2014b; Harris and Norton, 2018; Nolen-Hoeksema and Watkins, 2011). A theoretical model of comorbidity between chronic pain and emotional disorders based on the heuristic developed by Nolen-Hoeksema and Watkins (2011) has been proposed in Chapter I, Sections 2.3 - 2.4, Fig.3. The model suggests that chronic pain and emotional disorders indeed share many distal and proximal transdiagnostic risk factors. Common distal factors include genetic predisposition and chronic uncontrollable stress in childhood or adulthood. Distal risk factors via several mechanisms (e.g., conditioning, modelling, cognitive schemas) may induce occurrence of common proximal risk factors, such as neuroticism/negative affectivity, helplessness, dysregulated stress response, cognitive deficits, and altered pain processing. Importantly, distal and proximal risk factors are not disorder-specific, they equally predispose to emotional as well as chronic pain disorders. Occurrence of a specific disorder is determined by moderators (environmental or biological) that act upon proximal risk factors and shift the trajectory towards a specific disorder. For example, threatening events and uncertain circumstances increase the likelihood of developing anxiety disorders, experiences of loss and failure promote depressive disorders, medical conditions with acute pain predispose to chronic pain disorders. Current or lifetime comorbidity between chronic pain, depression, or anxiety is probably determined by the influence of different moderators on the same proximal risk factors simultaneously or at different points in time.

Thus, transdiagnostic factors play a pivotal role in the pathogenesis of both emotional and chronic pain disorders. Having a “pure” chronic pain disorder without any comorbid emotional disorder means that appropriate moderators that could induce development of emotional disorders have not been encountered yet, but distal and proximal risk factors that predispose to mood and anxiety disorders are already present. Targeting such transdiagnostic factors and mechanisms of their development may be an effective strategy for treatment and prevention of chronic pain as well as emotional disorders. Although the list of putative transdiagnostic risk

factors is long, multiple lines of evidence emphasize the role of uncontrollable stress, which is a distal risk factor strongly associated with every known proximal factor (Nolen-Hoeksema and Watkins, 2011). Therefore, it is important to identify neural mechanisms involved in nociceptive and emotional processing that could also mediate or oppose negative effects of uncontrollable stress.

The model of pain processing suggested by Garcia-Larrea et al. (Bastuji et al., 2016; Garcia-larrea et al., 2013) is described in Chapter I, Section 3.3, Fig.2. According to their model, perception of pain is constructed by a hierarchically organized network that performs processing of noxious signal in three consecutive phases: nociceptive, perceptive-attentional, and reappraisal-emotional. During the nociceptive phase, early sensory, motor, and affective aspects of pain are processed respectively by the posterior insular/secondary somatosensory cortex (pIC/SII), posterior midcingulate cortex (pMCC), and amygdala. The second phase is performed mainly by the anterior insular cortex (aIC), anterior midcingulate cortex (aMCC), dorsolateral prefrontal cortex (dlPFC), and posterior parietal cortex (PPC). They are involved in cognitive/attentional modulation and conscious perception of pain. Finally, noxious information undergoes the reappraisal-emotional phase of processing associated with activations in the hippocampus, ventral posterior cingulate cortex (vPCC), medial prefrontal cortex (mPFC) including its rostromedial part, perigenual cingulate cortex (pgACC), and rostrolateral prefrontal cortex (rlPFC). During this last phase, initial sensory, affective, motivational aspects of noxious stimulation are reappraised and modulated (facilitated or inhibited) based on previous experiences and various contextual factors.

This model of pain processing is similar to the appraisal model of emotion described in Chapter I, Sections 4.2-4.3, Fig.3. According to the appraisal theory, simple perception of a stimulus or event is not enough to start an emotional response, some minimal cognitive processing (appraisal) is required to begin the reaction (Brosch, 2013; Brosch and Sander, 2013; Sander et al., 2018). Emotional response starts with a rapid and relatively coarse low-level appraisal based on simple stimulus-outcome or stimulus-stimulus associations performed by sensory cortices and amygdala. After initial low-level appraisal, the amygdala through its

connections with multiple systems initiates emotional responses, such as changes in action tendency, physiological reactions (e.g., increased heart rate, skin conductance, secretion of stress hormones), motor expression, and subjective feeling (Brosch, 2013; Brosch and Sander, 2013; Sander et al., 2018). Early low-level appraisals are then followed by more reflective and contextualized appraisals performed by higher order prefrontal regions that take into account current context, semantic knowledge, and autobiographical memories (Cunningham et al., 2007; Sharpe and Schoenbaum, 2016). Reappraised information from the cortex is then fed back to subcortical regions to modulate (facilitate or inhibit) initial reactions (Cunningham et al., 2007). According to Dixon et al. (2017), the higher-level reappraisal is performed simultaneously in various PFC regions allowing multifaceted evaluation. Different subregions of the PFC are selectively involved in evaluation of specific aspects of the event.

Of particular interest with regards to uncontrollability is the rmPFC. This region has been associated with evaluation of controllability of the current negative event based on one's personal history of coping with the same or different stressful events in the past (Dixon et al., 2017; Kerr et al., 2012; Maier and Seligman, 2016; Ono et al., 2018). Whether it is possible to control the stressor depends not only on the nature of the stressor itself, but also on the abilities and attributes of a person who is dealing with the stress. When the stressor is encountered for the first time, evaluation of its controllability will depend more on the outcomes of similar situations experienced in the past. It has been demonstrated that animals with a history of control behave in a novel uncontrollable situation as if it is controllable. In contrast, animals subjected to uncontrollable stress in the past evaluate novel controllable stress as uncontrollable (Maier and Seligman, 2016). Multiple past experiences are generalized by the rmPFC into self-concepts or self-schemas (beliefs about one's personal attributes) that can significantly bias interpretation of current events and prediction of future events (Bowman and Zeithamova, 2018; D'Argembeau, 2013; Gilboa and Marlatte, 2017; Somerville et al., 2010; van der Cruijsen et al., 2018).

Negative self-concepts may significantly enhance perceived uncontrollability and its effects on processing of nociceptive and emotional signals. For example, it has been shown that facilitatory influence of perceived uncontrollability of pain on perceived pain intensity is mediated by helplessness, which is a belief that one's actions cannot influence outcomes (Müller, 2013, 2011). Acute pain patients with low self-efficacy (a belief about one's ability to cope with stress) are more likely to develop chronic debilitating pain disorder, and at higher risk of developing depression (Ferrari et al., 2019). On the contrary, higher self-efficacy plays protective role against chronification of acute pain (Puschmann et al., 2020) as well as against depression (Tahmassian and Jalali Moghadam, 2011). These findings suggest that the rmPFC might play important role in evaluation of controllability. Its dysfunction may contribute to increased sense of uncontrollability and subsequent development of proximal transdiagnostic risk factors, such as hyperalgesia and negative affectivity.

The lateral part of the rostral PFC (the rlPFC) might be involved in development of cognitive deficit, which is another proximal transdiagnostic risk factor. Chronic pain patients and patients with emotional disorders often display impairments in cognitive flexibility (Cáceda et al., 2014; Tamburin et al., 2014), which is generally defined as the ability to appropriately adjust one's behaviour to a changing environment (Dajani and Uddin, 2015). It has been suggested that the rlPFC plays an important role in cognitive flexibility. In case the ongoing behaviour becomes inappropriate, the rlPFC initiates switching to the best alternative course of action (Koch et al., 2018). Impaired cognitive flexibility may lead to persistence of strategies and behaviours that are no longer adaptive. For example, patients suffering from an injury may continue to use strategies that were useful during the acute period of a disease (e.g., resting, sparing of the affected organ, avoiding certain activities that could provoke pain) long after the injury has healed. Similarly, individuals with impaired cognitive flexibility may continue to evaluate some stressful situation as uncontrollable even if it has become objectively controllable. Thus, dysfunction of the rlPFC might also contribute to persistence of pain and emotional distress via impaired cognitive flexibility.

Considering all the above, the general hypothesis of the thesis was that chronic pain disorders are characterized by dysfunction of the rmPFC and rlPFC that may enhance perceived uncontrollability and impair modulation of regions involved in initial low-level nociceptive and emotional reactions thereby contributing to hyperalgesia and significant negative affectivity. To test this hypothesis, resting-state functional and effective connectivity analyses were chosen as main methods of research. Taking into account the distinction between chronic primary and chronic secondary pain disorders described above, connectivity of the rmPFC and rlPFC were investigated in patients with CLBP (primary pain disorder) and OA (secondary pain disorder). Considering that at later stages of the disease secondary pain disorders may become similar to primary pain disorders, the OA group was additionally divided into two subgroups based on duration of pain.

Functional connectivity (FC) of the rmPFC and rlPFC in CLBP. The CLBP group showed reduced FC of the rmPFC with the retrosplenial cortex (RSC), posterior part of the ventral pallidum (VP), and mediodorsal (MD) thalamus (Fig.8). The RSC plays important role in mental reconstruction of complex events, which is necessary for autobiographical memory retrieval, imagination, and future planning (Vann et al., 2009). The posterior VP is associated with encoding and associative learning of rewarding events (K. S. Smith et al., 2009). The MD thalamus plays a key role in rapid integration of object/reward/response information (Mitchell and Chakraborty, 2013). Reduced interaction of the rmPFC with these regions may obstruct retrieval of positive autobiographical memories and impair attribution of positive outcomes to personal actions. This may undermine formation of positive self-concepts, increase perceived uncontrollability, and contribute to development of proximal risk factors, such as negative affectivity and hyperalgesia. Indeed, pain intensity scores negatively correlated with FC between the rmPFC and pIC/S2 area, which is involved in early processing of sensory aspects of pain. Also, CLBP patients showed reduced FC of the rmPFC with the medial pulvinar nucleus of the thalamus, midbrain reticular formation, and periaqueductal grey (Fig.8). These structures are implicated in early subconscious processing of threat, hyperarousal, hypervigilance, and generation of rapid defensive fight-flight responses (Terpou et al., 2019).

Reduced FC of the rmPFC with these brainstem regions may contribute to increased negative affectivity.

Overall, results of this study were consistent with the general hypothesis that chronic pain patients are characterized by impaired regulation of early low-level nociceptive and emotional responses by the rmPFC. The results also suggested that this impairment may stem from reduced interaction of the rmPFC with memory systems that hampers formation of positive self-concepts and increases perceived uncontrollability.

Effective connectivity analysis in CLBP. In this study, possible neural mechanisms mediating the effects of uncontrollable stress, which is a distal risk factor, were investigated in more detail using the analysis of effective connectivity. According to the Learned Helplessness theory (Maier and Seligman, 2016), two proximal risk factors caused by uncontrollable stress, i.e., passive coping (helplessness) and negative affectivity, are mediated by inhibitory influence of the dorsal raphe nucleus (DRN) on dorsal periaqueductal grey (dPAG) and excitatory influence of the DRN on basolateral amygdala, respectively. Helplessness and negative affect are default behavioral reactions to uncontrollable stress. However, if stress becomes controllable or if there was a history of successful control in the past, then the prelimbic cortex (the rmPFC in humans) inhibits the DRN and prevents development of helplessness and negative affect. The controllability of the stressor is estimated by the rmPFC based on the analysis of contingencies between previous actions and their outcomes encoded in the striatal memory system. Inspired by this theory, causal interactions between the rmPFC, stress-related brainstem structures (DRN, vPAG, dPAG), and memory systems (ventral striatum, hippocampus, amygdala) were investigated in CLBP using the spectral dynamic causal modelling (spDCM). In general, results of the study were compatible with the Learned Helplessness theory; however, they suggested different mechanisms of passivity and negative affect. Passive coping behavior (helplessness) in chronic pain conditions might be better explained by hyperactivation of the vPAG and inhibition of the anterior hippocampus, whereas emotional distress is probably due to increased activity of the dPAG. Also, results of the study suggest that the rmPFC not

only can inhibit the DRN when the situation is deemed controllable, but it can also activate the DRN when the situation is considered as uncontrollable. Supporting this suggestion, effective connectivity from the rmPFC to DRN was excitatory in CLBP and inhibitory in healthy controls probably reflecting differences in self-concepts between the groups. Healthy people usually have positive self-concepts and even tend to overestimate their abilities (Jones et al., 2019). A belief that one can cope with any stressful situation may facilitate inhibition of the DRN activity even when stress is objectively uncontrollable. In contrast, CLBP patients are known to have negative, depreciating self-concepts (de Moraes Vieira et al., 2014) that may increase perceived sense of uncontrollability and contribute to hyperactivation of the DRN. Similar to the previous study, the DCM analysis also found evidence of impaired interaction of the rmPFC with memory systems. Patients showed weaker connectivity with the hippocampus and stronger connectivity with the amygdala suggesting that the rmPFC is in short supply of contextual information from the hippocampus but relatively overloaded with conditioned associations provided by the amygdala. This may contribute to inaccurate evaluation of controllability, overgeneralization, and impaired extinction of fears. Suppression of hippocampal functions probably results from excessive inhibitory influence coming from the DRN.

In general, functional and effective connectivity studies in CLBP are consistent with each other. Both studies suggest impaired modulation of low-level nociceptive and emotional reactions by the rmPFC that may be due to impaired interaction of this region with memory systems.

Functional connectivity of the rmPFC and rlPFC in OA. The key finding of this study was that patients with longer duration of OA (>7 years) showed increased negative functional connectivity of the rmPFC with multiple brainstem nuclei, such as the PBC, LC, DRN, MRN, VTA, MRF, and PAG, that together comprise the ascending reticular activating system (ARAS). The main function of the ARAS is generation and regulation of a general arousal state in the brain (Edlow et al., 2012). Low or high levels of arousal in the CNS can respectively suppress or amplify emotional and nociceptive reactions (Venkatraman et al., 2017). Prolonged experience of emotional stress as well as chronic pain have been associated with

hyperactivation of the ARAS and subsequent development of pathological anxiety and hyperalgesia (Finan and Smith, 2013; Morris et al., 2020; Taylor and Westlund, 2017; Thome et al., 2019). Hyperactivation of the arousal system may result from increased bottom-up nociceptive signaling from the dorsal horn and sensory areas. Alternatively, it may stem from reduced top-down regulation by the higher order prefrontal regions. Negative FC between the rmPFC and ARAS observed in patients with longer duration of OA may reflect increased inhibition of the ARAS by the rmPFC and suppression of pain-induced arousal and anxiety. In support of this interpretation, evaluation of psychometric data showed that despite longer duration of pain, patients did not display signs of significant emotional distress or hyperalgesia probably because the rmPFC successfully inhibits the ARAS and prevents negative consequences of hyperarousal. Patients with shorter duration of OA did not differ from HC with regards to FC between the rmPFC and ARAS suggesting that hyperactivation of the arousal system and compensatory inhibition of the system develops at more advanced stages of the disease. Interestingly, functional connectivity analysis in CLBP also showed impaired interaction between the rmPFC and parts of the ARAS, such as MRF and PAG, indicating that these brainstem structures might be hyperactivated in CLBP patients too. Effective connectivity analyses in CLBP also showed increased activation of the DRN and PAG. Thus, hyperactivity of the brainstem arousal system seems to be a common feature of primary pain disorders and secondary pain disorders at later stages. Amplification of nociceptive and emotional responses in hyperarousal state may explain two main characteristic symptoms of primary pain, i.e., hyperalgesia and significant emotional distress. Occurrence of this mechanism in a secondary pain disorder may determine the transformation of a secondary pain disorder into primary pain disorder. However, results also imply that the rmPFC may oppose this process. Interestingly, in contrast to CLBP patients, patients with OA did not display impaired connectivity of the rmPFC with memory systems. Perhaps, preserved ability to retrieve positive episodic memories and generalize them into positive self-concepts helps patients with OA to maintain the sense of control.

Regarding the rlPFC, FC of this region did not significantly differ between patients with longer and shorter duration of OA. However, in comparison with HC, both groups showed reduced connectivity with several frontoparietal cortical regions that collectively comprise the multiple demand network (MDN) (Duncan, 2013) (Fig. 21-23). Reduced FC between the rlPFC and MDN may undermine the ability to perform cognitive branching, which is important for planning, analogical reasoning, multitasking, prospective memory, and selection or identification of the most advantageous behavioural strategy. Altered connectivity and dysfunction of the rlPFC may also contribute to reduced cognitive flexibility and persistence of maladaptive coping strategies due to impaired exploration of alternative options beyond the ongoing behaviour (Koch et al., 2018). In contrast to OA patients, patients with CLBP did not show impaired connectivity of the rlPFC suggesting that cognitive factors might play more important role in secondary than in primary pain disorders.

In summary, results of the research suggest that chronic uncontrollable stress (distal transdiagnostic risk factor) may cause development of proximal transdiagnostic risk factors, such as negative affectivity and hyperalgesia, via hyperactivation of the brainstem arousal system. In turn, hyperactivity of the brainstem arousal system may result from impaired regulation of the system by the rmPFC which evaluates the controllability of the stress through the lens of previous experiences. Impaired retrieval of positive memories of control by the rmPFC may increase the sense of uncontrollability thereby contributing to hyperarousal and development of proximal transdiagnostic risk factors.

2.0 Limitations and methodological issues

The studies presented above have several limitations that should be appropriately addressed in the future. First limitation is a cross-sectional design of all three studies that did not allow to differentiate between premorbid features,

effects of pain per se, and adaptive changes. Prospective or longitudinal studies might be helpful in disentangling these effects.

Next limitation is the exploratory nature of performed seed-to-whole-brain functional connectivity analyses. Resultant statistical maps showed altered functional connectivity of the seeds with widespread clusters consisting of multiple brain regions. For example, FC of the rmPFC in CLBP showed reduced FC of the ROI with a single cluster of brain regions consisting of the retrosplenial cortex, parahippocampal cortex, ventral pallidum, thalamus, and several brainstem nuclei. FC of the rmPFC with the whole cluster was reduced, however, connectivity with some of the regions within the cluster could also be negative, i.e., anticorrelated. Clustering of multiple anatomically distinct structures makes it difficult to accurately investigate the relationships between two specific regions. Explanatory region-to-region connectivity might be more informative in that regard.

Head motion is another factor that may have confounded results of the studies especially the one that investigated functional connectivity in OA. Currently, there is no agreement on the nature of motion-related artifacts and best strategies to correct for the effects of movement. In presented studies, head motion parameters were regressed out during preprocessing and at the group-level. However, given that head movement is strongly associated with many neurobiological factors (Siegel et al., 2017), some important non-motion related variance might have been erroneously removed (Bright and Murphy, 2015). Thus, it is difficult to infer whether observed group differences were partially caused by head motion itself, by applied motion correction, or by neurobiological factors. Further investigation of the nature of motion-related artifacts and improvement of motion correction strategies are needed.

Also, the studies lacked important behavioral and physiological data to support some of the proposed mechanisms. Future studies should try to incorporate data on self-efficacy, self-esteem, and other relevant self-concepts that could be used to examine how individual differences in self-concepts correspond with the differences in rmPFC connectivity. Additionally, considering that hyperarousal might be a fundamental mechanism of hyperalgesia and emotional

distress, more elaborate investigation of this mechanism using parameters of physiological arousal, such as heart rate variability or skin conductance, is also needed.

Inclusion of behavioral data on self-concepts and experiments on controllability of stress, as well as measurements of physiological arousal, would help to mitigate the problem of reverse inference (Poldrack, 2006), which is another limitation of this thesis. Reverse inference is a kind of reasoning that assumes engagement or impairment of a certain brain function using only neuroimaging data without directly testing that function experimentally but interpreting the results based on other studies that have linked a specific structure with a specific function (Poldrack, 2011). Such inference would be valid if the region of interest had been associated with only one function (Poldrack, 2006). However, most of the brain areas can be activated by a wide range of tasks and cognitive processes. For example, primary visual cortex can be activated not only by visual but also by auditory (Pockett et al., 2013) and tactile (Nordmark et al., 2012) stimuli. Primary motor cortex that has mainly been linked with performance of voluntary movements is also active during tasks on working memory, visual and auditory tasks that do not involve movements (Kukleta et al., 2016; Tomasino and Gremese, 2016). Similarly, activity in the rmPFC has been associated not only with processing of self-referential information (D'Argembeau, 2013) but also with processing of rewards (Ramnani et al., 2004) and thinking about the future (Okuda et al., 2003). The rlPFC can be activated not only by tasks on cognitive branching (Mansouri et al., 2017) but also when improvising jazz (Limb and Braun, 2008) and detecting deception (Karim et al., 2010). Given that the region of interest may be involved in many tasks with different demands, it is difficult to confidently infer what is a specific role of that region in all the tasks that it has been associated with. Although a combination of neuroimaging and behavioural data may not fully answer this question, as the region of interest may be also involved in other tasks not formally tested in the study, it provides more specificity and evidence to the inference (Poldrack, 2006).

Another method to increase specificity of neuroimaging data is to use smaller regions of interest, as large regions may have many functionally distinct

subdivisions (Poldrack, 2006). The rostral prefrontal cortex (Brodmann area 10) is the largest single cytoarchitectonic area of the brain (Bludau et al., 2014). Future studies should also try to identify its subdivisions that are more specifically involved in evaluation of controllability. However, that would be a difficult task as it has been estimated that one voxel, the smallest spatial unit in fMRI, contains about 5 million neurons and $2.2–5.5 \times 10^{10}$ synapses (Logothetis, 2008), whereas activation of approximately 37 neurons can be sufficient to drive a specific behavior (Dalgleish et al., 2020). Thus, even if a region of interest is as small as one voxel, it may still consist of diverse neuronal populations with different specializations making it difficult to assertively associate activity in this voxel with a certain process (Kragel and LaBar, 2016).

Considering these issues, the focus of research on establishing neural substrates of mental functions has recently shifted from single structures to distributed networks and dynamic interactions between multiple areas across the brain. It has been suggested that even though a certain brain structure can be activated by many tasks and be associated with many functions, the pattern and timing of co-activations or interactions of that region with the rest of the brain may be unique for each experimental condition and function (Celeghin et al., 2017). One of the methods that allows investigation and comparison of co-activation patterns across different conditions is multi-voxel pattern analysis (MVPA) that uses machine learning tools to decode mental states from neuroimaging data. It has been demonstrated by several studies that the degree to which a pattern of brain activation is predictive of the engagement of a specific mental process can be accurately estimated by MVPA (Poldrack, 2011). Although MVPA has been criticized for yielding unstable results (Anderson and Oates, 2010) and low reproducibility (Kragel and LaBar, 2016), it would be useful to investigate the role of the rmPFC in assessment of controllability using this method too.

3.0 Implications for treatment

Results of the present research might have important implications for treatment of chronic pain and emotional disorders. Recently, Hanlon et al. (2019) have suggested that the rostral prefrontal cortex may be an important, transdiagnostically relevant target for transcranial magnetic stimulation (TMS). According to the authors, inhibition of the rostral prefrontal cortex using repetitive TMS may be an effective therapeutic strategy for treatment of many emotional disorders (Hanlon et al., 2019). Considering that emotional disorders and chronic pain have common pathogenetical mechanisms of development, TMS of the rostral prefrontal cortex might be also effective in chronic pain. However, as described above, the rmPFC may facilitate emotional distress as well as prevent it depending on whether it evaluates the stress as controllable or uncontrollable. Thus, inhibition of the rmPFC using TMS could be beneficial in cases where the rmPFC contributes to emotional distress but detrimental in cases where it plays a protective role.

The rmPFC is involved in generation of self-concepts which may have significant impact on assessment of controllability. Psychotherapeutic interventions aiming to improve self-efficacy and self-esteem might be effective in treatment and prevention of chronic pain and emotional disorders. Results of the connectivity analyses suggest that negative self-concepts may develop due to impaired interaction between the rmPFC and memory systems which hampers recollection of positive memories and construction of positive self-concepts. Helping patients to call to mind and generalize positive memories, such as past episodes of successful control, could be used to increase self-efficacy and perceived control. spDCM study also showed the rmPFC received less information from the hippocampus and more information from the amygdala. Such imbalance may contribute to reduced contextualization of negative memories, overgeneralization, and impaired extinction of fears (de Voogd et al., 2020). Therefore, psychological treatment should also try to improve contextualization of pain- or threat-related associations.

Finally, results of this research might be relevant for computerized and non-computerized neurocognitive therapies. Neurocognitive therapies apply structured

exercises or games with the aim of improving certain neurocognitive processes such as attention, working memory, and other cognitive functions (Brunoni et al., 2014; Semkovska and Ahern, 2017). A meta-analysis of studies that used neurocognitive therapy for treatment of major depression showed that this type of intervention can improve cognitive functions targeted by the training. However, the impact on mood was only small to moderate (Motter et al., 2016). In another randomized study, patients with depression showed better neurocognitive performance after the training, but improvement in cognitive functions (attention, working memory, long-term memory, planning) was not associated with better mood (Semkovska et al., 2015). Such moderate results in relation to the main symptom of depression are probably due to targeting of wrong neurocognitive processes. Most of the exercises were aiming to enhance functioning of the dlPFC. Perhaps, training of the rmPFC might be more efficient in relation to negative affect. As mentioned earlier, evaluation of controllability of negative events performed by the rmPFC is based on the analysis of contingencies between previous actions and their outcomes (Maier and Seligman, 2016). If, for example, 7 out of 10 previous attempts to control a negative event were unsuccessful, and only 3 of them were successful, then making a judgment based on more frequent past experiences would determine the event as uncontrollable. However, the ability to remember and consider rare outcomes would probably help to maintain an optimistic view. There is evidence suggesting that events that occur with different frequencies are processed by different parts of the rmPFC. The most anterior part of the rmPFC specializes on retrieval of low-frequency events, whereas the most posterior part is engaged during retrieval of high-frequency events (Krueger et al., 2007). Cognitive exercises that enhance retrieval of low-frequency events might improve the ability to consider rare episodes of control and preserve the sense of controllability despite the negative odds.

VII. References

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VIII. Appendices

1.0 Supplementary material for chapter III (FC in CLBP)

Supplementary Table S1.

Demographics and clinical data of CLBP patients and HC

Participant	Age	Sex	Pain duration	P.int	BDI	FD
cbp_01	51	2	1	8	15	0.06
cbp_02	62	1	38	8.7	1	0.07
cbp_03	49	2	14	8.4	12	0.07
cbp_04	62	2	2	8.4	13	0.04
cbp_06	54	2	8	7.5	6	0.13
cbp_07	50	1	30	6.9	4	0.15
cbp_08	54	1	30	6.2	4	0.09
cbp_09	62	1	25	7.4	3	0.12
cbp_10	46	1	11	5.9	13	0.08
cbp_11	49	1	41	6.3	4	0.16
cbp_12	52	1	5	5.7	6	0.03
cbp_13	58	1	10	5.4	9	0.1
cbp_14	32	1	12	7.8	5	0.03
cbp_16	48	1	1	8.7	12	0.07
cbp_19	39	2	10	4.6	0	0.09
cbp_20	56	2	11	4.3	0	0.06
cbp_21	49	1	7	6.5	17	0.09
cbp_22	47	1	32	7.94	0	0.08
cbp_23	58	1	20	6.89	10	0.11
cbp_24	52	1	1	4.2	0	0.08
cbp_26	41	2	25	3.9	0	0.06
cbp_27	49	2	7	5.77	0	0.06
cbp_28	52	1	37	7.2	4	0.06
cbp_29	52	2	15	2.66	5	0.05
cbp_30	48	1	10	4.8	2	0.03
cbp_31	40	2	7	6.8	10	0.09
cbp_32	48	2	10	8.21	19	0.15
cbp_33	21	2	11	5.8	19	0.05
cbp_34	55	2	20	6.92	2	0.07
hc_01	40	2			0	0.09
hc _02	60	2			0	0.04
hc _04	48	2			3	0.07
hc _05	48	2			0	0.05
hc _06	49	2			0	0.1
hc _07	53	2			0	0.09

hc _08	31	1			0	0.02
hc _09	46	2			4	0.07
hc _10	47	1			0	0.04
hc _11	60	1			0	0.12
hc _12	21	2			0	0.02
hc _14	54	1			1	0.1
hc _15	51	1			0	0.05
hc _17	64	2			0	0.14
hc _18	46	1			1	0.05
hc _19	38	1			0	0.03
hc _20	44	1			1	0.03
hc _21	42	2			3	0.11
hc _22	40	1			0	0.07
hc _23	46	1			0	0.03
hc _24	40	2			0	0.03
hc _25	48	1			0	0.15
hc _26	59	1			0	0.05
hc _27	48	1			1	0.04
hc _28	51	1			4	0.03
hc _29	58	2			10	0.03
hc _30	57	2			6	0.06
hc _32	50	2			0	0.09
hc _33	60	1			8	0.06
hc _34	49	1			0	0.06

Legend: cbp – chronic back pain; hc – healthy control; P.int – pain intensity; BDI – Beck Depression Inventory; FD – framewise displacement. Sex is coded as 1 = male and 2 = female.

2.0 Supplementary material for chapter V (FC in OA)

Supplementary Table S2.

Demographics and clinical data of OA patients and HC

Participant	Age	Sex	PCS	STAI-T	BDI-II	PPTs	PPTk	P.dur	P.sev	FD
Patients with shorter duration of osteoarthritis (OA1 group)										
1	69	1	12	30	4	237.43	480.93	6	40	0.11
2	66	1	12	37	9	221.83	510.57	6	10	0.17
3	53	2	6	39	23	318.87	383.43	1	40	0.09
4	69	2	7	24	4	157.80	110.93	4	80	0.08
5	67	2	5	28	8	129.23	340.33	5	10	0.08
6	22	2	13	39	3	110.20	106.53	5	30	0.02
7	61	2	12	30	8	82.43	107.27	2	10	0.1
8	64	2	6	55	23	167.57	145.20	6	30	0.14
9	80	1	11	30	5	306.83	212.53	4	50	0.14
10	75	2	9	28	4	429.57	320.43	1	40	0.11
11	55	1	6	42	8	77.07	286.73	0.5	1	0.06
12	70	1	10	27	3	71.13	173.07	1	0	0.08
13	60	2	1	52	22	68.60	85.90	3	5	0.06
14	80	2	13	37	10	173.63	137.73	5	30	0.11
15	69	1	11	40	12	347.90	555.03	1	0	0.06
16	62	2	27	36	2	213.93	158.40	2.5	65	0.07
17	65	1	22	34	9	210.07	104.43	5	20	0.18
18	54	1	19	24	6	454.27	445.97	0.83	35	0.07
19	57	1	20	38	20	226.83	363.30	2	85	0.05
20	56	2	20	24	11	146.80	197.00	4	80	0.05
21	34	2	20	39	24	34.57	68.80	2	25	0.12
22	73	2	27	31	11	218.10	254.53	2.83	0	0.15
23	64	2	22	45	20	124.83	147.80	5	30	0.09
24	76	2	52	57	32	96.37	19.35	0.75	55	0.09
25	55	1	39	53.5	40	283.00	232.07	2	30	0.16
26	66	2	24	31	9	377.73	544.25	4	0	0.18
27	54	2	20	31	2	163.23	190.93	6	0	0.05
28	49	2	32	32	15	117.03	334.77	5	75	0.08
29	60	1	34	49	23	274.53	288.00	0.75	65	0.09
30	62	1	35	24	3	983.50	1019.37	3	60	0.1
31	49	1	17	49	13	173.60	275.27	4	10	0.14
32	52	1	30	28	9	235.73	146.40	1	70	0.04
33	46	2	19	44	18	385.10	654.93	4	50	0.08
Patients with shorter duration of osteoarthritis (OA2 group)										
1	65	2	1	28	19	223.47	257.73	20	10	0.1
2	80	1	1	28	9	294.53	467.03	10	5	0.12
3	63	2	3	37	13	182.27	223.63	10	10	0.06
4	66	2	12	38	6	217.63	257.90	27	80	0.1

5	66	2	4	33	3	225.80	248.27	10	70	0.12
6	66	2	0	23	2	495.17	616.00	7	10	0.11
7	69	1	9	31	11	280.57	297.00	10	1	0.06
8	55	1	3	23	2	550.47	683.53	7	20	0.16
9	65	1	0	31	2	544.70	431.13	30	30	0.06
10	60	2	4	29	9	160.20	142.23	24	20	0.18
11	58	1	2	29	3	172.33	173.83	10	30	0.1
12	69	1	5	24	2	209.63	266.57	10	0	0.19
13	75	2	18	42	12	102.97	96.83	8	55	0.16
14	69	1	6	24	5	146.87	64.43	10	20	0.1
15	58	2	6	34	3	138.33	83.27	10	10	0.06
16	64	2	5	42	3	249.90	244.93	15	50	0.1
17	63	1	20	49	28	254.10	379.30	37	30	0.19
18	73	2	0	43	13	222.03	228.23	10	50	0.11
19	62	1	8	28	5	361.47	304.93	12	35	0.19
20	66	1	13	34	19	413.73	478.60	48	0	0.08
21	59	1	10	32	4	351.00	326.13	15	45	0.09
22	70	1	23	32	13	224.87	173.30	30	50	0.11
23	68	2	15	33	9	311.60	174.97	30	20	0.03
24	48	2	24	54	15	80.17	104.93	10	70	0.17
25	62	1	40	51	19	206.70	123.33	7	80	0.11
26	52	2	48	72	27	66.87	64.20	13	75	0.09
27	64	2	48	55	31	142.67	126.57	20	0	0.15
28	71	2	13	29	12	229.23	317.43	10	90	0.15
29	73	2	11	34	5	166.90	535.90	13	40	0.07
30	67	2	17	38	8	384.50	445.07	9	25	0.12
31	74	2	13	30	4	209.53	243.97	16	0	0.07
32	53	2	22	64	29	399.60	439.70	13	40	0.06
33	58	1	16	42	16	1290.57	1374.00	30	10	0.17
34	32	2	17	49	16	152.47	264.90	12	20	0.05
35	55	2	17	37	13	204.37	315.33	10	60	0.16
Healthy controls										
1	70	1	7	25	6	572.07	796.80			0.12
2	72	1	11	33	7	516.00	697.00			0.07
3	81	1	24	30	9	234.63	361.07			0.06
4	46	1	5	24	0	221.70	309.10			0.05
5	79	1	0	21	6	312.17	312.43			0.06
6	73	1	17	35	7	320.50	372.03			0.08
7	44	1	1	24	0	485.87	619.93			0.06
8	64	1	4	34	6	307.33	580.23			0.08
9	63	1	9	26	2	657.40	849.47			0.09
10	45	1	3	28	3	271.07	462.30			0.05
11	48	1	0	48	13	463.97	653.63			0.03
12	74	1	23	32	5	154.30	239.70			0.06
13	71	1	11	30	4	182.10	200.67			0.07
14	76	1	11	43	19	128.33	215.47			0.04
15	54	1	11	25	0	193.53	359.30			0.05
16	78	1	6	32	5	322.03	388.83			0.2
17	62	1	7	25	1	118.37	347.50			0.06
18	71	1	11	31	7	324.53	161.57			0.06
19	79	1	6	25	5	487.83	494.37			0.15

20	48	2	0	31	2	101.10	178.27			0.09
21	64	2	1	39	9	619.53	894.77			0.09
22	67	2	17	37	2	180.67	208.20			0.06
23	74	2	2	31	5	124.10	169.00			0.07
24	53	2	4	31	5	437.23	703.37			0.05
25	66	2	17	30.375	1	133.00	271.33			0.17
26	70	2	28	32	6	177.77	380.83			0.09
27	48	2	3	29	3	278.33	314.60			0.06
28	76	2	2	38	8	200.70	290.10			0.09
29	71	2	9	47	3	283.13	262.43			0.11
30	65	1	2	44	3	216.40	248.70			0.06
31	63	2	3	26	9	202.00	362.23			0.08
32	65	2	3	44	0	186.20	275.47			0.04
33	59	2	1	25	4	250.17	321.93			0.02
34	64	2	5	34	6	140.30	280.57			0.14
35	67	2	1	24	27	280.47	343.73			0.1

Legend: OA – osteoarthritis; PCS – Pain Catastrophizing Scale; STAI - State-Trait Anxiety Inventory; BDI – Beck Depression Inventory; PPTs – pressure pain threshold at sternum site; PPTk - pressure pain threshold at painful knee site; P.dur – pain duration; P.sev – pain severity; FD – framewise displacement. Sex is coded as 1 = male and 2 = female.

Supplementary Table S3.

Medications used by OA patients

Participant	**Medication**
Patients with shorter duration of osteoarthritis (OA1 group)	
1	-
2	Tramadol, dihydrocodeine, ibuprofen, paracetamol, gabapentin
3	-
4	Paracetamol, aspirin
5	-
6	Paracetamol
7	-
8	Co-codamol, sertraline, valproate, ibuprofen
9	Tramadol, bisoprolol, aspirin, paracetamol
10	-
11	-
12	-
13	-
14	-
15	-
16	-
17	-
18	Paracetamol
19	Zapain (codeine), citalopram, gabapentin, bisoprolol, paracetamol
20	Naproxen, amitriptyline

21	-
22	Amitriptyline
23	Paracetamol
24	Duloxetine, amitriptyline
25	Paracetamol, aspirin
26	Morphine, seroxin, amitriptyline, pregabalin
27	-
28	-
29	Paracetamol, ibuprofen
30	Dihydrocodeine, amitriptyline, pregabalin
31	Cortisone
32	Paracetamol, ibuprofen
33	paracetamol
Patients with longer duration of osteoarthritis (OA2 group)	
1	-
2	Aspirin
3	Citalopram
4	Aspirin, mirtazapine
5	-
6	Codeine, naproxen
7	-
8	-
9	-
10	Gabapentin
11	-
12	Paracetamol
13	Co-codamol
14	Dihydrocodeine, amitriptyline
15	-
16	-
17	Tramadol, aspirin
18	Codeine, amitriptyline, paracetamol
19	Tramadol, amitriptyline, citalopram
20	Tramadol, lyrica, ibuprofen
21	Co-codamol, naproxen, amitriptyline
22	-
23	Co-codamol, aspirin
24	Zapain, paracetamol
25	Amitriptyline, aspirin
26	-
27	-
28	Paracetamol
29	-
30	-
31	Dihydrocodeine
32	-
33	-

34	-
35	-