fMRI Correlates of ICD-11 Taxonomies of Chronic Primary Pain and Chronic Secondary Musculoskeletal Pain: Systematic Reviews and Meta-analyses

Khetam Al-Faraj

Supervised by

Dr. Elia Valentini and Dr. Paul Hanel

Department of Psychology

University of Essex

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Declaration Statement

I hereby declare that this thesis is my own original work. To the best of my knowledge, it does not contain any material previously published or written by another person, nor does it include substantial portions of material that have been accepted for the award of any other degree or diploma at the University of Essex or any other educational institution, except where due acknowledgment is made in the thesis. Contributions to the research made by others, with whom I have worked at the University of Essex or elsewhere, are explicitly acknowledged. Additionally, I declare that the intellectual content of this thesis is the result of my own efforts, except where assistance in project design, conception, style, presentation, and linguistic expression has been acknowledged.

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List of Abbreviations

ACC	Anterior cingulate cortex
ALE	Activated likelihood estimation
aIns	Anterior Insula
BA	Brodmann Area
BOLD	Blood Oxygen Level Dependent
CBMA	Coordinate-based meta-analysis
cFWE	Cluster-level FWE
CG	Cingulate gyrus
Claus	Claustrum
CNS	Central nervous system
CPP	Chronic Primary Pain
CSMP	Chronic Secondary MSK Pain
CT	Cerebellar tonsil
daIns	dorsal anterior Ins
DMN	Default mode network
FC	Functional connectivity
FCDR	False Cluster Discovery Rate
FDR	False Discovery Rate
FWE	Family-wise Error
FWHM	Full width at half maximum

Ins	Insula
IASP	International Association for the Study of Pain
IBS	Irritable bowel syndrome
ICD	International Classification of Disease
IFG	Inferior Frontal Gyrus
IPL	Inferior parietal lobe
IRR	Inter-rater reliability
ISLL	Inferior semi-lunar lobule
LN	Lentiform Nucleus
MCC	Mid-cingulate gyrus
MFG	Medial frontal gyrus
MKDA	Multi-level Kernel Density Analysis
MS	Multiple Sclerosis
MSK	Musculoskeletal
NAc	Nucleus accumbens
Para	Parahippocampus
PCC	Posterior cingulate cortex
PD	Parkinson's disease
PD1	Parkinson's without symptoms
PD2	Parkinson's with symptoms
PFC	Prefrontal cortex

PVM	Parameter voxel-based meta-analysis
PreG	Precentral gyrus
QoL	Quality of life
RRMS	Relapsing-remitting MS
rTPJ	Right temporoparietal junction
SDM	Signed difference map
SI	Primary somatosensory cortex
SII	Secondary somatosensory cortex
SMA	Supplementary motor area
SNS	Somatosensory nervous system
SP	Spontaneous pain
SPMS	Secondary progressive MS
STG	Superior Temporal Gyrus
Thal	Thalamus
Tu	Tuber
vaIns	ventral anterior Ins
vdaIns	ventral and daIns
vFWE	Voxel-level FWE

Contents

بسم الله الرحمن الرحيم

General Abstract

Importance Chronic pain encompasses complex mechanisms that remain incompletely understood. The World Health Organisation's recent classifications of chronic primary pain and chronic secondary musculoskeletal pain in International Classification of Disease, 11th revision, highlights the need to examine their neural substrates systematically. Neuroimaging studies have shown inconsistent results, underscoring the importance of synthesising evidence on neural mechanisms underlying chronic pain.

Objective This thesis investigates the neural substrates associated with chronic primary pain and chronic secondary musculoskeletal pain using fMRI meta-analyses.

Data extraction and Synthesis Twenty-three whole-brain coordinate-based meta-analyses, explores whether differences in brain activity during provoked and ongoing pain converge spatially within and between chronic primary pain, chronic secondary musculoskeletal pain, and pain-free individuals. Analyses applied activation likelihood estimation, incorporating robust statistical controls for multiple comparisons to reduce false positives by enhancing sensitivity and spatial specificity.

Results For chronic primary pain, meta-analyses of 48 studies (75 experiments, 1,206 patients, 846 pain-free) conjunction analysis revealed significant convergence in the dorsal anterior insula, mid-cingulate cortex, and medial frontal gyrus (MFG). Contrasts highlighted stronger activation in the ventral anterior insula for chronic primary pain and the superior frontal gyrus for pain-free. Behavioural data confirmed higher pain levels in chronic primary pain patients without publication bias.

For chronic secondary musculoskeletal pain, 28 studies (62 experiments, 3,217 patients, 1,079 pain-free) showed significant differences in the subcallosal gyrus, inferior frontal gyrus (IFG), and MFG, compared to pain-free. Combined chronic secondary musculoskeletal pain (symptoms and no symptoms) analyses highlighted cerebellar and parahippocampal activity. While both chronic primary pain and chronic secondary musculoskeletal pain showed involvement of the claustrum, IFG, and anterior cingulate cortex, variability across studies was high.

Conclusions and Relevance This thesis calls for larger meta-analyses integrating within- and between-subject designs to refine chronic primary pain and chronic secondary musculoskeletal pain classifications. Improved methodological consistency and reporting are crucial for understanding shared and distinct neural substrates, advancing diagnostic frameworks and translational potential in neuroscience.

1. The Paradox of Chronic Pain: Introduction

1.1. The Faces of Pain: Prevalence and Impact

"The wounds that cannot be seen are more painful than those that can be treated by a doctor."
- Birch Lane in 'In the Words of Nelson Mandela' (1998)

Pain presents in many forms; it can occur without clear reasons or with known causes. It may be fast or gradual, lasting for short periods or longer. It can feel akin to aching, burning, throbbing, shooting, or stabbing. Though it is the body signalling a defence mechanism, for the sufferer, it often feels as though the body is at war with itself. Millions wake up daily to a heavy burden—a relentless ache that colours their reality and shadows their every move. In 2019, the United States National Health Interview Survey brought startling news to light: around 50.2 million adults—nearly one in five—endure daily pain, affecting them on most days of the week (Yong et al., 2022). This survey identified common knee, hip, foot, and back pain sites. With recurrent tension-type headaches impacting approximately 1.9 billion people worldwide and intricate genetic predispositions linked to chronic pain (Mills et al., 2019). While, chronic pain disproportionately affects women and older adults (Saxena et al., 2018; Meucci et al., 2015), it impacts individuals of all ages and backgrounds. The impact of chronic pain goes beyond mere discomfort. It disrupts daily routines and hinder social interactions and work performance. Therefore, many turn to opioids, often underestimating the serious risks of addiction and withdrawal symptoms that can follow (Højsted and Sjøgren, 2007).

Analysing the epidemiology of chronic pain provides insight into its prevalence within the population and the potential reasons behind its spread. Data spanning decades in the United States highlighted the prevalence of musculoskeletal (MKS) or joint pain and indicated its trajectory over time, revealing higher occurrences in women and older adults (Magni et al., 1990, 1993). Disparities in chronic pain prevalence were further explored in studies focusing on older women and socio-economically disadvantaged communities, attributing these differences to diverse factors such as malnourishment, limited health education, and inadequate healthcare access due to financial constraints or lack of health insurance (Van Hecke et al., 2013; Greenspan et al., 2007). Recent reports from leading health organisations showcased varying rates and types of chronic pain across different regions (Fayaz et al., 2016; Vos et al., 2017). For

instance, low-income countries may have less access to healthcare or treatment, therefore increasing the risk of developing overlooked illnesses that lead to chronic pain—underscoring the role of social and economical factors as possible reasons behind the prevalence of chronic pain in specific communities and countries, compared to others (Petrova et al., 2022; Umeh and Feeley, 2017).

The widespread prevalence of chronic pain, affects a substantial portion of the global population. This problem highlights the urgent need for targeted interventions and treatments tailored to individual patients' needs. Increased research efforts are necessary to address this complex issue for comprehensive research to develop more effective solutions. Recognising chronic pain as a distinct condition rather than just a symptom (Mills et al., 2019) prompts a shift toward more personalised and holistic approach, emphasising the need for improved strategies to address this growing global problem.

1.2. The Dilemma of Pain

Grasping the complexity of pain requires exploring its definition and evolution. The term *'Pain'* originates from the Latin word Poena, meaning *"punishment or penalty."* Documented in the Oxford Dictionary since the 14th century, it refers to an unpleasant physical sensation or mental distress, derived from the same Latin root (Duncan, 2017). According to Zalta et al. (2011), two conflicting threads shape the common conception of pain. One views pain as a physical phenomenon, characterised by intensity and localised sensation in the body (Rababa and Bani-Khair, 2018). The other defines it as a subjective experience, emphasising the sensory and emotional aspects of tissue damage (Addis, 1986). Together, these perspectives frame pain as both a sensation and holistic influences on the body.

The evolution of pain has been extensively documented in literature, with early philosophers and physicians debating the distinctions between emotional and physical pain. In the 4th century BCE, Plato (c. 427–348 BCE) proposed that pain and pleasure are interconnected, with pain arising from imbalance and pleasure from balance (Wolfsdorf, 2013). However, this theory was later criticised for its limitations (Evans, 2007).

In the 5th century BCE, Hippocrates (c. 460–375 BCE) viewed pain as an objective phenomenon caused by material changes but did not link physical and emotional pain (Scullin, 2012). By the 2nd century CE, Galen (c. 129–216 CE) argued that pain resulted solely from physical injuries or breaches in bodily continuity (Tashani and Johnson, 2010).

Expanding on Galen's work, Ibn Sina (980–1037 CE) in the 10th and 11th centuries introduced additional causes of pain, such as inflammation, and expanded pain classifications to include types such as stabbing, itching, and compressing (Emami, 2023). Both Galen and Ibn Sina agreed that pain perception originates in the brain, contrasting with earlier ideas linking pain to imbalances in bodily fluids (Möbus, 2020).

Figure 1: Descartes model of pain perception (Descartes, 1962, 1644)

In the 17th century, Descartes revolutionised pain theory by describing it as a brain-centred perception, drawing an analogy to pulling a rope to ring a bell (Descartes, 1644; Foster, 1901) in the Treatise of Man (1664, Figure 7) see Figure 1). Using the analogy of pulling a rope attached to a bell, which results in a bell ring at the other end (Ronald and Wall Patrick, 1965). Similarly, with pain when the foot is near a noxious stimulation (e.g., fire), the particles of the fire that are in contact with the skin activate a delicate thread attached to the skin (pain receptors). Hence, assuming that there is a direct connection from the receptors to the brain when experiencing pain (Ronald and Wall Patrick, 1965). He proposed that noxious stimuli activate pain receptors, transmitting signals directly to the brain (Ronald and Wall Patrick, 1965). Descartes' theory was built on prior concepts (Moayedi and Davis, 2013), underscoring the interplay connections between neural mechanisms and emotional factors contributing to pain perception and the broader understanding of pain.

From a psychological perspective, pain is multidimensional, encompassing subjective experiences, cognitive influences, emotional impacts, psychological risk factors, and behavioural consequences. In the 1960s, Melzack (Melzack et al., 1968) described chronic pain as comprising three dimensions: sensory-discriminative, affective-motivational, and cognitive-evaluative. These dimensions relate to factors such as the intensity, location, and duration of pain, as well as its unpleasantness, cultural values, appraisals, and distractions. Cognitive influences include catastrophic thinking, self-efficacy, and locus of control (i.e., internal or external), all of which impact pain perception (Cosio, 2023).

Consequently, Melzack hypothesised that pain is influenced by "higher" cognitive activities that affect perceived intensity and unpleasantness. This aligns with the revised definition of pain by the IASP, which states that "pain is a personal or subjective experience shaped by biological, psychological, and social factors" (IASP, 2011). This definition underscores that pain is a unique experience for each individual.

Individuals who catastrophise their pain tend to experience greater pain severity and disability (Turner et al., 2002). In addition to cognitive influences, pain can also have significant emotional effects, demonstrating both top-down and bottom-up interactions. The emotional

ramifications of pain can profoundly affect an individual's well-being, potentially leading to irritability, anxiety, and depression (Vadivelu et al., 2017; Qiu et al., 2022; Yao et al., 2023). Conversely, these emotional states can impact the perception of pain, illustrating a bidirectional relationship (Vadivelu et al., 2017).

As psychological distress, such as depression, increases, so does the risk of developing chronic pain conditions (Vadivelu et al., 2017). This heightened psychological distress which interferes with daily routines and simple tasks. For instance, pain can disrupt attention, making it difficult for individuals to function normally. Initially, pain grabs the patient's attention, forcing them to focus inward and prompting the body to appraise the sensation as an alarm. Consequently, this heightened awareness can, in turn, lead to problem-solving behaviours aimed at managing the discomfort (Cosio, 2023). Furthermore, Cosio (2023) suggested that pain perception may be unique to an individual's attachment style, with those exhibiting an anxious attachment style reporting greater pain experiences than those with an avoidant attachment style. Together, these insights highlight the unique and multidemensional experience of pain for sufferers.

The Neuromatrix

In 1965, Ronald Melzack and Patrick Wall examined various theories of pain (Melzack and Wall, 1965). Later, in the 1990s, Melzack further expanded on these ideas by introducing the concept of *The Neuromatrix*, which has revolutionised the medical and biological boundaries by emphasising the active role of the brain in filtering, modulating, and selecting sensory inputs (Melzack, 1990). According to this concept, pain output is not simply a direct response to sensory input, such as injury or inflammation (i.e., the Cartesian concept), but rather a complex phenomenon influenced by the neural network within the brain (Melzack, 2001). Moreover, it involves three main dimensions that contribute to the patterns observed in the neuromatrix (i.e., sensory, affective and cognitive), Pain and the Neuromatrix in the Brain (2001, p. 1382, Figure 1) and Extending the Neuromatrix (2020, p. 23-43) see Figure.2. Hence, indicating several factors that contribute to the activity in the brain and shapes our experience of pain.

The neuromatrix concept, as defined by Melzack, encompasses three key aspects. Firstly, the neuromatrix is described as "something within which something else originates, takes form, or

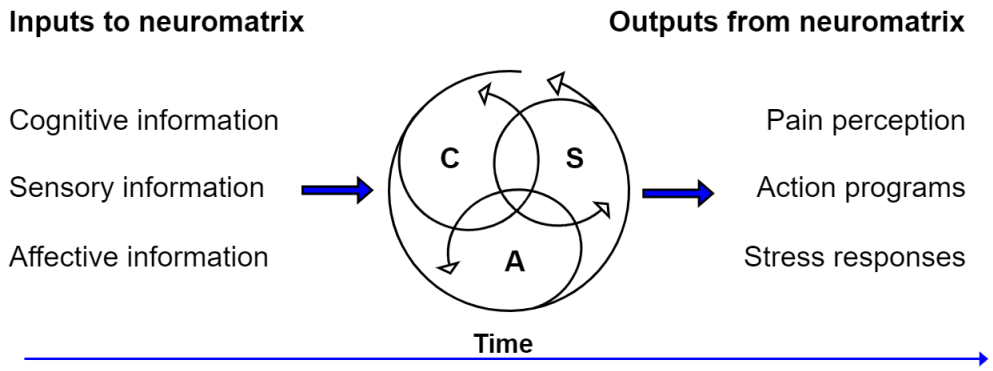

Figure 2: Body-Self Neuromatrix: Adopted from (Melzack, 2001; Fitzgerald and Fitzgerald, 2020)

develops" (Melzack, 2001). Melzack emphasises that the neuromatrix is not merely the stimulus, peripheral nerves, or a single brain centre (Melzack, 2001). In essence, the neuromatrix operates within the context of the neurosignature, while the neurosignature also exists within the neuromatrix. Importantly, while an input can trigger neurosignatures responsible for the perception of pain, it is not the direct cause of their origin or formation. Secondly, Melzack uses the analogy of a "die" or "mould" to illustrate the distinct characteristics of the matrix. Just as a die leaves a mark, the matrix has its unique signature that leaves imprints on nerve impulse patterns. This trait makes the neurosignature relatively easy to detect within the brain. Thirdly, the definition of the neuromatrix adopts a biological perspective, describing it as an array of interconnected circuit elements performing specific functions within the matrix. Melzack proposes that these arrays of neurons are genetically designed to produce the signature pattern and can be modified by experience (Melzack, 2001). Moreover, the integrated neurosignature pattern of the body-self plays a crucial role in creating awareness and initiating action. One study supports this concept in chronic pain (Moseley, 2003), suggesting that the two primary mechanisms contributing to the persistent nature of chronic pain are nociceptive and non-nociceptive. Each mechanism heightens the central nervous system (CNS) conviction that the body is in danger, which increases activity in the brain. This process further enhances sensitivity to both noxious and non-noxious inputs, leading to significant changes in the peripheral and CNS. Consequently, the concept of neuromatrix

illuminates the distributed activations and information flow throughout the brain, forming a widespread network that generates patterns and contributes to the overall perception of the body and the sense of self.

This perspective is particularly evident in people experiencing conditions such as phantom limb pain or fibromyalgia. Studies have shown that patients who have lost a limb or sensation in a specific region continue to perceive the presence of the missing limb (Ramachandran, 1998; Ramachandran and Hirstein, 1998). Hunter et al. (2005) have proposed that changes in peripheral nerve activity may underlie this phenomenon of phantom limb perception. Nevertheless, others reported that both the peripheral and CNS contribute to the sensation experienced in the phantom limb (Devor, 1999). Hunter et al. (2005), suggesting that deafferent cortical neurons respond to new peripheral inputs while retaining the original meaning, possibly explaining the excitation of these neurons when stimulated by new receptive fields. For instance, Devor (1999) presented evidence from amputees' thalamic mapping, which revealed larger-than-usual thalamic stump representation extending to brain regions associated with the now missing limb. This is important because it sheds light on the cortical reorganisation that takes over as one of the compensatory mechanisms, through neighbouring representation in the primary somatosensory cortex (SI) or motor cortex, thus resulting in phantom limb pain (Subedi and Grossberg, 2011; Kaas et al., 2008).

On the other hand, studies indicate that fibromyalgia is associated with central sensitisation, which exacerbates activity in the pain neuromatrix (Gracely and Ambrose, 2011). As a result, neural resources in the brain are enhanced, leading to increased nociceptive activity that disrupts attention and pain processing (Duschek et al., 2013; Reyes del Paso et al., 2012). This heightened activity in the pain neuromatrix mediates hyperalgesia and allodynia in fibromyalgia (Gracely and Ambrose, 2011), while also affecting cognitive processes related to pain. Moreover, fibromyalgia as a widespread pain condition it coexists with symptoms such as fatigue, sleep disturbances, depression, and anxiety (Wolfe, 2010). These factors illustrate how demanding this condition can be on attention, affecting psychological well-being, cognitive performance, while simultaneously increasing sensitivity to nociceptive inputs.

The neuromatrix provides a comprehensive view of pain perception, suggesting that pain is not solely a result of nociceptive input. It is influenced by cognitive, emotional, and sensory factors, leading to the generation of a neurosignature pattern. Factors such as psychological stress can further exacerbate the pain experience, influencing the pattern of neurosignatures (Genoese et al., 2022). The lack of specific neuronal response for pain has supported the conclusions of researchers that no specific neuronal response is unique to pain (Wager et al., 2013). Thus, pain perception involves an integrative process of multiple brain systems rather than simple pain-specific regions.

The Pain Matrix The concept of the pain matrix has significantly advanced our understanding of the neuromatrix, facilitated by the development of neuroimaging techniques. Ploghaus et al. (1999) characterised the pain matrix as a network of cortical regions involved in the mediation of pain. Ingvar (1999) posited that the patterns observed within the pain matrix constitute pain perception, suggesting these regions are pain-specific brain structures. The Basic Pain Matrix Model (2015, p. 1, Figure 1), see Figure 3 comprising of the primary somatosensory cortex (SI), secondary somatosensory cortex (SII), insula (Ins), thalamus (Thal), and anterior cingulate cortex (ACC). Earlier research identified the ACC as consistently activated during pain experiences, while the Ins, somatosensory cortex, Lentiform Nucleus (LN), and Thal also demonstrated significant responses to noxious stimuli (Derbyshire et al., 1997). However, other researchers contested this view, arguing that these regions are not exclusively dedicated to noxious stimuli and may also respond to non-noxious inputs (Davis et al., 2015). This perspective suggests that no specific set of regions or neurons is exclusively responsible for pain perception; rather, these regions contribute to a broader salience detection system.

The specificity of the pain matrix has been scrutinised, with research demonstrating that activations in these regions can occur in the absence of pain, indicating a fluid and dynamic system (Mouraux and Iannetti, 2018; Garcia-Larrea and Peyron, 2013). Some researchers have referred to this concept as a ‘signature’ or ‘representation’ of pain, reflecting neural processes associated with both functional and dysfunctional pain states in humans (Apkarian et al., 2005; Tracey and Mantyh, 2007; Treede et al., 1999; Iannetti et al., 2013). Furthermore, structures

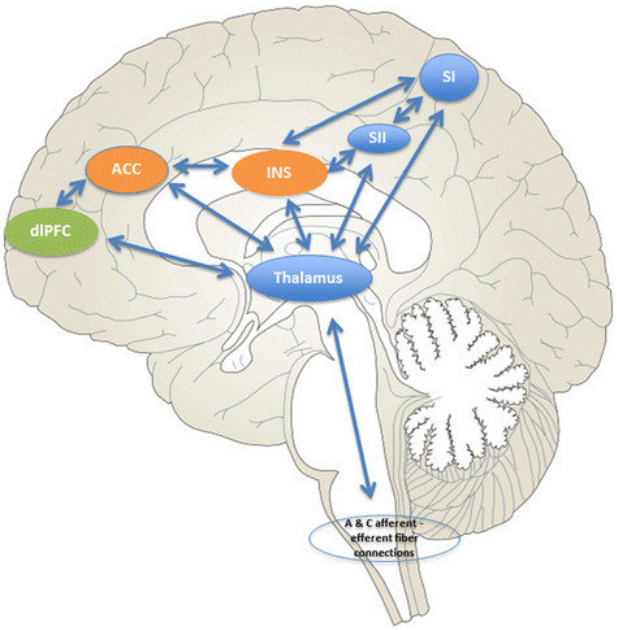

Figure 3: Basic Pain Matrix Structures: Adopted from (Monroe et al., 2015)

outside the pain matrix can be activated during pain experiences due to technical, biological, methodological, or individual variability, complicating the interpretation of these findings (Mouraux and Iannetti, 2009; Lui et al., 2008). Consequently, these observations are insufficient to conclude that these regions are exclusively devoted to pain perception.

Two principal arguments have been advanced in support of the notion that the observed neural patterns are pain-specific. The first argument posits that perceived pain intensity must correlate strongly with neural responses within the pain matrix (Legrain et al., 2011; Iannetti et al., 2005). Derbyshire et al. (1997) explored inconsistencies in the regions activated during pain experiences, suggesting that heterogeneity across studies may be attributable to variations in stimulus intensity (Mouraux and Iannetti, 2018; Derbyshire et al., 1997). Once pain intensity exceeds a certain threshold, it disrupts neural responses within the pain matrix, contributing to variability across studies.

The second argument proposes that factors modulating pain simultaneously influence the magnitude of responses within the pain matrix (Legrain et al., 2011). As previously discussed,

the observed activity may represent a ‘signature’ of underlying pain function or dysfunction in the brain (Apkarian et al., 2005). For example, Hofbauer et al. (2001) utilised positron emission tomography to investigate the regulation of pain through hypnosis, measuring cerebral activity before and after hypnotic intervention. Their findings revealed that modulating pain intensity through hypnosis produced significant changes in pain-evoked activity within both limbic and somatosensory nervous systems (SNS). In contrast, specific modulation of pain unpleasantness altered activity within the ACC but not within SI or SII (Rainville et al., 1997, 1999). Other researchers have reported activity in SI and SII in the absence of ACC involvement, leading to the suggestion of a ‘double dissociation’ between the affective and sensory dimensions of the pain matrix (Hofbauer et al., 2001). These findings underscore the need for objective measures to link painful experiences with neural activity within the matrix (Borsook et al., 2010).

Subsequent research has questioned whether the pain matrix represents a singular or definitive neural correlate of pain. While its activations may be partially pain-specific, they are also influenced by factors unrelated to nociception (Iannetti et al., 2013; Legrain et al., 2011). For instance, the pain matrix has been shown to exhibit activity that is independent of nociceptive stimulus intensity, influenced by non-nociceptive factors, and responsive to non-painful stimuli (Iannetti et al., 2008; Mouraux et al., 2004; Mouraux and Plaghki, 2007; Lui et al., 2008; Mouraux and Iannetti, 2009).

Some researchers have conceptualised the pain matrix as operating on three hierarchical levels (Fenton et al., 2015). The first level, the primary cortical pain matrix, includes SI, SII, the parietal operculum, and posterior insula (pIns), which are implicated in the localisation and perception of pain. The second level, the secondary cortical pain matrix, encompasses the anterior insula (aIns), ACC, hippocampus, and amygdala, which mediate the affective dimensions of pain. The third level pertains to the cognitive interpretation of pain and involves the frontal cortex and posterior cingulate cortex (PCC), specifically the middle and posterior cingulate gyri (Xiang et al., 2018).

These levels are not discrete but interact dynamically; for instance, neural communication between the pIns and aIns appears contingent on their respective primary functions (Ploghaus

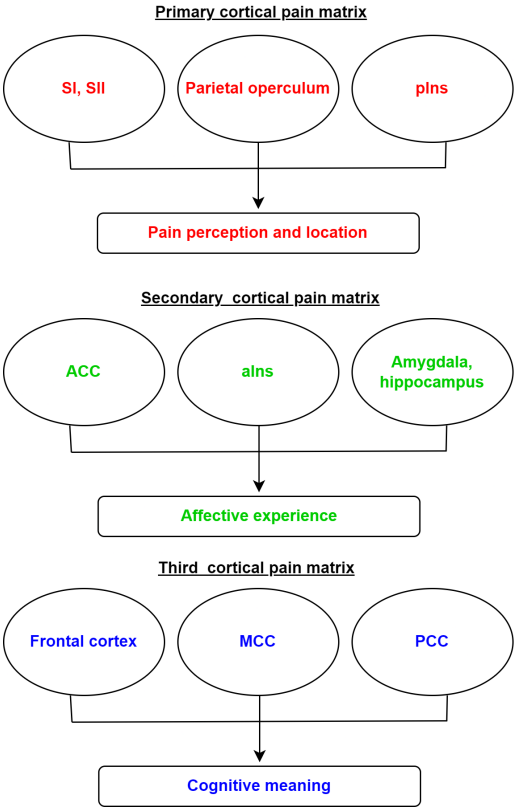

Figure 4: Three levels of the Pain Matrix: Adapted from (Xiang et al., 2018)

et al., 1999; Xiang et al., 2018). The Three-Level Pain Matrix Model (2018, p. 3, Figure 1) see Figure 4) underscores the intricate and multidimensional nature of pain, integrating mental, emotional, and sensory mechanisms. This holistic perspective aligns with the biopsychosocial model, which provides a more comprehensive framework for understanding pain (Derbyshire et al., 1997).

The Biopsychosocial Model

The biopsychosocial model posits that pain is a subjective experience shaped by biological, psychological, and social factors (Wideman et al., 2019). These factors often coexist. A conceptual model of the biopsychosocial interactive processes involved in health and fitness (2007, p. 30, Figure 2), see Figure 5. The biological component includes genetics, nociception, tissue injury, disease characteristics, nervous system features (e.g., pain threshold, tolerance,

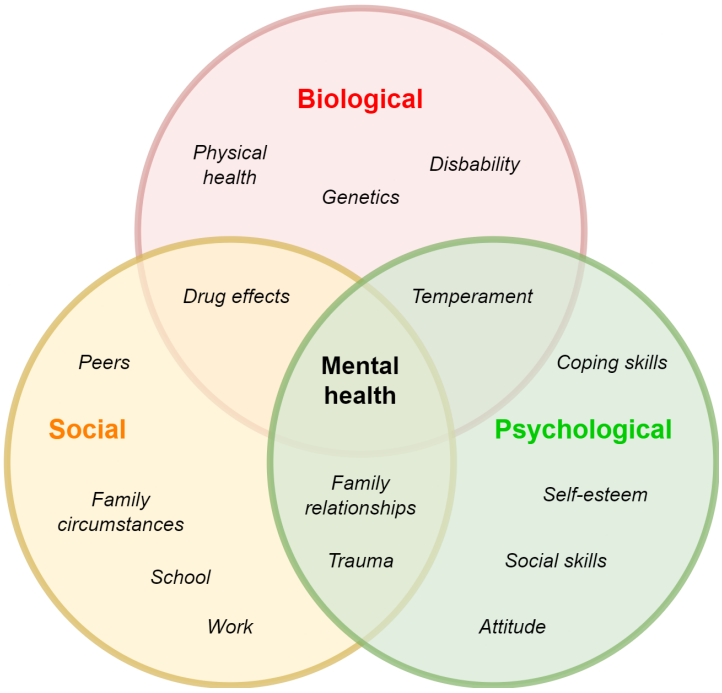

Figure 5: Biopsychosocial model of health: Adopted from (Gatchel et al., 2007; Fillingim, 2017)

central sensitisation), hormonal influences, and lifestyle factors. The psychological dimension encompasses cognition, emotions, coping mechanisms, personality traits, and recovery expectations. The social component covers social expectations, support systems (emotional and financial), educational background, living conditions, employment, financial status, social deprivation, prior pain experiences, substance misuse, discrimination, and cultural influences (EFIC, 2022).

Unlike traditional models that focus on singular treatment strategies, the biopsychosocial approach is multidisciplinary, addressing pain through biological, psychological, and social interventions. For instance, pain management, surgery, and pharmacotherapy target biological factors, while psychological therapies, such as cognitive behavioural therapy and patient education, address psychological aspects. Physiotherapy or exercise may also be included depending on treatment goals. This integrated approach combines evidence-based pharmacotherapy, psychological strategies, and social support.

The European Pain Federation advocates for the comprehensive application of the biopsychosocial model in clinical care, research, education, and policy (EFIC, 2022), see Figure 5. Similarly, in the International Classification of Disease 11th edition highlights the complexity of chronic pain, recognising its biological, psychological, and social dimensions (Barke et al., 2022). It supports the biopsychosocial framework by emphasising the need for a comprehensive understanding of chronic pain, accounting for individual differences in pain-related diseases or disorders.

The biopsychosocial model views pain as a complex, dynamic phenomenon rather than a purely biological or psychological issue. It adopts a holistic perspective, considering patients' thoughts, emotions, behaviours, and social environments (Smart, 2023). Evidence suggests that clinical biopsychosocial assessments in physiotherapy help clinicians identify principal pain mechanisms and psychosocial factors that can be modified to improve outcomes (Wijma et al., 2016). This assessment uses the PSCEBSM framework (Pain–Somatic, Medical, Cognitive, Emotional, Behavioural, Social, and Motivational factors) during data collection and practical guidance (Wijma et al., 2016).

By incorporating psychosocial factors, the biopsychosocial model addresses elements often overlooked in other frameworks, particularly in the context of chronic pain, where these factors play a significant role in the persistence of pain and disability (van Dijk et al., 2023). Moreover, it provides insights into patients' personal circumstances, beliefs, and social contexts, enabling personalised treatment approaches. This contrasts with the traditional "one-size-fits-all" biomedical model, offering improved patient outcomes through personalised care (van Dijk et al., 2023).

1.3. Pain Mechanisms

1.3.1. Chronic Pain: Definitions

The IASP, adopted by the World Health Organisation, define *pain* as:

> *"An unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage"* -Raja et al. (2020)

The definition emphasises several key components (Vader et al., 2021): 1) Pain is a subjective experience that is influenced by various aspects (i.e., biological, psychological, and social) by varying degrees. 2) Pain is not always the result of the sole activity in sensory neurons (i.e., pain and nociception are distinct from one another). 3) The concept of pain is learned through one's life experience. 4) Reports of a patient's experience of pain should be respected. 5) With an adaptive role that comes with the experience of pain, adverse effects may be accompanied as well. Hence, pain impacts one's social and psychological well-being. 6) Verbalising is a way to express pain but is not the only way. For instance, someone may be unable to communicate pain (e.g., human or animal); this does not negate pain. These distinctions are important as they contribute to the individual's perception and experience of pain.

Chronic pain is defined as pain that persists or recurs for over three months, exceeding the usual healing period (IASP, 2011). In some patients, chronic pain becomes the primary or predominant clinical issue (IASP, 2011). Pain is generally classified into three mechanistic types: *nociceptive pain*, resulting from tissue damage; *neuropathic pain*, caused by nerve damage; and *nociplastic pain*, which arises from altered nociception in the absence of tissue damage (van Helvoort et al., 2021; Thakur et al., 2014).

For example, migraine is often considered nociceptive pain (Chakravarty and Sen, 2010). As a neurological disorder involving functional and structural changes in the brain, the underlying mechanisms of migraine may include central and neuroinflammation (Mungoven et al., 2021). Interestingly, growing literature is suggesting microglia and astrocytes play a role in chronic pain pathogenesis and glial activation. These findings suggest this to be as one of chronic pain key mechanisms underlying the pathogenisis (Ji et al., 2018b; Milligan and Watkins, 2009). Earlier research has classified migraine as neuropathic pain (Biondi, 2006). Although distinct from other pain types, primary headache disorders, including migraines, can exhibit characteristics resembling nociplastic pain mechanisms in specific cases (Bułdyś et al., 2023; Raja et al., 2020).

On the other hand, fibromyalgia involves chronic pain with unclear pathology. Fibromyalgia is associated with dysfunction of the CNS of unknown origins causing central sensitisation

(Albrecht and Rice, 2016). Nevertheless, this process underlying mechanisms are yet to be answered (Albrecht and Rice, 2016). This ambiguity surrounding fibromyalgia pathology has led to frequent changes in the diagnostic criteria. Notably, in 2011 the International Association for the Study of Pain (IASP) revised the definition of neuropathic pain, explicitly excluding fibromyalgia from this classification (Cheng et al., 2018). Some researchers have concluded that fibromyalgia is predominantly a nociplastic pain condition (Fernández-de Las-Peñas et al., 2023). However, fibromyalgia may cause neuropathic pain, resulting from a disease or lesion affecting the SNS, such as nerve damage. Furthermore, fibromyalgia is considered a central sensitisation syndrome, characterised by widespread pain, and may present as neuropathic or nociplastic pain (Martínez-Lavín, 2022; Nijs et al., 2023).

Nociceptive pain is closely associated with the MSK system and includes conditions such as osteoarthritis, Parkinson's disease, and multiple sclerosis (Perrot et al., 2019). Harmful stimuli can activate nociceptors within the body's joints, bones, or muscles, leading to physical discomfort or potential tissue damage. These nociceptors, often referred to as "silent nociceptors," are triggered by harmful stimuli (Puntillo et al., 2021).

Although many MSK conditions are categorised within distinct pain types (e.g., myocardial infarction as nociceptive pain and Parkinson's disease as MSK-related pain), they can present overlapping symptoms with other conditions (e.g., multiple sclerosis and fibromyalgia). This overlap complicates the diagnostic process and highlights the need for a nuanced approach to pain classification and management.

1.3.2. Aetiology

Experimental studies that utilise quantitative sensory testing (QST) provide compelling evidence for pain research and valuable insights into pain mechanisms (Weaver et al., 2022). Findings from QST suggest that both peripheral and central sensitisation mechanisms contribute to localised and widespread chronic pain syndromes (Courtney et al., 2017). Moreover, features such as psychological and psychosocial (e.g., somatic awareness and pain-related catastrophising) may reflect partially altered peripheral and central nervous system which processes sensory stimuli. These features often are significantly correlated with somatosensory

amplification measures of QST (Edwards et al., 2021). For instance, measures of emotional functioning used in phenotyping participants during analgesic trials, measurements such as the HADS would be considered a core phenotype measure for assessing negative affect.

Moreover, many chronic pain syndromes exhibit impairments within the CNS. Central sensitisation is a key mechanism in chronic pain, which leads to heightened responsiveness of neurons within the CNS (Latremoliere and Woolf, 2009). It originates in the dorsal horn of the spinal cord and the brain, central sensitisation does not just amplify responses after prolonged exposure; it can also cause pain in response to normally non-painful stimuli (allodynia) or increase pain sensitivity (hyperalgesia). Prior work has linked this process to long-term potentiation, suggesting its role in persistent pain sensitisation (Woolf, 2011). The IASP defined it as,

"Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input."

In contrast, peripheral sensitisation occurs at nociceptors outside the CNS, leading to increased pain sensitivity at the site of injury, widespread pain, or inflammation (Wang and Thyagarajan, 2022). The IASP defined peripheral sensitisation as,

"Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields."

Therefore, this multifaceted nature of chronic pain may contribute to a complex aetiology influenced by biological, psychological, and/or social factors (Courtney et al., 2017; Elsenbruch, 2011). For instance, visceral hyperalgesia in conditions such as irritable bowel syndrome (IBS) arises from a combination of factors, including increased gut permeability, altered peripheral pathways, and central processing changes (Elsenbruch, 2011). Moreover, specific subtypes of IBS suffer from depression and anxiety more than another IBS subtype (Fond et al., 2014). Nevertheless, the precise aetiology is not fully understood (Barreau et al., 2007).

Moreover, chronic pain resulting from surgery or injury can lead to neuropathic pain, characterised by nerve damage affecting the peripheral nerves, spinal cord, and SNS (Colloca

et al., 2017). Of note, damage to the SNS is a mark of transition from acute [1]to chronic pain (Carr and Goudas, 1999; Chapman and Vierck, 2017). Such damage amplifies responses to noxious and non-noxious stimuli (Colloca et al., 2017), further affecting chronic pain pathophysiology. This underscores the bidirectional relationship between condition symptoms and underlying mechanism of pain.

Chronic pain conditions exhibit considerable heterogeneity due to their diverse pathophysiological origins, with pain arising from nociceptive mechanisms (e.g., inflammatory pain), neuropathic mechanisms (e.g., nerve injury), or a combination of these (Waseem and Gwinn-Hardy, 2001; Perrot et al., 2019; Svendsen et al., 2003). The coexistence of different pain types in patients, along with diverse symptoms occurring simultaneously, makes diagnosis challenging which, in turn, may contribute to the heterogeneity (Freynhagen et al., 2019). In cases where the integrity of the SNS is compromised by underlying disease, chronic pain often stems from neuropathic rather than nociceptive mechanisms (Scholz, 2014). To add, ephatic transmission which is unintended electrical (ephaptic) cross-talk or communication between adjacent fibres occurs with neuropathic pain (McAllister and Calder, 1995). Particularly, in neuropathic pain, demyelinating conditions such as multiple sclerosis, increase in neuronal excitability leading to amplified pain signals. This mechanism may play a significant role in the development of neuropathic pain in chronic pain. Conversely, nociplastic pain, which differs from nociceptive pain, develops gradually due to altered nociceptive function. However, differentiating between nociceptive, neuropathic, and nociplastic pain remains challenging, as these types may coexist (Bidari and Ghavidel-Parsa, 2022; Nijs et al., 2021). Notably, a key criterion for classifying nociplastic pain is that it cannot be explained by nociceptive or neuropathic mechanisms (Kosek et al., 2021; Nijs et al., 2021), thus underscoring the complexity of pain mechanisms and the diagnostic challenges they pose.

In response to the lack of clear aetiology and pathophysiology in many chronic pain conditions, the IASP introduced the diagnosis of chronic primary pain. This classification is based on the biopsychosocial framework, aiming to standardise diagnostic and treatment approaches. Unlike

[1]According to IASP (2011), "Acute pain is pain that lasts from a few seconds to three months, and is usually associated with actual or threatened tissue injury".

previous classifications, chronic primary pain can be diagnosed even when the biological or psychological factors contributing to the pain is not identified (Nicholas et al., 2019; Fillingim et al., 2014). Essentially, chronic primary pain is viewed as a multidimensional diagnosis with pain that is the primary condition, originating in the brain without structural abnormalities or pathological impact (Nicholas et al., 2019). Examples include conditions such as fibromyalgia, chronic lower back pain, migraine, and IBS.

In contrast, the IASP also introduced the classification of chronic secondary MSK pain, which encompasses chronic pain conditions resulting from persistent inflammation, structural abnormalities, or underlying diseases (Perrot et al., 2019). This classification highlights that secondary pain arises from ongoing nociceptive input in MSK structures, caused by local or systemic aetiologies, or related to deep somatic lesions (Perrot et al., 2019). Thus, in chronic secondary MSK pain, pain is secondary to an underlying disease and may initially present as a symptom. Examples include conditions such as Parkinson's disease and multiple sclerosis.

To address this problem, recent progress in pain research has focused on identifying neurological pain signatures for specific chronic pain conditions. Experimental findings revealed pain markers for conditions such as experimentally induced acute pain with pain-free individuals, subacute back pain, and fibromyalgia (Wager et al., 2013; Baliki et al., 2012; Lopez-Sola et al., 2017). Though, current pain signatures remain in preliminary stages and require further validation with larger and diverse populations (Martucci and Mackey, 2018). These signatures offer promise for objective neural substrates, which can lead to a consensus with accurate diagnosis, effective treatments, and a better quality of life (QoL) for patients (Shetty et al., 2024).

1.3.3. Impact on Quality of Life

Researchers approach the concept of QoL from multiple perspectives, often finding it complex to measure. The World Health Organisation defines QoL as an individual's subjective assessment of their life circumstances, shaped by their cultural and value systems, as well as their personal goals, expectations, standards, and concerns (Organisation, 2012). In contrast, the global perspective recognises QoL as a multidimensional phenomenon encompassing various

domains, including, but not limited to, physical and psychological well-being (Spilker et al., 1990; Spilker, 1992). Therefore, QoL can be understood as a multidimensional personal evaluation that influences overall well-being and life experiences.

Over the years, extensive research has been dedicated to tackling the complex challenges related to chronic pain with the goal of improving patients' QoL. These efforts encompass different approaches, including pharmacological treatments, physical therapies (NHS, 2017), a comprehensive biopsychosocial approach (Hadi et al., 2017), and interventions to improve body-mind connections (psychomotor therapy) (Oliveira et al., 2024). In a cross-sectional study investigating interoceptive sensibility skills [2], impact on improving chronic pain patients with MSK pain QoL (by increasing self-efficacy, improving pain management, and decreasing pain catastrophising). The highest interoceptive sensibility skills reported by most participants was high attention regulation towards bodily sensation, body trust, and self-awareness/regulation. In contrast, the lowest interoceptive sensibility skills reported moderate attention regulation, low body trust and awareness, hence more worried about bodily sensation. On the other hand, mixed IS indicated good skills of managing attention, anxiety and body trust, however poor awareness of mind-body connections (Oliveira et al., 2024). Hence, chronic pain generally requires high interoceptive sensibility skills for better pain outcomes and self-regulation. Therefore, learning how to cope and regulate stress and emotions accompanied with pain is crucial to improve patients' overall QoL.

Together, these initiatives underscore the importance of finding effective methods to manage and treat chronic pain. Moreover, establishing a universal definition of QoL that is specific to chronic pain may provide a new lens of how to view their experiences on a spectrum and avoid comparing their experiences to the general healthy population QoL. Consequently, this may have a significant impact on patients' overall well-being, providing a more thorough and tailored assessment of the areas that require attention. To effectively address these challenges, it is crucial to explore the aetiology of chronic pain, as understanding its underlying mechanisms can inform treatment strategies and patients' pain management.

[2] Introception is a self-reported experience of the internal state of the of their body, which is crucial for emotional regulation, health regulation, and illness adaptation (Oliveira et al., 2024)

1.3.4. Nociceptors

It is essential to differentiate between pain and nociception, acknowledge the subjective nature of painful experiences, account for the adverse effects of pain, and explore both verbal and non-verbal expressions (IASP, 2011). These components highlight the multifaceted nature of pain and the intricate interplay between objective localisation and subjective experiences. This revised definition allows a broader understanding of pain, encompassing its various degrees in terms of biological, psychological, and physiological aspects.

The definition of nociception provided by the IASP describes it as "The neural process of encoding noxious stimuli" (IASP, 2011; Mersksey and Bogduk, 1994). Nociception refers to the physiological process triggered by a noxious or painful stimulus, where specialised receptors known as nociceptors detect and transmit signals indicating potential threats to the body. Painful stimuli can manifest in various forms, such as extreme cold or heat, electrical shocks, chemicals, or mechanical external stimuli. These stimuli serve as crucial alerts to the body, indicating a disruption in homeostasis (Melzack, 2001).

Understanding the role of nociceptors is a fundamental starting point to examine how pain is perceived and processed in the brain. Nociceptors are receptors sensitive to noxious stimuli with specialised sensory nerve endings that respond to and detect harmful stimuli (Dubin et al., 2010). They exhibit high specificity and sensitivity and can adapt to repeated stimuli by reducing their sensitivity over time (Campbell and LaMotte, 1983). This adaptation results in the transmission of signals from sensory neurons to the brain, leading to the perception of pain. In the context of chronic pain, sensory neurons (nociceptors) can be persistently activated to detect danger or inflammation (Walters et al., 2023).

Nociceptors are sensory neurons that are triggered during noxious stimuli found in the skin, viscera, or muscles and consist of nerve endings with large receptive fields (Dubin et al., 2010; Russo and Brose, 1998; Latremoliere and Woolf, 2009). Two primary fibres associated with nociceptors in these neurons are C-fibres (small, unmyelinated) and A-δ fibres (thinly myelinated). The latter is responsible for fast and sharp pain (i.e., first pain of high intensity), prompting an immediate response to harmful stimuli (Dubin et al., 2010; Ploner et al., 2002).

The former is responsible for slow and dull pain (i.e., second pain of high intensity) (Dubin et al., 2010; Russo and Brose, 1998; Das, 2015; Ploner et al., 2002). On the other hand, A-β fibres detect non-painful stimuli (i.e., touch or pressure of low intensity) (Das, 2015). Essentially, nociceptors respond to noxious stimuli when it reaches a specific threshold, which triggers voltage-gated sodium channels [3] (Schaible, 2007; Almeida et al., 2004; Argoff, 2011). Of note, changes in the voltage-gated sodium channel demonstrate sensitisation of the sensory neurons (Bennett et al., 2019). This signal passes the dorsal root ganglion and the spinal cord's dorsal horn, nociceptive neurons (C-fibres, A-δ , and A-β fibres), respond to noxious stimuli. Another type of neuron receives this input from all three types of fibres (i.e.g, mechanical, thermal, or chemical), termed as wide dynamic range (Basbaum et al., 2009; Almeida et al., 2004; D'Mello and Dickenson, 2008). The wide dynamic range neuron was associated with chronic pain plasticity when overstimulated (D'Mello and Dickenson, 2008), see Figure 6. Moreover, chronic neuropathic pain is known to be spontaneous and ongoing type of pain. It is commonly associated with ectopic potentials [4], compared to nociceptive pain - often caused by sustained discharge at ectopic sites (Ma et al., 2019). Notably, the subthreshold membrane potential oscillations of the dorsal root ganglion neurons are necessary to trigger ectopic repetitive firing (Ma et al., 2019). However with direct CNS injury, ectopic activity predominantly arises in the peripheral nervous system, while it initiates and regulates central sensitisation. This process alters the sensory modality of afferents from touch to pain (Woolf, 1983). Therefore, when peripheral analgesics is introduced to the body it aids in preventing ectopic discharge from accessing the CNS, eliminating ongoing pain and allodynia (Gracely et al., 1992).

In the context of MSK pain, ectopic potentials may be present if prolonged inflammation or injury leads to nerve sensitisation, resulting in ectopic discharge; amplifying pain (Solomons, 2022; Ridehalgh and Ward, 2023). Therefore, coexistence of nerve inflammation (neuropathic

[3] Voltage-gated sodium channels: are crucial for sensory neuron excitability, initial transduction of sensory stimuli, and neurotransmitter release. The Voltage-gated sodium channels biophysical characteristics play a functional role in pain signalling.

[4] Ectopic potentials refer to abnormal electrical discharges that originate outside their usual locations in the nervous system. These can arise from damaged or sensitised peripheral nerves and contribute to pain by causing spontaneous or exaggerated nerve firing.

pain) within MSK pain, may contribute to the ectopic activity.

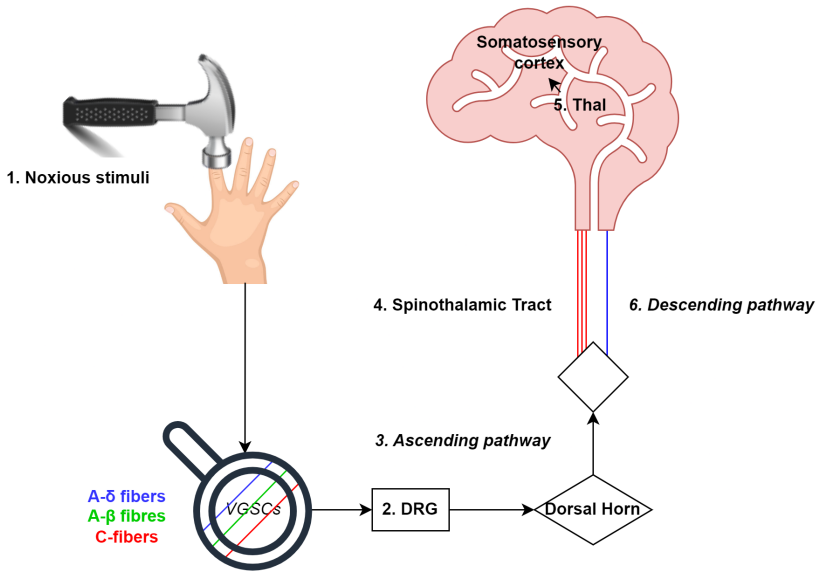

Figure 6: Nociceptors Pain Pathway. Abbreviations: DRG; Dorsal root ganglion, Thal; Thalamus, VGSCs; Voltage-gated sodium channels.

Then, the second-order neurons travels from the dorsal horn to the spinal cord's midline through the ascending pathway and the spinothalamic tract to the thalamus (Thal). The third-order neurons then projects to the somatosensory cortex to process pain (Xiang et al., 2018; Russo and Brose, 1998; Das, 2015; Wang and Thyagarajan, 2022). Noxious information is processed and modulated in the brain and sent through descending pathways through the spinal cord (Basbaum et al., 2009). In the context of chronic low back pain, the dysfunctional descending modulation system and imbalance in the glutaminergic, GABAergic, and dopaminergic pathways (Lu et al., 2016), may be the main contributor to spontaneous and persistent pain (Hazra et al., 2022). Moreover, a maladaptive descending modulatory system results in pain outlasting biological usefulness and cause, such that an increased descending facilitatory output ongoing feed-forward compensatory circuit between the peripheral, spinal cord, and the brain leading to chronic pain (Bee and Dickenson, 2009). Hence, this pathway demonstrates the complex mechanisms involved that underlie pain perception, see Figure 6. With advanced neuroimaging techniques we can better understand the underlying mechanisms of chronic pain

during experimentally induced and spontaneous pain.

1.4. Identifying Biomarkers

1.4.1. Functional magnetic resonance imaging

Functional magnetic resonance imaging (fMRI) is a non-invasive imaging technique that offers excellent spatial resolution to detect regional, time-varying brain metabolic changes in response to experimental tasks or resting-state (Clare, 1997). fMRI primarily focuses on T2 contrast, which is sensitive to blood oxygenation levels (Kim et al., 2021). The hemodynamic response associated with increased neural activity results in a decrease in deoxygenated haemoglobin, as indicated by changes in the blood oxygen level dependent signal (BOLD) (Glover, 2011). These scans target whole brain coverage or a particular ROI, see Figure 7. This technique has become instrumental in the study of cognitive processes (Wang et al., 2016), clinical applications (Soares et al., 2016), pharmacological efficacy (Wise and Preston, 2010), and therapy monitoring (Kononen et al., 2012), making it a vital tool to understand communication between different areas of the brain.

fMRI detects the effects of heightened neural activity, including increased cerebral blood flow and variations in BOLD contrasts. Researchers can monitor neural activity using both invasive methods, such as injecting a contrast agent with perfusion-weighted MRI (Belliveau et al., 1991), and non-invasive methods such as Arterial spin labelling (Wierenga et al., 2014). Although arterial spin labelling is advantageous for studying neurobiological activation mechanisms, it is more sensitive to motion and has longer acquisition times compared to BOLD. During fMRI studies, various stimuli are used to manipulate brain states, and the technique employs Echo Planar Imaging to collect data rapidly. The processed images undergo a series of pre-processing steps, including motion correction and noise filtering, to produce accurate brain activation maps (Glover, 2011).

fMRI also provides an avenue for identifying biomarkers—measurable characteristics that reflect brain responses to specific exposures or interventions (Group et al., 2016; Babrak et al., 2019). In chronic pain, brain activity alterations hold promise as objective biomarkers, offering a more reliable alternative to subjective pain reports (Zhang et al., 2022). However, challenges

persist in replacing pain ratings, which remain the gold standard for objective biomarkers (Zhang et al., 2022).

Identifying consistent, valid, and reliable pain biomarkers has been a major focus of research for decades (Litcher-Kelly et al., 2007; Melzack and Wall, 1965; Melzack, 1999; Mouraux and Iannetti, 2018). Such biomarkers are essential for accurate diagnosis and reliable conclusions. In pain research, recognising pathophysiological differences is crucial to addressing some of the inconsistencies in the literature (White et al., 2012). Although standardised taxonomies such as the International Classification of Disease 11th edition aim to address shared pain symptoms and characteristics, it does not directly account for pathophysiological differences in chronic pain (Voscopoulos and Lema, 2010; Perrot et al., 2019; Nicholas et al., 2019). Consequently, characterising both pain-evoked and spontaneous pain activations based on these taxonomies is key to enhancing our understanding of class-specific neural substrates.

In this light, this problem can be addressed by reporting both convergence and divergence in research findings, see Figure 7. Essentially, convergence receives multiple inputs into a single input or area in the brain. In contrast, divergence receives single input and is distributed across multiple outputs. The problem with the latter, when conducting a CBMA divergences tend to be dismissed, the objective of CBMA will be discussed in the next section 1.4.2.

Moreover, studies should capture activations for pain alongside deactivations during baseline/rest, thereby reducing bias towards significant activations (Müller et al., 2018). Detailed and standardised reporting of patient characteristics—such as pain type, duration, and medication—alongside adherence to International Classification of Disease 11th edition classifications can mitigate confounding variables. Moreover, phenotype of patients with chronic pain (e.g., neuropathic or MSK pain) entails a broad array of variables including psychosocial factors, pain qualities and other symptom characteristics, sleep patterns, responses to noxious stimulation, endogenous pain-modulatory processes, and response to pharmacologic challenge (Edwards et al., 2021). These may be more specific for some conditions or produce a broad phenotypic variability depending on patient responses. Therefore, transparency is crucial in reporting for such variables to better understand true convergences and facilitate meaningful

interpretations.

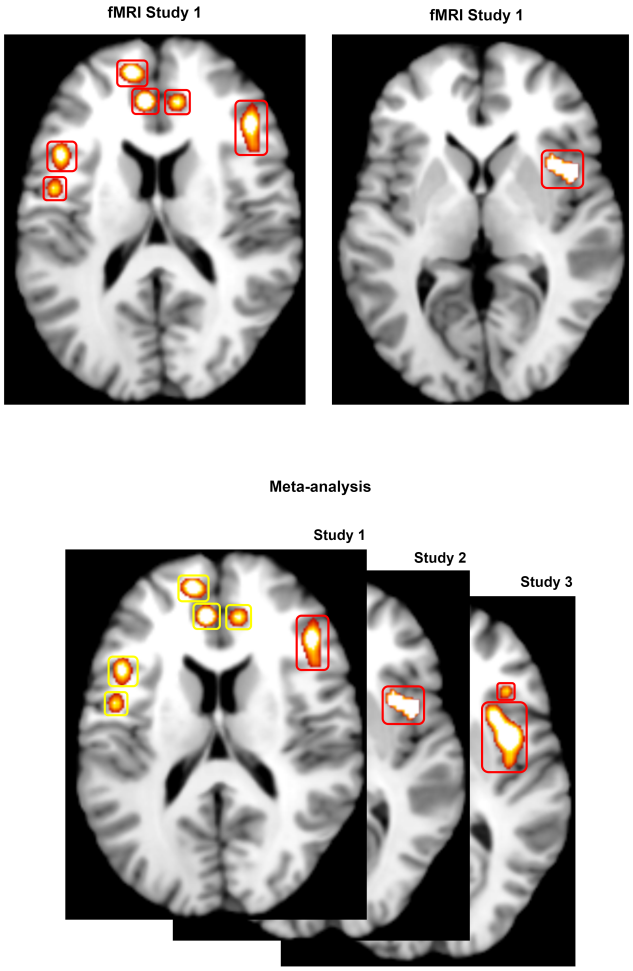

Figure 7: Difference between "Activation" and "Convergence" in fMRI Studies. The first panel illustrates the increased BOLD signal associated with activation patterns in specific brain structures during a particular task, demonstrating the activated structures in red. The second panel presents a meta-analysis of fMRI studies, indicating the consistent convergence across multiple independent studies. In this panel, the structures identified as convergent are marked in red, while the structures that did not converge are indicated in yellow.

Theoretical studies suggest that increasing sample sizes enhances the reliability of identified convergence(s) (Knight and Fu, 2000; Zhao and Yu, 2006). Additionally, adopting a whole-brain approach in primary research can minimise the biases towards specific ROIs (Müller et al., 2018). Following a standardised and comprehensive methodological approach can significantly reduce variability in the literature, addressing existing gaps with greater certainty.

1.4.2. Coordinate-based meta-analysis methods

Neuroimaging meta-analysis is an important method for addressing heterogeneity, identifying inconsistencies, and enhancing statistical power in studies of neural substrates related to pain in chronic primary pain and chronic secondary MSK pain conditions (Wang et al., 2022). While some meta-analyses highlighted convergences of areas such as the bilateral Ins and striatum, along with the supramarginal gyrus (Wang et al., 2022; Wager et al., 2007; Tanasescu et al., 2016), others report aberrant activity patterns or even the absence of such activity (Jensen et al., 2016; Xu et al., 2021).

Researchers use meta-analytic methods to systematically synthesise a large number of primary studies to gain a clearer understanding of pain-related neural substrates. Unlike, primary studies, a meta-analysis provides an overview of the literature significantly reducing errors, allowing for the exploration of moderators (e.g., methods, demographics), among many other strengths.

The False Discovery Rate (FDR) [5] method is a common statistical approach used for multiple comparisons (Genovese et al., 2002). However, it was suggested to be not an optimal approach for neuroimaging meta-analyses as its controlling FDR is not equivalent to controlling for the FDR activations (Eickhoff et al., 2012; Chumbley and Friston, 2009). On the contrary, another widely used CBMA method is ALE combined with cluster-level FWE (cFWE) inference correction. This approach demonstrated to be faster and more rigorous analytical approach that addresses issues of null distribution and multiple comparison corrections (Eickhoff et al., 2012). While, FDR is considered a less conservative method that may lead to false positives due to low sensitivity (Müller et al., 2018; Lindquist and Mejia, 2015), cFWE has demonstrated higher sensitivity. In contrast, voxel-level FDR or vFWE corrections showed lower sensitivity, but greater spatial specificity compared to cFWE (Eickhoff et al., 2012, 2016).

Previous meta-analysis employed uncorrected thresholds (e.g., $p < 0.001$) without accounting for multiple comparisons, driven by the low likelihood of detecting convergences if corrections were applied which ensures increased sensitivity (Lindquist and Mejia, 2015). However, this approach raises the risk of Type I errors (false positives) (Lindquist and Mejia, 2015; Eickhoff

[5] FDR is similar to FCDR method - however it focuses on clusters (Tench et al., 2013).

et al., 2012, 2016). Implementing corrections for multiple comparisons establishes a more rigorous statistical threshold, reducing the chance of Type I errors and preventing findings that may occur by chance (Eickhoff et al., 2012, 2016). While stricter thresholds may result in fewer detected effects, they enhance the reliability and robustness of the results.

A previous comparative review presented 11 whole-brain statistical maps, indicating that the average required p-value for whole-brain corrections is $p < 0.05$, which may yield 95% of true activations (Nichols and Hayasaka, 2003). However, it remains uncertain how many voxels represent true effects or whether a more stringent threshold would improve results (Lindquist and Mejia, 2015; Nichols and Hayasaka, 2003). This ambiguity is a significant issue in the literature, leading to variability with findings and interpretations from primary studies and meta-analyses; possibly due to overlooked true convergences or false positives (Eickhoff et al., 2016; Lindquist and Mejia, 2015). Importantly, the total number of experiments substantially affects the number of identified clusters, as the likelihood of overlap increases with more experiments, reducing the likelihood of Type II error (Eickhoff et al., 2012).

While researchers have previously utilised Parameter voxel-based meta-analysis (PVM) and ALE methods to identify consistent activation patterns, these approaches employ different statistical techniques. PVM uses random effects to account for variability across studies and focuses on reporting activations within a specific local neighbourhood (Costafreda et al., 2009). In contrast, ALE interprets activation likelihood as both fixed and random-effects statistics (Wager et al., 2007), estimating activation probabilities at each voxel across studies. ALE statistics are generated using a Gaussian kernel, differentiating it from PVM and other methods such as Multi-level Kernel Density Analysis (MKDA), thereby providing robust control over false positive results (Costafreda et al., 2009).

On the other hand, integrating different methods was suggested to enhance statistical power while maintaining well-controlled FWE rates (Ge et al., 2022). A study adopted the integrated cluster-wise significance measure method, a computationally efficient method, based on probabilistic approximation theories. The findings indicated that integrated cluster-wise significance measure method outperforms cFWE by identifying clusters with stronger average

signals, larger extents, and reduced dependence among voxels (Ge et al., 2022). Furthermore, the study underscores the application of both cFWE and vFWE demonstrated limited by floating-point representation, complicating the distinction between two clusters with similar p-values but different sizes and voxel-wise p-values (Ge et al., 2022).

Moreover, signed difference map (SDM) coordinate-based method investigates convergence across functional and structural neuroimaging experiments (Radua and Mataix-Cols, 2012; Pan et al., 2017). Hence, ALE, signed difference map, and KDA share a common goal of delineating brain activations locations with above-chance convergence of reported coordinates (Eickhoff et al., 2012). However, they exhibit notable differences, see Table 1.

Table 1: Comparison of CBMA meta-analytic methods for neuroimaging studies

Method	Neighbourhood Activations	Strengths	Limitations
ALE	Uses Gaussian kernel to estimate activation probabilities and limit excessive summation from neighbouring foci. Accounts for spatial uncertainty with permutations and corrections (Eickhoff et al., 2012).	Balances sensitivity and specificity; robust control over false positives; does not rely on effect sizes (Eickhoff et al., 2012).	Tightly grouped foci may appear as smaller clusters, potentially affecting interpretation (Eickhoff et al., 2012).
SDM	Uses 3D Gaussian kernel to account for spatial uncertainty similar to ALE; prevents spurious overlap of (- and +) values (Radua and Mataix-Cols, 2012; Eickhoff et al., 2012).	Integrates effect sizes; flexible for structural and functional convergence detection (Radua and Mataix-Cols, 2012).	Reduced sensitivity to small limbic structures; prone to false negatives (Radua et al., 2010).
KDA	Similar to ALE in reporting locations of coordinates above-chane, however it uses spherical kernal and tests how many foci are reported close to any individual voxel (Eickhoff et al., 2012; Kober and Wager, 2010).	Smoothing kernals provide the best match of the natural spatial resolution of the data with the most statistically powerful, similar to MKDA (Kober and Wager, 2010).	Similar to ALE, single study with large number of peaks can disproportionately influence results (Kober and Wager, 2010).
MKDA	Applies spherical kernel; accounts for multilevel data and adjusts for study quality(Kober and Wager, 2010).	It prevents a single contrast map with multiple peaks from disproportionately influencing meta-analysis; hence more generalisable results (Kober and Wager, 2010).	Can produce more Type II errors of missed regions (Kober and Wager, 2010).

A limitation of ALE is that it reports brain convergence in a specific area (Eickhoff et al., 2012). When a group of nearby foci activations is detected, researchers may interpret them as a large cluster. As the cluster size increases, it indicates stronger and more consistent spatial convergence across studies. Paradoxically, some studies report foci that are very proximal, and clustering improves as the Gaussian overlaps more tightly (Eickhoff et al., 2012). As a result, the tightly grouped foci appear as smaller clusters, although studies may have contributed

significantly to the cluster; hence affecting the interpretation of the findings. This highlights the importance of improved transparency when reporting the number of sample sizes, experiments, and studies that contribute to the identified structure within a cluster.

Moreover, ALE directly utilise the coordinates provided in studies to identify spatial convergence in the literature, meaning they do not rely on researchers reporting effect sizes (Eickhoff et al., 2012; Tahmasian et al., 2018; Salimi-Khorshidi et al., 2011). Additionally, CBMA requires separate meta-analyses to obtain results for deactivation foci, which is a drawback (Salimi-Khorshidi et al., 2011). However, cFWE inference correction has proven to be the most appropriate approach by ensuring low false positives in the results (Eickhoff et al., 2016; Müller et al., 2018). Nevertheless, all mentioned methods are widely validated and produce reliable findings for coordinate-based meta-analyses (Eickhoff et al., 2012; Salimi-Khorshidi et al., 2009). Therefore, the most suitable method depends on the research aims and data availability (Müller et al., 2018).

1.4.3. Activated Likelihood Estimation: FWE

According to Eickhoff et al. (2012), ALE provides the most accurate approximation of the Monte Carlo test null distribution. By applying FWE correction, ALE effectively controls and reduces false positives, forming the foundation of its inferential approach (Han et al., 2019; Lindquist and Mejia, 2015). Nevertheless, several limitations existed previously in ALE when it was first introduced by (Turkeltaub et al., 2002; Laird et al., 2005b). These limitations include the effects of varying sample sizes, differences in activation intensities, the use of non-Gaussian distributions to model foci, and the influence of the number of foci reported by different studies (Laird et al., 2005b). For instance, some studies may report a larger number of foci contributing to a cluster than others, leading to a stronger influence on the results since all foci are equally weighted in the ALE method. Previously, some of these issues were addressed by using the FDR, selecting the p-value and incorporating the first contrast analysis (Laird et al., 2005b). Subsequently, a "random effects" model was introduced to compute experiment-level MA activation images and analytical p-values (Eickhoff et al., 2009). Contrast analysis was then reintroduced to work alongside the random effects model (Eickhoff et al., 2011).

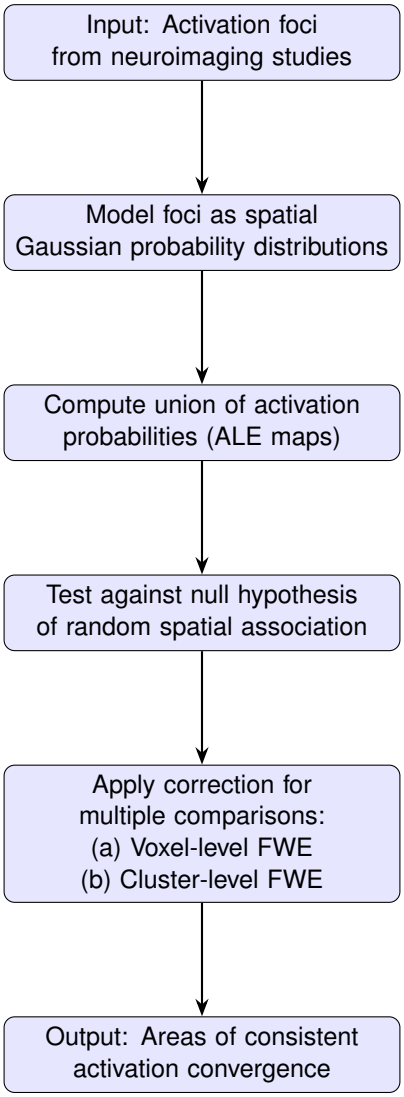

Figure 8: Workflow of the ALE meta-analysis process (Eickhoff et al., 2016).

Currently, ALE employs random-effects models to identify above-chance convergence across experiments, disproving the null hypothesis that foci within each experiment are uniformly distributed across the brain (Eickhoff et al., 2012). Each focus is modelled as a Gaussian probability distribution, and by combining these probabilities, areas of consistent spatial convergence are identified across multiple neuroimaging studies (Eickhoff et al., 2009; Laird et al., 2005a,b; Turkeltaub et al., 2002) (see Figure 8).

Reported foci are treated as spatial probability distributions centred on specific coordinates. ALE maps are then generated, allowing the computation of activation probabilities for each voxel across all included studies (Eickhoff et al., 2009). Permutation tests differentiate true foci convergence from random clustering, with the ALE null distribution created by redistributing an equivalent number of foci randomly across the brain. High ALE values indicate consistent convergence across studies (Tench et al., 2014).

This process 'smears' activation points across a brain region using a Gaussian spatial variance model (Eickhoff et al., 2009). MA activation are generated for each experiment and aggregated to produce an ALE map (Turkeltaub et al., 2012). The null hypothesis of random spatial association between experiments is tested to identify true convergence of foci (Eickhoff et al., 2012; Turkeltaub et al., 2002; Eickhoff et al., 2016).

Family wise error

This correction method ensures the probability of (Type I error) across multiple comparisons remain under a specified threshold (e.g., $p < 0.05$). Cluster-level and voxel-level inference results resemble non-parametric approaches (Eickhoff et al., 2012). Moreover, this method employs Gaussian random field, however it uses a nonlinear approach due to the nature of ALE score [6]. Therefore, the threshold applied (t_0) functions as a multiple comparisons and corrects a set of number of voxels N test by controlling for the FWE rate at α_{FWE}. In addition, it uses an upper bound FWE threshold and assumes independence with each voxel (Eickhoff et al., 2012):

[6] ALE calculates combined probabalistic representations of activation foci and models them by Gaussian, though a Gaussion distribution of the statistical field cannot be assumed as the non-linear operates by computing the ALE scores (Eickhoff et al., 2012).

Formula Explanations

1. Threshold for observing an ALE-score above t_0

$$P_{ao} = \sum_{i=b_{t_0}}^{\max(b)} p_i^c$$

This formula calculates the probability of observing an ALE-score greater than the threshold t_0 *under the null-distribution by summing probabilities from the corresponding bin to the maximum bin* [7].

2. Probability of observing at least one ALE-score exceeding t_0 ***across*** N ***voxels***

$$1 - (1 - P_{t_0})^N$$

This formula computes the probability of observing at least one ALE-score greater than t_0 *in* N *random voxel realisations, assuming independence.*

3. FWE corrected threshold

$$1 - \left(\left(1 - \sum_{i=b_{t_0}}^{\max(b)} p_i^c\right)\right)^N$$

This formula identifies the smallest threshold t_0 *such that the FWE rate remains below the desired* α_{FWE}.

1.4.4. Cluster-level and Voxel-level Inferences

Common methods for correcting multiple comparisons include cFWE and voxel-level FWE (vFWE) inferences, based on Gaussian random fields (Eickhoff et al., 2012).

The vFWE controls the probability of observing a given z-value under the assumption of random foci distribution (Eickhoff et al., 2012). It requires voxels to exceed a strict threshold for statistical significance, ensuring strong false-positive control and high spatial specificity but reduces sensitivity by limiting the detection of real effects (Eickhoff et al., 2016). Voxel inference focuses on single points, assigning each voxel an ALE score that indicates activation

[7] The null-distribution is converted from continuous data into a set of categories or series of bins, each bin represents a specific range of ALE score.

count. The p-value reflects the probability of observing a value under the null hypothesis (Eickhoff et al., 2012).

In contrast, cFWE controls the probability of observing a cluster of a given size under the random foci assumption (Eickhoff et al., 2012; Woo et al., 2014). It detects larger clusters, enhances sensitivity to spatially extended signals and accounting for voxel correlation, but offers less spatial specificity and carries a slightly higher false-positive risk (Eickhoff et al., 2012). Cluster-level inference identifies significant clusters by grouping voxels exceeding a threshold (e.g., 0.001) (Eickhoff et al., 2012). Random experiments simulate the null distribution by matching real-data characteristics (smoothness, sample size, and foci number), and ALE analysis repeats this process for real and simulated data (1,000–10,000 repetitions). Clusters with p-values below significance (e.g., 0.05) are deemed significant, with the maximum ALE score indicating cluster size (Eickhoff et al., 2012). Researchers often prefer cFWE for its balance between sensitivity and specificity (Müller et al., 2018; Eickhoff et al., 2016). The effectiveness of cFWE and vFWE depends on factors such as sample size, number of experiments, and spatial smoothness (Button et al., 2013; Müller et al., 2018).

1.5. Thesis Rationale

This research aims to leverage the new classification system for chronic primary pain and chronic secondary MSK pain, along with recommended meta-analysis practices, to overcome prior limitations in methodological differences, reconcile conflicting findings, and address variability in the literature of chronic pain (Müller et al., 2018; Lindquist and Mejia, 2015). The present work builds on insights from previous meta-analyses by employing faster and more precise analytical methods (Eickhoff et al., 2016, 2012; Laird et al., 2005b, 2011). ALE is widely regarded as the most suitable rigorous analytical approach for meta-analysis as it effectively reduces false positives, enhances sensitivity, and spatial specificity by employing stringent statistical thresholds for FWE correction (Eickhoff et al., 2016; Laird et al., 2011; Lobo et al., 2023). Thus, by controlling the risk of Type I errors, thereby increasing the reliability of the findings (Eickhoff et al., 2012).

I have chosen ALE for this research because it allows us to summarise meta-analysis results and identify consistent activation convergences across neuroimaging studies. This method will be used alongside fMRI and resting-state fMRI (rs-fMRI) to assess the links between BOLD activity during provoked and spontaneous pain in chronic pain conditions compared to pain-free.

The primary research question of this thesis is as follows:

'Are the pain biomarkers identified during provoked and spontaneous pain in neuroimaging studies of chronic primary pain and chronic secondary MSK pain reliable and valid?'

This question evaluates the diagnostic utility of the new taxonomies compared to pain-free individuals (Nicholas et al., 2019; Perrot et al., 2019) and identifies consistent converging pain-related brain responses during provoked and spontaneous pain.

First, what were the pain-specific convergences associated with provoked pain in chronic primary pain, compared to pain-free? Second, which brain structures exhibited pain-specific convergence during resting states in chronic secondary MSK pain, compared to pain-free? This was addressed by conducting a systematic review and CBMA on fMRI and rsfMRI to identify consistent neural patterns associated with pain processing.

The primary outcome of the first question aimed to identify BOLD signal links to pain (e.g., provoked pain) versus no pain (e.g., rest or innocuous stimuli) in chronic primary pain, compared to pain-free. Additionally, we analysed the relationship between pain ratings (e.g., visual analogue scale) and the concomitant BOLD signal. This analysis enabled us to test whether the structures identified by the meta-analysis could predict the presence (and variation) of subjective pain.

The primary objective of the second question is to identify neural patterns related to spontaneous MSK pain within specific conditions of chronic secondary MSK pain, compared to pain-free. To account for symptoms such as freezing of gait or depression, we assessed pain-related converging patterns between chronic secondary MSK pain without symptoms (P1) compared to those with symptoms (P2), and Parkinson's disease without symptoms (PD1) compared to those with symptoms (PD2).

To address multiple comparisons in our meta-analysis, we employed two thresholding methods. The ALE method summarised coordinates showing consistent activity across studies, using vFWE and cFWE to enhance spatial specificity and sensitivity, respectively (Eickhoff et al., 2016).

For Chapter 2: Selective Focus on chronic primary pain: An Examination of Four Conditions within the ICD-11 Framework We conducted 13 meta-analyses, total of 48 studies, consisting of a combination of within-subjects and between-subjects experiments (k =75) experiments. We established the corrected statistical thresholds for the analyses: for cFWE at $p < 0.01$ (Lobo et al., 2023), and vFWE at $p < 0.05$ (Eickhoff et al., 2012).

A version of this chapter has been submitted to *The Journal of Pain* and is currently being reviewed.

Meta-analyses outline:

Using cFWE-correction:

1. Conjunction meta-analysis of within-subjects experiments
2. Contrasts: chronic primary pain > pain-free (Within-subjects)
3. Contrasts: pain-free > chronic primary pain (Within-subjects)
4. chronic primary pain meta-analysis (Within-subjects)
5. Pain-free meta-analysis (Within-subjects)
6. Chronic primary pain > pain-free meta-analysis (Between-subjects)
7. Pain-free > chronic primary pain meta-analysis (Between-subjects)
8. Pooled (chronic primary pain and pain-free) meta-analysis (Between-subjects)

Using vFWE-correction:

1. chronic primary pain meta-analysis (Within-subjects)
2. Pain-free meta-analysis (Within-subjects)

3. Chronic primary pain > pain-free meta-analysis (Between-subjects)

4. Pain-free > chronic primary pain meta-analysis (Between-subjects)

5. Pooled (chronic primary pain and pain-free) meta-analysis (Between-subjects)

For Chapter 3: Exploring Chronic Secondary MSK Pain: A Focused Analysis of Two Conditions within the ICD-11 Framework This chapter includes 10 meta-analyses, total of 28 studies and 62 between-subjects experiments (k =62). We set the corrected statistical threshold for cFWE and vFWE at $p < 0.05$ (Eickhoff et al., 2012; Müller et al., 2017). We conducted 12 follow-up sub-group meta-analyses of Parkinson's disease studies, to account for group differences. Given the smaller number of experiments, we opted for a more lenient cFWE threshold. These thresholds are based on optimal performance recommendations in the literature (Eickhoff et al., 2016, 2012), ensuring a thorough statistical evaluation of our data.

Meta-analyses outline:

Using cFWE-correction:

1. chronic secondary MSK pain > pain-free meta-analysis (Between-subjects)

2. Pain-free > chronic secondary MSK pain meta-analysis (Between-subjects)

3. P1 > P2 meta-analysis (Between-subjects)

4. P2 > P1 meta-analysis (Between-subjects)

5. Pooled (P1 and P2) meta-analysis (Between-subjects)

Using vFWE-correction:

1. chronic secondary MSK pain > pain-free meta-analysis (Between-subjects)

2. Pain-free > chronic secondary MSK pain meta-analysis (Between-subjects)

3. P1 > P2 meta-analysis (Between-subjects)

4. P2 > P1 meta-analysis (Between-subjects)

5. Pooled (P1 and P2) meta-analysis (Between-subjects)

Follow-up Parkinson's disease Subgroup Meta-analyses outline:

Using cFWE-correction:

1. Parkinson's disease > pain-free meta-analysis (Between-subjects)
2. Pain-free > Parkinson's disease meta-analysis (Between-subjects)
3. Contrasts: Pain-free > Parkinson's disease meta-analysis (Between-subjects)
4. Contrasts: Parkinson's disease > pain-free meta-analysis (Between-subjects)
5. PD1 > PD2 meta-analysis (Between-subjects)
6. PD2 > PD1 meta-analysis (Between-subjects)
7. Pooled (P1 and P2) meta-analysis (Between-subjects)
8. Contrasts: PD2 > PD1 meta-analysis (Between-subjects)

Using vFWE-correction:

1. Parkinson's disease > pain-free meta-analysis (Between-subjects)
2. Pain-free > Parkinson's disease meta-analysis (Between-subjects)
3. PD1 > PD2 meta-analysis (Between-subjects)
4. PD2 > PD1 meta-analysis (Between-subjects)

2. Selective Focus on Chronic Primary Pain: An Examination of Four Conditions within the ICD-11 Framework

2.1. Literature Review

Pain is a protective mechanism, alerting the body to danger and playing a crucial role in survival. However, pain can occur without direct tissue damage, as in chronic pain, which is problematic due to its persistent nature and adverse effects on an individual's overall QoL (Pandelani et al., 2023). Chronic pain is associated with various conditions, including IBS, fibromyalgia, migraine, and chronic lower back pain (Nicholas et al., 2019). These entail complex aetiologies, often involving diverse pathologies.

These conditions have a profound impact on individuals' daily functioning and societal productivity. For instance, in 2017, chronic lower back pain affected 7.5% of the global population—approximately 577 million people (Vos et al., 2017; Meucci et al., 2015). A systematic review and meta-analysis of 53 studies across 38 countries (n =395,385) estimated that 9.2% of individuals experience IBS (Oka et al., 2020). In a cross-sectional survey, fibromyalgia prevalence was reported to range between 1.2% and 5.4% (Jones et al., 2015). Similarly, migraine affect about 1 in 7 people globally, with women experiencing a higher prevalence than men (Sacco et al., 2012). The considerable prevalence of these conditions underscores their significant impact on daily performance and societal efficiency.

The persistent and severe pain often compels sufferers to peruse various treatments, including opioid medications (Højsted and Sjøgren, 2007; Tagliaferri et al., 2020). However, the use of such powerful medicines can lead to complications, such as addiction and withdrawal symptoms. While, research has explored various approaches to manage chronic pain and enhance QoL, including pharmacological interventions, moderate to vigorous physical activity (Geneen et al., 2017), and biopsychosocial treatment models (Hadi et al., 2017), these options can be financially burdensome, particularly for patients in low- and middle-income countries. The economic burden of chronic pain in the United States is substantial, with annual costs estimated between £440 billion and £498 billion, surpassing the combined expenses for cancer, heart disease, and diabetes treatments (Society, 2012). This staggering figure underscores the significant impact of chronic pain as a pervasive, long-term health condition affecting approximately 100 million Americans. Despite its prevalence and economic impact, many cases

remain untreated or inadequately managed, leaving patients feeling overwhelmed and struggling to cope. Given the widespread prevalence and significant costs of chronic pain disorders, there is an urgent need to deepen our understanding of the underlying pathophysiological mechanisms. This is essential for developing more effective and accessible treatments, as well as improving clinical practices and research initiatives (Stanos, 2012). Advancing knowledge in these areas is essential to mitigate the profound personal and societal impacts of chronic pain.

2.2. Pathophysiology of chronic pain

Chronic pain is classified into three categories: 1) nociceptive pain, which is associated with tissue damage or disease; 2) neuropathic pain, which originates from disease or damage to the somatosensory nervous system (SNS); and 3) mixed pain, a combination of nociceptive and neuropathic pain (Baron, 2006; Baron et al., 2010). Furthermore, in 2017, IASP introduced nociplastic pain as an additional mechanistic pain descriptor, where pain arises from altered nociception despite no clear evidence of tissue damage, resulting in activation of peripheral nociceptors, or evidence of SNS lesion disease that causes pain (Kosek et al., 2021). Though central sensitisation is often a dominating mechanism of nociplastic chronic pain conditions. Neurophysiologically, it is not synonymous to the term central sensitisation (Kosek et al., 2021). Additionally, peripheral sensitisation mechanism may contribute to nociplastic pain (Kosek et al., 2021).

The most common types of pain are neuropathic and nociceptive pain (Cohen and Mao, 2014). Nociceptive pain may arise from noxious stimuli that cause tissue damage, with the underlying pathophysiology involving nociceptor activity and the release of inflammatory mediators (Kosek et al., 2016). Nociceptors are primarily classified into two painful types found in the skin: Aδ mechanosensitive nociceptors and C-fibre polymodal nociceptors (Amthor, 2016), see section 1.3.4. These nociceptive mechanisms can lead to conditions such as allodynia or hyperalgesia, where pain is elicited by innocuous sensations or an exaggerated pain response. Therefore, nociceptive and neuropathic pain show significant overlap and may be conceptualised as points on a continuum of chronic pain, rather than entirely separate categories (Cohen and Mao, 2014), see Table 2.

Additionally, nociceptive pain may result from the activation of peripheral nerve endings (i.e., nociceptors) in response to noxious stimuli. This type of pain, arising from actual or potential tissue damage, can be categorised as visceral or somatic (Cohen and Mao, 2014). Neuropathic pain, on the other hand, is caused by lesions or diseases of the SNS (Cohen and Mao, 2014). This type of pain involves pathophysiological mechanisms in both the peripheral and CNS (Baron, 2009). Thus, while neuropathic and nociceptive pain involve distinct neurobiological and pathophysiological mechanisms, they often interact and overlap (Cohen and Mao, 2014).

Clinical Characteristic	Neuropathic Pain	Nociceptive Pain
Cause	Injury to the nervous system, often accompanied by maladaptive changes in the nervous system	Damage or potential damage to tissues
Descriptors	Lancinating, shooting, electric-like, stabbing pain	Throbbing, aching, pressure-like pain
Sensory Deficits	Common—for example, numbness, tingling, pricking	Uncommon; if present, they have a non-dermatomal or non-nerve distribution
Motor Deficits	Neurological weakness may be present if a motor nerve is affected; dystonia or spasticity may be associated with central nervous system lesions and sometimes peripheral lesions (such as complex regional pain syndrome)	May have pain-induced weakness
Hypersensitivity	Pain often evoked by non-painful (allodynia) or painful (exaggerated response) stimuli	Uncommon except for hypersensitivity in the immediate area of an acute injury
Character	Distal radiation common	Distal radiation less common; proximal radiation more common

Table 2: Classification of neuropathic and nociceptive pain, according to (Cohen and Mao, 2014)

Some conditions can exhibit both types of pain (i.e., neuropathic and nociceptive). For instance, fibromyalgia is characterised by widespread MSK pain and tenderness, which may be triggered by non-noxious stimuli, such as touch. In this case, the condition can be categorised as

nociceptive pain resulting from persistent activation of nociceptors—specialised nerve endings that typically respond to noxious stimuli, such as tissue damage, inflammation, or chemical irritation. Thus, in some cases, the primary cause of pain may stem from ongoing tissue damage rather than nerve damage itself (as in neuropathic pain) (Schaible and Richter, 2004; Nicholson, 2006). Consequently, chronic pain conditions often involve complex underlying mechanisms that reflect a mixed type of pain.

While there are clear differences between the two types of pain, nociceptive pain involves transduction, which converts mechanical signals into electrochemical ones, whereas neuropathic pain arises from direct nerve stimulation (Cohen and Mao, 2014). The distinction between the two may also relate to the extent of nerve damage (e.g., large or small nerve injury). Despite these differences, both types of pain share common neurotransmitters, neuropeptides, cytokines, and enzymes, highlighting a significant overlap in their underlying mechanisms (Cohen and Mao, 2014).

Furthermore, the key mechanisms of pain in chronic pain conditions are central sensitisation (e.g., fibromyalgia, chronic low back pain) (Dydyk and Givler, 2020; Volcheck et al., 2023; Tao et al., 2019). Dysfunctional pain modulation, where the body fails to regulate pain signals in conditions of widespread pain (Tao et al., 2019). Neuroimmune interactions, chronic pain arising due to neuroinflammation involving glial cells, cytokines, and immune mediators in complex regional pain syndrome (Wen et al., 2023; Ji et al., 2018b). Maladaptive neuroplasticity, where changes in brain structure and function affect pain perception in chronic pain, causes pain processing to become hyperactive, leading to pain catastrophising (Volcheck et al., 2023; Tao et al., 2019; Malfliet et al., 2017).

Given the key differences in the pathophysiology of nociceptive, neuropathic, and nociplastic pain, treatment approaches for these conditions may vary significantly. For example, individuals experiencing nociceptive pain often respond more effectively to opioids than those with neuropathic pain, as noted by Smith (2012); Schembri (2019). Additionally, opioids tend to be more effective in managing peripheral neuropathic pain (up to 12 weeks) compared to supraspinal neuropathic pain and are least effective for central neuropathic pain (Schembri,

2019). This highlights the complexity of chronic pain and the intricate interplay of mechanisms underlying different types of pain. Enhancing our understanding of these mechanisms will enable us to improve patient outcomes and develop more effective therapeutic strategies.

2.3. IASP: chronic primary pain classification

Chronic pain experiences vary across conditions due to differences in aetiology that reflect distinct pathophysiological mechanisms. Chronic pain may result from ongoing peripheral pathology or arise spontaneously without an identifiable trigger (Woolf and Doubell, 1994). For example, recent studies continue to debate whether migraine attacks originate from peripheral or central mechanisms (Do et al., 2023; Meylakh and Henderson, 2022). In contrast, IBS is believed to involve both mechanisms, though its underlying causes remain largely unclear (Enck et al., 2016). Recognising these diverse aetiologies, the IASP categorises chronic pain into two primary diagnoses: chronic peripheral neuropathic pain and chronic central neuropathic pain (Scholz et al., 2019).

The primary diagnostic frameworks, the Diagnostic and Statistical Manual 5th edition and International Classification of Disease 10th edition , do not reflect the latest advancements in pain research or account for pathophysiological factors contributing to chronic pain (Nicholas et al., 2019). To address these gaps, the IASP introduced the chronic primary pain framework in the International Classification of Disease 11th edition. This comprehensive classification system standardises the categorisation of chronic pain while excluding acute pain conditions. According to Nicholas et al. (2019), chronic primary pain occurs in body systems, and body sites, or combination of body sites (see Table 3).

Through extensive deliberation, the IASP proposed a classification for International Classification of Disease 11th edition that serves as a valuable tool by coding syndromes within these categories based on detailed clinical histories. This approach reduces ambiguities between chronic and acute pain, while accounting for different mechanistic pain types, offering a clearer understanding of chronic pain manifestations (Nicholas et al., 2019).

The updated framework includes conditions such as fibromialgia, migraine, chronic lower back pain, and IBS. It provides clear definitions and shared characteristics within these conditions

Category	Examples
Body systems	Nervous, MSK, gastrointestinal systems
Body sites	Face, low-back, neck, upper-limb, thorax, abdominal, pelvis, urogenital region
Combination of sites	Widespread pain

Table 3: chronic primary pain: Body systems, sites, and combinations (Nicholas et al., 2019)

(Nicholas et al., 2019). Primary pain is recognised as a diagnostic concept, with most, if not all primary pain conditions are considered nociplastic pain (Kosek et al., 2021). Notably, this mechanistic term acknowledges different dimensions of nociplastic mechanisms (Kosek et al., 2021). Moreover, chronic primary pain is defined as pain persisting in one or more anatomical regions (see Table 4). Rather than focusing on the cause of pain, the chronic primary pain framework emphasises the pain itself. It avoids oversimplifying pain as being purely physical or psychological, and recognises that these factors often overlap. By highlighting the long-term nature of chronic pain and adopting a biopsychosocial perspective, the framework lays the foundation for transformative advancements in pain management.

Most, if not all primary pain conditions are considered nociplastic pain (Kosek et al., 2021). Notably, this mechanistic term acknowledges different dimensions of nociplastic mechanisms, and "primary pain" is recognised as a diagnostic concept (Kosek et al., 2021). Chronic primary pain is defined as pain persisting in one or more anatomical regions (see Table 4). Rather than focusing on the cause of pain, the chronic primary pain framework emphasises the pain itself. It avoids oversimplifying pain as being purely physical or psychological, recognising that these factors often overlap. By highlighting the long-term nature of chronic pain and adopting a biopsychosocial perspective, the framework lays the foundation for transformative advancements in pain management.

Since the 1980s, the relationship between chronic pain and psychopathology, particularly depressive disorders, has received considerable empirical and theoretical attention (Dersh et al., 2002). Chronic pain is strongly correlated with depression and may contribute to its onset (Sheng et al., 2017), manifesting as chronic stress, loss of interest or pleasure, or sleep disturbances, which further exacerbate depressive symptoms (Blackburn-Munro and

Criterion	Definition
1	Pain in one or more anatomical regions that persists or recurs for longer than 3 months.
2	Associated with significant emotional distress (e.g., anxiety, anger, frustration, or depressed mood) and/or significant functional disability (interference in activities of daily life and participation in social roles).
3	Symptoms are not better accounted for by another diagnosis.

Table 4: Criteria for the Definition of chronic primary pain (Nicholas et al., 2019)

Blackburn-Munro, 2001; Surah et al., 2014). Consequently, patients with chronic pain face a higher risk of developing depression (Sheng et al., 2017).

Additionally, growing evidence suggests that long-term opioid use increases the risk of depression (Salas et al., 2017). A "chicken or egg" debate persists regarding whether chronic pain precedes depression. Thereby heightening pain sensitivity and lowering pain thresholds (Schiavone et al., 2012), whether depression arises as a consequence of chronic pain (Salas et al., 2017), or whether depression causes chronic pain e.g., *"Which comes first—depression or chronic pain?"*.

This bidirectional relationship complicates efforts to determine causality and highlights the need for integrated approaches that addresses comorbidities. During COVID-19, depression symptoms were associated with MSK pain due to reduced physical activity and increased sedentary behaviour (Christofaro et al., 2022). On the other hand, patients who develop chronic pain due to an injury may experience drastic lifestyle changes, shifting from being outgoing and motivated to socially isolated and demotivated. Addressing this complex interplay requires consideration of both the pathophysiological and psychopathological dimensions of chronic pain. A deeper understanding of its varied manifestations across different conditions is crucial for identifying potential neurological markers of pain and associated comorbidities.

2.4. The Quest for Neurological Markers of Pain

As discussed in the earlier chapter, the concept of the neuromatrix is central to understanding how the brain processes physical pain, particularly in cases where modulating inputs from tissue

damage is absent. This deprivation leads to central pain, characterised by an abnormal activity pattern known as the 'neurosignature' (Canavero, 1994). Several regions are implicated in this process, including the spinal cord, brain stem, Thal, limbic system, Ins cortex, somatosensory cortex, motor cortex, and PFC. Together, these areas contribute to the sensation of pain (Melzack, 2001; Trachsel and Cascella, 2021).

However, the activation of these regions is not exclusive to pain perception. Rather, it reflects the complex and dynamic integration within neural networks, enabling other perceptual outputs beyond pain (Iannetti and Mouraux, 2010). In line with this, Loeser and Melzack (1999) proposed that the neuromatrix is adaptable and capable of modifying input and output influences. Consequently, the type and intensity of these inputs play a crucial role in shaping how pain is perceived and represented.

While some authors support the concept of the neuromatrix (Liang et al., 2019), others have criticised it for failing to address the social constructs of pain and the variability in individual pain experiences (Trachsel and Cascella, 2021). These criticisms underscore the importance of accounting for individual differences—such as personality traits, genetic predispositions, and medical history—as key factors influencing the variability in patients' pain experiences and the corresponding neural representations of pain.

Critics further contend that the neuromatrix inadequately explains the biological processes underlying implicit threat evaluation and its emergence into conscious awareness (Moseley, 2007). For instance, the CNS generates various outputs when tissue is perceived to be under threat. The perception of threat, rather than the actual threat to the tissue, determines the CNS response. Suggesting an unconscious evaluative process preceding conscious awareness. Consequently, the neuromatrix relies on the degree of perceived threat, suggesting that pain may be the conscious interpretation of an indirect perception of tissue threat (Butler and Moseley). Therefore, without direct tissue damage threat, emotional and psychological components of pain perception may contribute to one's awareness and experience of pain, thus influencing the neurosignatures.

Building upon the neuromatrix, the pain matrix concept was introduced to specifically address

the neural functions dedicated to pain perception, asserting that these functions are multimodal (Davis, 2000). The distinction between the two concepts lies in their focus: while the neuromatrix encompasses non-nociceptive processes with outputs related to pain, it is not confined solely to cortical regions (Davis, 2000). In contrast, the pain matrix posits that its sub-components respond to both nociceptive and non-nociceptive inputs (Mouraux et al., 2011; Xiang et al., 2018), although some studies refute the existence of nociceptive-specific neural activity due to discrepancies attributed to methodological differences or variability in conditions (Mouraux and Iannetti, 2009; Zhang et al., 2021; Derbyshire et al., 1997; Legrain et al., 2011). Other researchers assert that the pain matrix involves at least partially pain-specific cortical activity within certain brain structures (Wiech, 2016; Iannetti and Mouraux, 2010; Tracey, 2005) Pain processing within the pain matrix involves three major systems: the lateral and medial systems, which serve as the two afferent pain pathways, and the descending system. Key brain regions include the SI, SII, the Ins, and ACC (Legrain et al., 2011; Henry et al., 2011; Fabbro and Crescentini, 2014; Xiang et al., 2018). However, ongoing debates question the exact boundaries and specificity of this network. Some researchers suggest that activation of the pain matrix reflects a general "flow and integration of information" rather than exclusively pain-specific activity, further supported by findings that these structures are activated during non-painful sensory modalities, including visual, auditory, and tactile stimuli (Tracey, 2005; Zhang et al., 2021; Mouraux and Iannetti, 2009; Mouraux et al., 2011; Lui et al., 2008; Liberati et al., 2016). This raises the question of whether research should focus on identifying pain-specific structures or those consistently activated during painful experiences.

Despite these debates, some structures within the pain matrix, such as the Thal, ACC, PCC, Ins, amygdala, and periaqueductal grey, consistently respond to nociceptive stimuli. While, the original neuromatrix posited that no cortical regions are solely dedicated to pain perception (Derbyshire et al., 1997; Reddan and Wager, 2018; Iannetti and Mouraux, 2010; Melzack, 1999). Studies also suggest that the pain matrix may play a role in chronic pain processing rather than nociceptive stimuli alone, as seen in increased connectivity with chronic migraine patients compared to episodic migraine patients (Lee et al., 2019; Bantick et al., 2002). These

findings highlight the complex integration of multidimensional components that contribute to variability and overlap in chronic pain processes.

The idea of a "pain connectome" suggests that pain is encoded as a dynamic system-level integration involving a spatiotemporal signature (Kucyi and Davis, 2015). Additionally, the "salience network," including the aIns, MCC, right temporoparietal junction (rTPJ), and bilateral dorsolateral PFC, modulates attention to pain, with chronic pain patients displaying abnormal functional activities in these regions (Bosma et al., 2018; Hemington et al., 2016; Hong et al., 2014). In line with this, the aIns is identified with acute and ongoing pain (Labrakakis, 2023) and is associated with responses to unpleasant, pleasant, and distressing stimuli, highlighting its multifaceted role, distinct from the functions of the pIns (Frot et al., 2022; Danziger et al., 2009).

While some cortical regions within the pain matrix, such as the posterior and medial operculum, are linked to sensory perception of pain from thermal, mechanical, and heat stimuli, they are also involved in broader somatosensory processing, responding to non-painful stimuli such as itch and tactile sensations (Garcia-Larrea and Mauguière, 2018). This suggests that while certain regions have pain-specific functions, they are multifunctional, contributing to the perception of other sensory experiences as well.

Interestingly, some studies have identified lateralisation of pain matrix activity to the right hemisphere during provoked pain, with painful stimuli activating the contralateral somatosensory cortex and bilaterally in the mid/pIns, aIns, and PCC (Symonds et al., 2006; Bingel et al., 2003). This activation varies depending on the side of the body where pain is applied, and compensatory mechanisms may influence activity in older patients with reduced tissue integrity in one hemisphere (Tyler et al., 2010; Tanasescu et al., 2016).

Neural responses within the pain matrix may also vary with pain intensity, with some individuals perceiving stimuli as tickling or tingling, while others report pain in the absence of stimuli (Derbyshire et al., 1997; Neri and Agazzani, 1984; Craig and Weiss, 1972). These findings highlight the need to account for the variability introduced by factors such as pain intensity, location, and demographic differences, which often act as confounders in research.

Altogether, these findings raises questions regarding the specificity of the pain matrix in pain perception, the applicability across diverse populations, and the overlap during nociceptive and non-nociceptive stimuli. The multifaceted influences shaping pain perception contribute to heterogeneity in research findings, often driven by uncontrolled variables. To address this, implementing standardised criteria for pain thresholds and stimulus types could reduce variability and enhance comparability across studies. Neuroscience continues to provide critical insights into these complexities, advancing our understanding of pain perception and its underlying mechanisms.

2.5. Meta-analytic evidence of specific neural substrates of pain

Recent research, such as that by Reckziegel et al. (2019), emphasises the challenge of identifying consistent pain-specific patterns for provoked pain. Past studies have encountered inconsistencies due to varying methodologies, underpowered analyses, and the diverse nature of chronic pain. Despite these challenges, ongoing efforts to bridge the gap by conducting more comprehensive research on chronic pain patients and pain-free participants during provoked pain (Tanasescu et al., 2016, 2015; Wager et al., 2013; Treede et al., 1999; Friebel et al., 2011; Xu et al., 2021; Jensen et al., 2016). Nevertheless, current research still needs to address the differences among chronic pain conditions. This variability highlights the need for a more focused selection of conditions for analysis, emphasising comparable categories of chronic pain. In response to this challenge, the IASP's new diagnostic framework for chronic primary pain establishes a standardised system for categorising chronic pain conditions.

Conducting a neuroimaging meta-analysis to evaluate the classification of chronic primary pain represents a crucial step towards addressing the factors contributing to heterogeneity in the literature. Such an analysis can identify inconsistencies in existing findings and enhance statistical power by integrating data from multiple studies. This approach facilitates the development of a comprehensive understanding of the pain-specific neural structures associated with a clinical population sharing similar characteristics, such as chronic pain considered to be primary, the presence of emotional or physical disability, and a pain duration exceeding three months (Nicholas et al., 2019). By accounting for key factors within the clinical population, this

method improves the precision and reliability of research outcomes and reduces the likelihood of inconsistent findings. Ultimately, we can uncover common neural mechanisms underlying chronic primary pain and enhance our understanding of its pathophysiology in the context of current clinical practices.

Building on the exploration of the complexities of chronic pain and the necessity for precise analysis discussed in the previous section, the following focuses on the integration of within-subject and between-subject experimental designs in prior meta-analyses (Friebel et al., 2011; Jensen et al., 2016; Wang et al., 2022; Xu et al., 2021). While some studies have differentiated between these experimental types (Tanasescu et al., 2016; Xu et al., 2020), the significance of this distinction cannot be overstated.

Within-subject experiments compare conditions within the same group, whereas between-subject experiments examine differences between distinct groups. Consequently, it is critical to establish whether the research investigates within-group or between-group effects, as this distinction directly impacts the interpretation of findings (Müller et al., 2018). Moreover, the interpretation of results may differ when comparing experimental or meta-analytical level (Müller et al., 2018). For instance, a meta-analysis experiment focusing on group comparison reports the convergence differences in brain activations between those groups. In comparison, a meta-analytical contrast analysis demonstrates the differences in convergence in brain activation (Müller et al., 2018) (e.g., patients showing stronger activity in the Ins compared to pain-free). Equally important is the need to address discrepancies in systematic thresholding, wherein control data are sometimes reported as uncorrected while patient data are corrected. Such methodological inconsistencies introduce potential bias that can significantly affect research outcomes (Turkeltaub et al., 2012; Müller et al., 2018; Xu et al., 2021).

A recent systematic review and meta-analysis examined differential brain responses to noxious stimuli in chronic pain patients compared to healthy controls using fMRI data (Xu et al., 2021). This review employed the ALE method with cluster-corrected statistical thresholding and p-value threshold of $p < 0.05$. Using this threshold, no significant differences were identified in between-groups (patients vs pain-free). However, this choice of thresholding is critical, as more

conservative thresholds, such as $p < 0.0001$, can yield drastically different results. While $p < 0.05$ might produce over 20,000 voxels, $p < 0.01$ could yield approximately 6,500 voxels (Mirman et al., 2018). These variations in voxel counts underscore the substantial influence of statistical thresholding on study outcomes. Thus, creating heterogeneity in analytical strategies and risks inaccurate conclusions, including false positives or negatives, which can diminish the diagnostic value of neuroimaging as a tool for identifying reliable biomarkers.

The authors reported employing rigorous controls for Type I errors to minimise false positives, using cFWE correction (Xu et al., 2021). Controlling for false positives is critical, as reporting unthresholded whole-brain maps without such correction can lead to inflated findings (Eickhoff et al., 2016; Müller et al., 2018). To further reduce the risk of false positives, cFWE is recommended for high sensitivity in studies with at least 17 experiments (Müller et al., 2018), whereas vFWE correction offers greater spatial specificity, requiring a minimum of 8 experiments (Eickhoff et al., 2016). While both methods control the FWE rate, vFWE independently evaluates each voxel, thereby reducing the risk of false positives at the voxel level and increasing the likelihood of detecting smaller clusters of activity. In contrast, cFWE is more liberal, accounting for larger regions of activity that surpass a certain threshold by controlling false positives at cluster level.

The study further reported no significant differences in subjective pain scores between patient and control groups (Xu et al., 2021). This finding possibly reflects the heterogeneity of the included patient population, which varied in classification under the International Classification of Disease 11th edition framework. Participants included patients with diverse chronic pain conditions, such as fibromyalgia, chemotherapy-induced neuropathy, and knee osteoarthritis (Treede et al., 2015). Additional variations in pain paradigms, such as differences in the duration and location of painful stimuli. These methodological differences and experimental design factors highlight the urgent need for standardised, robust analytical techniques in neuroimaging research in pain research to ensure the reliability and clinical relevance of results.

Another meta-analysis investigated functional brain reorganisation in chronic pain and experimental models of hyperalgesia (Tanasescu et al., 2016), including 180 experimental

cutaneous pain studies. Neuropathic conditions were categorised based on symptoms and underlying aetiology by IASP taxonomy, the side of the body where the pain is administered, and the pain modalities administered. To reduce the false positive rate and detect differences in the brain structure, the researchers employed ALE approach to identify consistent activations across studies and contrast meta-analysis. For ALE, False Cluster Discovery Rate (FCDR) was applied with a set correction of 0.05, and contrast meta-analysis 0.1 correction. It is worth noting that FWE correction is a stricter method than FCDR and may result in fewer convergences, depending on the selected threshold. Although FCDR offers the advantage of controlling for the expected proportion of false positives among null hypotheses, its more lenient approach has limitations in studies investigating subtle differences, as mentioned earlier in section 1.4.2.

The subgroup findings for pain administered to specific body sites revealed activations in the right mid and pIns, MFG, and putamen (Tanasescu et al., 2016). In contrast, when pain was applied to other body areas one cluster showed activation in the precentral gyrus (PreG). Furthermore, patterns between patients and pain-free were similar, with no spatial differences observed in the contrast meta-analysis (Tanasescu et al., 2016).

Notably, their findings indicated a significant difference when comparing pain stimuli on the right side to those on the left. Various painful stimuli exhibited considerable overlap in brain activity patterns (Tanasescu et al., 2016), but the most substantial difference was observed between mechanical and thermal stimuli. As such, pain paradigm emerges as an additional variable of interest, potentially serving as a moderator that influences pain processing. Therefore, a comprehensive understanding of these variables and their underlying mechanisms in chronic pain requires further research (Tanasescu et al., 2016).

Similar to the previously mentioned meta-analysis (Xu et al., 2021), the limitation of this previous meta-analysis is chronic pain classifications variability (Tanasescu et al., 2016). Most chronic pain conditions in this meta-analysis fall under the neuropathic pain syndromes and primary nociceptive MSK disorders, which entail different classifications (e.g., fibromyalgia, osteoarthritis, trigeminal neuralgia, and post-herpetic neuralgia). However, the analysis mainly

focused on subdividing these groups into sites of pain and less focused on the classification of chronic pain. Nevertheless, this study attempted to account for subgroup differences (e.g., MSK pain or fibromyalgia). However, their findings were similar, particularly when comparing neuropathic and nociceptive subgroups to pain-free. In addition, no significant difference was observed when comparing chronic pain conditions to pain-free during mechanical pain, even after applying a lenient threshold of 0.1. Therefore, several factors may contribute to the findings heterogeneity (i.e., conditions, pain paradigm, pain site). This suggests functional reorganisation may be moderated by pain aetiology and phenotype (Tanasescu et al., 2016). Pain paradigms significantly influence the activation of different structures within the pain matrix. Previous meta-analyses have highlighted the distinctions between various pain paradigms, such as thermal, mechanical, and electrical stimuli, and their specific effects on pain processing (Friebel et al., 2011; Tanasescu et al., 2016). One meta-analysis investigating patterns of brain activity during thermal pain in chronic neuropathic pain identified several consistent activation clusters, including the bilateral rolandic and parietal opercula, supramarginal gyrus, right Ins, and adjacent putamen (Friebel et al., 2011). When comparing neuropathic pain patients with pain-free, the analysis revealed significant activation in regions such as the right supplementary motor area (SMA), MCC, right ACC, aIns, and Thal. These findings underscore the consistent activation of the primary SI in response to thermal stimuli. Notably, the ACC showed prominent activation in patients with chronic neuropathic pain, particularly during thermal pain.

Several factors contribute to the heterogeneous findings reported in the literature. Some of these factors are challenging to address in meta-analyses due to the potential loss of experiments and statistical power (Müller et al., 2018). The main variables include differences in the aetiology, intensity, and modality of pain stimuli, as well as the body site affected (e.g., clinically affected or unaffected regions) (Wager et al., 2013; Geraghty et al., 2021; Nicholas et al., 2019; Tanasescu et al., 2016). Additionally, the methodological approaches used to analyse data can significantly influence the outcomes (Eickhoff et al., 2012; Tench et al., 2013). These challenges highlight the importance of enhancing sensitivity to improve the identification of

reliable pain biomarkers associated with chronic pain. A careful selection and consideration of these variables are essential, striking a balance between achieving homogeneity and maintaining statistical power (Müller et al., 2018).

2.6. Activation likelihood estimation

The expanding body of fMRI literature underscores the importance of standardised statistical methodologies in meta-analyses to ensure robust and reliable results (Eickhoff et al., 2016; Müller et al., 2018). This has led to adopting statistical techniques such as the FDR (Laird et al., 2005b). However, concerns regarding FDR's susceptibility to generating spuriously significant clusters have prompted scrutiny of its effectiveness for interpreting fMRI data (Chumbley and Friston, 2009; Tanasescu et al., 2015; Eickhoff et al., 2016, 2012).

On the other hand, the ALE method was developed initially based on permutation-derived p-values, ALE has evolved into a random-effects model that enhances statistical precision by modelling activation patterns across experiments (Turkeltaub et al., 2002; Eickhoff et al., 2009). Contrast analysis was later reintroduced to function with random effects, improving the method's flexibility (Eickhoff et al., 2011), detailed can be found in section 1.4.3. Further refinements included adjustments to MA images to limit the influence of experiments with excessive foci, alongside recommendations for re-evaluating datasets to minimise redundancies (Turkeltaub et al., 2012). Additionally, cFWE and vFWE corrections were introduced to offer high sensitivity and spatial specificity. Among these, cFWE is recommended for its optimal performance in many applications (Eickhoff et al., 2012; Turkeltaub et al., 2002; Xu et al., 2020; Frahm et al., 2022). These advancements highlight that the choice of statistical method, threshold, and the number of studies included are critical factors influencing the outcomes of meta-analyses, particularly in chronic pain research (Eickhoff et al., 2016; Müller et al., 2018; Laird et al., 2005b).

2.7. Rationale of the present study

Neuroimaging meta-analysis is a critical tool for addressing heterogeneity in chronic pain research, identifying inconsistencies, and enhancing statistical power. To bridge gaps in

meta-analyses exploring neural pain substrates of chronic pain population. This study leverages the new chronic primary pain classification system to address pathophysiological inconsistencies while adhering to recommended best practices in neuroimaging meta-analysis (Wang et al., 2022; Müller et al., 2018; Lindquist and Mejia, 2015). Our investigation builds on prior research, comparing classifications of chronic pain conditions with pain-free individuals during provoked pain (Xu et al., 2021; Friebel et al., 2011; Tanasescu et al., 2016; Giesecke et al., 2004; Russo et al., 2012; Burgmer et al., 2012; Bouhassira et al., 2013). Prior work reveal discrepancies possibly rooted in the unique pathophysiological mechanisms underlying specific conditions (Scholz et al., 2019).

For example, while some meta-analyses report consistent activation in areas such as the Ins, striatum, and supramarginal gyrus (Wang et al., 2022; Wager et al., 2007; Tanasescu et al., 2016), others observed aberrant activity patterns or even the absence of activation in these regions (Jensen et al., 2016; Xu et al., 2021). Such variability is further compounded by factors including gender bias, sample population characteristics, differing statistical methodologies, the diversity of pain paradigms, and limited sample sizes. These challenges highlight the intricate and multifaceted nature of chronic pain research. The present meta-analysis examines pain classification, patient demographics, and methodological differences to identify contributors to pain processing and their influence on chronic primary pain during provoked pain.

To the best of our knowledge, we conducted the first meta-analysis to consider chronic primary pain as a new diagnosis, specifically within the realm of provoked pain (Wang et al., 2022). The primary objective is to identify distinct BOLD signal patterns associated with provoked pain versus no pain (e.g., rest or innocuous stimuli) in chronic primary pain patients compared to pain-free individuals. Using CBMA, we applied both cFWE and vFWE corrections to account for multiple comparisons. This dual approach ensured statistical robustness for both within-subjects (e.g., pain versus no pain) and between-subjects experiments (e.g., patients versus pain-free individuals), preserving the integrity of the meta-analytic results.

In line with contemporary best practices in the field (Nicholas et al., 2019; Lobo et al., 2023; Müller et al., 2018; Eickhoff et al., 2016; Lindquist and Mejia, 2015), we implemented rigorous

statistical controls to enhance reliability. We anticipated spatial convergence within the pIns, given its central role in the cortical pain matrix and its involvement in pain localisation and perception (Bergeron et al., 2021; Tanasescu et al., 2016; Xiang et al., 2018). Additionally, we conducted a meta-analysis of pain ratings between patients and pain-free, examining study heterogeneity, potential moderating effects, and methodological discrepancies.

This comprehensive and tailored clinical approach aims to improve the robustness and validity of chronic pain research by addressing methodological inconsistencies and shedding light on the complex nature of chronic pain. By identifying neural markers of chronic primary pain while using rigorous analytical methods, this work seeks to advance our understanding of chronic pain pathophysiology by identifying shared neural activity responses to provoked pain.

2.8. Methods

2.8.1. Pre-registered feasibility study

According to the 10 rules for neuroimaging meta-analyses, 17-20 contrasts are required to perform a well-powered meta-analysis on neural data (Müller et al., 2018). Hence, we identified nine studies satisfying the chronic primary pain classification and selection criteria, which allowed us to analyse 17 experiments in a pilot study (Turkeltaub et al., 2012). This recommended step was made to help identify where the P-value threshold should be set (i.e., between 0.007 and 3.67E-09 in the CG), minimise "within-group" effects, and avoid over-sampling experiments from studies. The following procedures and analyses conducted in this meta-analysis were pre-registered on PROSPERO (ID: CRD42022303560), completed on 30 Dec 2023. This ensures transparency and adherence to predefined research protocols; a practice increasingly recognised as crucial in neuroimaging meta-analyses (Hardwicke and Wagenmakers, 2023).

In total, we identified 48 articles, a total of 75 experiments that followed the Preferred Reporting Items for systematic review and meta-analysis, reporting guidelines (Page et al., 2021) see Figure 9. All our data and relevant materials are accessible in the Open Science Framework (OSF) repository (`https://osf.io/xjbg2/`). By making our data accessible in

the OSF repository, we embrace open science principles and collaborative advancements in neuroscience.

2.8.2. Literature search and selection

Literature search included all the fMRI studies on chronic primary pain; fibromyalgia, chronic lower back pain, IBS, and migraine before 10 Jan 2024, performed by KA.

We selected databases that offer a comprehensive coverage of neuroscience and pain research literature (Scopus and EBSCOhost which includes APA PsychArticles, APA PsychInfo, CINAHAL, and MEDLINE). No date limit was set. Hand-searching process, forward and backward searching was conducted, aimed to capture potentially overlooked but relevant studies, thus maximising the breadth of our analysis.

Given the extensive range of our search terms, (details of Keywords and stopping rule in, https://osf.io/xjbg2/). We ensured a comprehensive capture of relevant literature. The cut-off (stopping rule) date for our search (10 Jan 2024) was strategically chosen to include the most recent studies while allowing sufficient time for analysis.

The eligibility was based on titles and abstracts, according to the inclusion and exclusion criteria. If this was unclear, full-text screening or a discussion between KA, PH, and EV would take place until a consensus is reached. The full-text screening of the final studies was performed by the authors of the review and MSc student AE. Any disagreements were resolved through a discussion.

Inclusion Criteria

Adhering to recent guidelines for neuroimaging meta-analysis (reference), inclusion criteria were as follows (Müller et al., 2018):

1. The study was peer-reviewed and in English.

2. The study assessed BOLD activity with fMRI and reported the specific coordinates of activated brain regions as (*x, y, z*) OR provide behavioural data (e.g., pain rating, depression, and anxiety).

3. The study included at least one chronic primary pain condition (i.e., fibromyalgia, IBS, migraine, and chronic low back pain).
4. The study provided between-group (i.e., patients versus pain-free) or within-group (i.e., pain versus resting state) experiments.
5. The study delivered experimental pain (e.g., mechanical or thermal) to all participants.
6. The study only included participants aged 18 years or older.
7. The reported results included the whole-brain or almost complete brain coverage (missing only one or two slices).
8. The study include at least 5 participants of patients and pain-free.

Exclusion Criteria

1. The study did not directly focus on the experience of pain *tout court* but instead investigated the effects of an independent variable (e.g., social pain, anticipation of pain, or pharmacology) on pain.
2. The study applied masks to the images, seed-based approach, ROI, or volumes of interest.
3. Studies reporting only resting-state fMRI for patients.

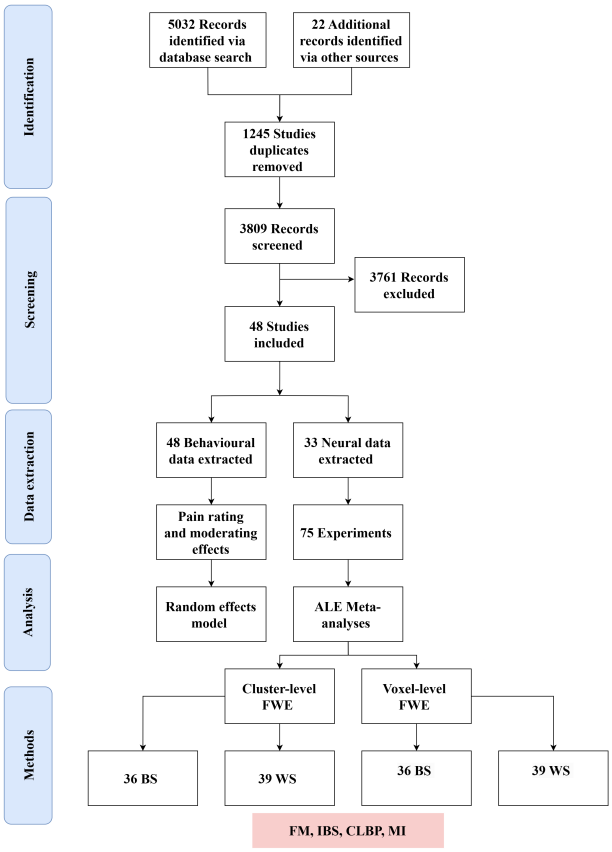

Figure 9: PRISMA flowchart detailing the screening process and meta-analyses methods. In total, 75 experiments from 48 articles were included in the meta-analysis. *Abbreviations*: PRISMA, Preferred Reporting Items for systematic review and meta-analysis; ALE, Activatied likelihood estimation; FWE, Family wise error; BS, Between-subjects; WS, Within-subjects; FB, Fibromyalgia; IBS, Irritable bowel syndrome; CLBP, Chronic Low Back Pain; MI, migraine

2.8.3. Inter-rater Reliability

The above databases returned titles and abstracts screened by four reviewers for initial eligibility (KA, JD, AE, EV, and PH), followed by full-text screening for potential article inclusion (KA). The Inter-rater Reliability (IRR) was calculated to ensure consistency and reliability of the study selection (Ekhtiari et al., 2022; Hartling et al., 2012; Moons and Vandervieren, 2023). The IRR was conducted during full-text screening stage of the potential studies that were considered to be included (n = 87) (Belur et al., 2021). Each rater independently full-text screened the selected studies to measure the agreement or consistency among different raters.

All eighty-seven were assessed for IRR (To view full scores, see OSF, IRR scores: https://osf.io/8rb65). The consistency of raters' responses between four raters from the initial selected 87 articles resulted in a Fleiss' Kappa of 0.52, indicating "moderate agreement". Any disagreements were resolved over a discussion between (KA, AE, EV, and PH).

Once the studies were finalised, data extraction and quality assessment were performed, in the next section. Data was manually extracted by at least one author and independently checked by a third party, ensuring all included studies met the inclusion criteria. Disagreements during this phase were also resolved by discussion between authors. The decisions made were documented in a report which was reviewed and discussed among the authors.

2.8.4. Data Extraction and Quality Assessment

Once final agreements on the articles to be included were reached, data extraction and quality assessment were performed by at least one author and independently verified by a third party (PH). In cases of disagreement regarding data extractions were recorded in a report that was discussed among the authors.

The extracted information for analysis included imaging results as coordinated clusters [*x, y, z*] in voxels, which were used for analyses. The fMRI studies consisted of pain paradigms such as thermal, mechanical, or electrical. The selection of provoked pain does not directly reflect the patient's clinical pain however it may heighten neural activity within the pain matrix, similarly to both clinical and pain-free populations (Geha and Waxman, 2016; Wager et al., 2013). This, in turn, helps clarify the structures shared between chronic pain and pain-free states during provoked pain, as well as the distinct structures in the pain matrix observed in chronic primary pain that may be relevant to the chronic ongoing pain.

We further extracted demographic variables, pain stimulus type, specific characteristics of the patients, medication, experimental class of included papers, behavioural data extraction (e.g., depression and/or anxiety), and average pain rating. If this information was not provided in the methodology, the corresponding author was contacted to obtain it. We contacted authors to request unpublished results, clarify data, and verify findings (Meursinge Reynders et al., 2017).

If a study induced different types of pain (e.g., electrical and thermal), these were treated as

separate data entries. We identified (k = 1) study that administered incision pain, (k = 9) electrical pain, (k = 18) thermal pain, (k = 26) mechanical pain.

The names of the depression scales used across studies included the Hospital Anxiety and Depression Scale (HADS) (k = 13), Beck's Depression Inventory (BDI) (k = 7), Depression score (k = 3), Depression not measured (k = 28), The Center for Epidemiologic Studies Depression Scale (CES-D), (k = 1), HADS anxiety (k = 12), Beck Anxiety Inventory (BAI) (k = 1), The State-Trait Anxiety Inventory (STAI) (k = 4), Anxiety score (k = 4), and Anxiety not measured (k = 26), see Table 5 & 6, for chronic pain conditions (chronic primary pain cond.) column, 1 = IBS, 2 = FB, 3 = CBP, and 4 = MI.

We extracted the following information from all included studies: study title, authors, number of patients and healthy participants, age, gender, pain modality, pain ratings, and psychological well-being scores (i.e., depression or anxiety; see Table 2). There were some differences in how pain was assessed across the studies (e.g., different rating scales). Most studies provided scores that ranged from 0 to 10 (i.e., no pain to extreme pain) on a numerical scale. Some studies did not provide pain rating scores or did not collect any pain ratings (k = 19).

For each selected study, we assigned a score according to the Downs and Black checklist for quality assessment (Downs and Black, 1998). This tool assesses the methodological quality of different studies. We focused on one item from the checklist: "Was there an adequate adjustment for confounding in the analyses from which the main findings were drawn?" This question revealed significant discrepancies across studies. Thus, confounding variables, such as psychological factors, medication, age, and gender, were described and taken into account for each study. The scores were either 0 = "No or Unable to determine" if the study did not report the variable, or 1 = "Yes," with the highest score suggesting good quality of external and internal validity (Ayoub et al., 2018; Raimo et al., 2021), see eTable B_D, in https://osf.io/hnmk5.

Table 5: **Studies Included in the Meta-analyses.**

Study	**# CPP (Pain-free)**	**M age CPP (Pain-free)**	**CPP cond.**	**Med.**	**# exp. sess. (days)**	**# con-trasts CPP**	**Dep. M CPP (Pain-free)**	**Dep. SD CPP (Pain-free)**	**Anx. M CPP (Pain-free)**	**Anx. SD CPP (Pain-free)**	**Pain rating (ES)**
Bouhassira 2013	10(11)	41.7(41.5)	1	NONE	2/3(1)	1	2.6(1.2)	1.3(4.4)	9.4(7.4)	4.5(2.7)	-0.33
Burgmer 2011	17(17)	52.59(49.53)	2	NONE	1/4(1)	2	21.24(9.65)	7.87(4.05)	21.24(9.65)	7.87(4.05)	0.98
Hall 2010	8(6)	39(45.8)	1	NONE	1/1(1)	2	N/A	N/A	N/A	N/A	.99
Gracely 2002	16(16)	52.6(45.8)	2	YES	1/1(1)	2	NONE	NONE	NONE	NONE	-0.69
Elsenbruch 2010	15(12)	42.4(31.4)	1	NONE	3/3(3)	2	3.9(1.7)	3.87(1.38)	7.4(4.6)	3.87(2.42)	1.11
Jensen 2009	16(16)	44(33)	2	NONE	1/1(1)	1	NONE	NONE	NONE	NONE	1.55
Baliki 2006	13(11)	49.2(48.7)	2	N/A	4/2(2)	1	10.9(6.5)	10.6(7.7)	12.6(5.9)	9.5(6.2)	-0.15
Cook 2004	9(9)	37(35)	1	NONE	2/2(7)	2	8.4(2.4)	7(2)	30.2(25.2)	3(4)	1.01
Geisecke 2004	16(11)	44,45(41)	2	NONE	1/2(1)	N/A	11.5(4.8)	7.5(5.9)	18.5(1.5)	4.4(4.4)	0.4
Hubbard 2020	38(15)	46.1(45.53)	2	YES	1/1(1)	2	NONE	NONE	NONE	NONE	0.22
Kano 2018	27(33)	22(22.3)	1	N/A	3/3(3)	2	38.4(36)	8.9(6.4)	42.4(36.4)	12.3(6.08)	0.36
Li 2018	16(16)	41.6(31.3)	3	NONE	1/1(1)	2	NONE	NONE	NONE	NONE	2.77
Matsuo 2017	11(13)	48(34)	3	NONE	1/1(1)	3	NONE	NONE	NONE	NONE	0.98
Pajul 2009	9(9)	47.9(47.2)	2	YES	1/1(1)	N/A	13.4(10.3)	4(4.7)	13.4(10.3)	4(4.7)	-0.16
Schwedt 2014	25(27)	36.2(33.7)	4	NONE	1/3(7)	2	2.8(4.7)	N/A	25.4(25.7)	N/A	NONE
Derbyshire 2002	16(16)	45.4(35.6)	3	NONE	1/1(1)	4	4.1(2.9)	2.4(2.5)	7.3(5.6)	2.9(2.9)	1.03

Table 6: **Studies Included in the Meta-analyses.**

Study	**# CPP (Pain-free)**	**M age CPP (Pain-free)**	**CPP cond.**	**Med.**	**# exp. sess. (days)**	**# con-trasts CPP**	**Dep. M CPP (Pain-free)**	**Dep. SD CPP (Pain-free)**	**Anx. M CPP (Pain-free)**	**Anx. SD CPP (Pain-free)**	**Pain rating (ES)**
Sidhu 2003	8(8)	28.5(28.5)	1	N/A	1/1(1)	2	NONE	NONE	NONE	NONE	N/A
Bonaz 2002	12	48	1	NONE	2/2(7)	N/A	63.4	7.4	58.5	8.2	N/A
Callan 2013	13(13)	51.8(48.7)	3	NONE	1/2(1)	2	NONE	NONE	NONE	NONE	N/A
Ellerbrock 2021	84(43)	47.2(48.1)	2	N/A	1/1(2)	N/A	7.2(0.5)	4(1.4)	7.9(3.1)	4.3(2.9)	2.79
Wong 2014	13(11)	37.2(37.1)	1	NONE	1/2(2)	N/A	4.7(2.8)	NONE	9.3(4.4)	NONE	2.79
Foss 2006	11(6)	37(34)	3	NONE	4/3(1)	N/A	NONE	NONE	NONE	NONE	N/A
Verne 2001	12(17)	31(31)	1	NONE	1/1(1)	N/A	7.4(4.0)	4.6(5.1)	40.9(30.4)	14.1(8.4)	0.78
Bouin 2002	86(25)	44.9(39)	1	N/A	2/1(1)	N/A	7.4(4.0)	4.6(5.1)	40.9(30.4)	14.1(8.4)	N/A
Mosch 2023	22(21)	50(47)	2	NONE	3/2(3)	4	NONE	NONE	NONE	NONE	0.42
Kwan 2005	9(11)	37.8(31.7)	1	NONE	2/2(3)	N/A	NONE	NONE	NONE	NONE	0.18
Lopez-sol 2017	37(35)	46.27(43.86)	2	NONE	2/1(1)	N/A	8.89	4.72	11.54	4.15	1.40
Yuan 2003	26(11)	47(39))	1	N/A	1/2(1)	N/A	8.89	4.72	11.54	4.15	0.02
Lawal 2005	10(10)	28.5	1	N/A	N/A	N/A	NONE	NONE	NONE	NONE	N/A
Chen 2015	15(20)	28.13(28.1)	4	NONE	1/1(5)	3	9.2(2.7)	5.97(2.43)	6.47(1.45)	3.87(1.7)	N/A
Russo 2012	16(16)	27.83(27.5)	4	NONE	1/3(7)	6	NONE	NONE	NONE	NONE	N/A
Guleria 2017	20(10)	30.5,27.5(28.5)	1	NONE	1/1(1)	7	NONE	NONE	NONE	NONE	NONE

Table 7: **Studies Included in the Meta-analyses.**

Study	**# CPP (Pain-free)**	**M age CPP (Pain-free)**	**CPP cond.**	**Med.**	**# exp. sess. (days)**	**# con-trasts CPP**	**Dep. M CPP (Pain-free)**	**Dep. SD CPP (Pain-free)**	**Anx. M CPP (Pain-free)**	**Anx. SD CPP (Pain-free)**	**Pain rating (ES)**
Russo 2016	20 (20)	32.1,31(28.2,29.2)	4	NONE	2/3(3)	2	4.2(3.3)	2.68(1.34)	6.5(4.8)	2.68(1.8)	N/A
Russo 2019	18, 17(15)	30.05,32.74(27.4)	4	NONE	2/2(4)	2	5.11,4.79	3.47,3.13	5.71,5.94	4.07,3.66	N/A
Stankewitz 2011	20,10,13(20)	29.5,32.5,33(27.5)	4	NONE	1/2(1)	2	NONE	NONE	NONE	NONE	-0.15
Maleki 2021	19	42.65	4	YES	2/2(1)	2	NONE	NONE	NONE	NONE	N/A
Mungoven 2022	25(29)	29.6(26.4)	4	YES	1/1(1)	1	NONE	NONE	NONE	NONE	N/A
Schulte 2020	7	31.29	4	NONE	N/A	2	NONE	NONE	NONE	NONE	N/A
Tessitore 2011	16(16)	27.8(27.5)	4	NONE	3/3(1)	N/A	NONE	NONE	NONE	NONE	N/A
Weissman 2003	34(28)	25.6(24.8)	4	NONE	1/1(7)	N/A	NONE	NONE	NONE	NONE	2.75
Maleki 2012	22(22)	42(42.65)	4	YES	1/3(1)	1	3.8(2.2)	4.0(3.8)	NONE	NONE	N/A
Buchgreitz 2006	60	50.5	4	N/A	1/1(1)	N/A	NONE	NONE	NONE	NONE	N/A
Bogdanov 2019	14(24)	33.2(41.5)	4	YES	1/2(1)	1	NONE	NONE	NONE	NONE	N/A
Rosenberger 2012	15(12)	42.4(31.4)	1	NONE	1/1(2)	2	NONE	NONE	NONE	NONE	1.89
Wasan 2011	16(16)	47.4(46.7)	3	N/A	1/3(1)	1	NONE	NONE	NONE	NONE	N/A
Jensen 2010	83(13)	43.8	2	NONE	1/1(2)	1	NONE	NONE	NONE	NONE	0.47
Kobayashi 2009	6(8)	33(29)	3	N/A	2/2(1)	2	NONE	NONE	NONE	NONE	2.52
WilderSmith 2004	10(10)	35(31)	1	NONE	8/1(7)	N/A	NONE	NONE	NONE	NONE	NONE

2.8.5. *Coding and Data Preparation*

Two coders (KA, JD) independently coded the data using the BrainMap software. The coding went through three software processes provided by BrainMap (Laird et al., 2011). First, we used Scribe software to encode the description and neural coordinates of each article into the BrainMap database (KA, JD). Second, I used Sleuth software to search the articles saved in the previous step, create a workspace, and view the coordinates. Third, I used GingerALE software (version 3.0.2) to perform ALE meta-analysis on coordinates in Talairach space. Since unbalanced number of patients and pain-free within experiments may lead to bias in the between-subject results (Xu et al., 2020), I selected the smaller subject size for both group. This was a more conservative approach when we encountered studies with unequal sample sizes, to ensure studies are less influenced by foci obtained from small studies (Eickhoff et al., 2009). We will use ANIMA to publish our results, thus fostering transparency and sharing of analytical tools to enable others to replicate or build on our research (Reid et al., 2016a,b).

2.8.6. *Activated Likelihood Estimation*

GingerALE is a software on Brainmap that employs ALE, used previously (Laird et al., 2010; Eickhoff et al., 2017; KHON). In this review, initially we used $p = 0.05$ cluster-level correction, which is a commonly used threshold (pre-registered). However, to increase the sensitivity of the outcomes, we amended this and used a smaller threshold. We conducted multiple comparisons of cluster-level corrected $p = 0.01$ for FWE, cluster-forming $p = 0.001$ (Lobo et al., 2023; Tahmasian et al., 2019). For vFWE, and threshold of $p = 0.05$ (Eickhoff et al., 2016). Both methods used threshold permutation of 1000 and minimum volume of 200.

We performed CBMA to find regions of consistent activation in response to provoked pain in chronic primary pain patients and Pain-free. The ALE method employs a Gaussian function with a defined Full width at half maximum (FWHM) to represent the uncertainty associated with the reported foci. The modelled activation maps are developed from centring Gaussian distributions of a FWHM value which is calculated based on sample sizes from each experiment, at the location of foci (Eickhoff et al., 2009). Notably, larger sample sizes in studies produce smaller FWHMs (Eickhoff et al., 2009). The average of standard deviation reflects the

distribution of the contributing foci to a peak location, corresponding to a FWHM value (Eickhoff et al., 2016).

The choice of applying ALE method over other meta-analysis methods was guided by its suitability for neuroimaging data (i.e., *x, y, z*; neural coordinates). We converted the neural coordinates from MNI to TAL space. The ALE procedure consisted of computing ALE values for each voxel, testing the null distribution of the ALE statistic at each voxel, and determining the threshold for the ALE image using a *p*-value or permutation-based FWE. The adoption of both, cFWE and vFWE, statistical approaches offered advantages for each method, allowing us to mitigate potential biases and enhance the reliability of our findings.

Single dataset meta-analysis was performed using each correction method (i.e., cFWE, vFWE) separately, patients, pain-free, and pooled. To obtain these results, the single dataset analysis which generated an ALE output file from each dataset (patient, control, and pooled) were loaded as inputs into a contrast analysis comparing them to each reference image on a voxel-level within a new group of contrasts, generating a distribution showing how frequently the permutation had a higher or lower effect than the reference image.

We computed meta-analysis of contrast datasets to obtain contrast and conjunction images. The contrast images *p*-value and Z scores are calculated by using the experiment-level MA images from the pooled datasets. By separating the pooled into two new groups with the same size as the groups in the dataset. These two groups form two new ALE images which undergo a subtraction process. Finally, the generated subtraction (e.g., patients) is compared against the other subtraction image (e.g., pain-free). This process repeats across multiple permutations and records values, each time the data value is larger than the generated data (Eickhoff et al., 2011). Contrasts dataset analysis process is done to create an analysis mask and identify structures that spatially converge in both patient and control datasets. This helps to avoid missing sub-threshold structures and overlooked relevant structures by combining the two datasets. Thus, for this analysis, we used $p = 0.05$ for FWE correction, *p*-value permutations of 10000 and min volume mm^3: 200.

We calculated 13 meta-analyses across within-subjects and between-subjects experiments using

two methods (i.e., cFWE and vFWE). Seven meta-analysis for the within-subjects experiments using two different cFWE and vFWE, which consisted of conjunction, contrasts, patients (k = 21), pain-free (k = 18), and pooled datasets (k = 39). We calculated six meta-analysis for the between-subjects experiments using cFWE and vFWE, which consisted of patients (k = 21), pain-free (k = 15), and pooled (k = 36).

2.8.7. Different Meta-analytic Groupings

Meta-analyses were grouped (pooled) based on the number of experiments. Separate analyses were conducted for (>17) experiments, while fewer experiments (<17) were pooled together (Eickhoff et al., 2016). Combined analysis used pooled between-subjects datasets of patients and pain-free (Müller et al., 2017), see section 2.8.7. If the experiments were less than (k =17, e.g., between-subjects analysis: pain-free (k = 12) we combined it into a single experiment; (e.g., pooled, k = 35), rather than patients compared to pain-free. Hence, combined analysis was conducted using the pooled datasets of the between-subjects analysis to report all experiments together (Müller et al., 2017). This step was made to reduce the possibility for the results to be influenced by single experiments (Müller et al., 2017; Eickhoff et al., 2016).

We accounted for multiple contrasts to avoid negatively impacting the results (Müller et al., 2018, 2017), the aim of this meta-analysis is to investigate the convergent activity in chronic primary pain elicited by varied experimental pain (Cieslik et al., 2015; Müller et al., 2018). This was done by treating two experiments as one from a study. For example, if a study chronic primary pain population underwent two experiments of heat stimuli at different temperatures (e.g., 53 degrees for moderate pain and 51 degrees for severe pain), we combined both contrasts as one (e.g., 53 degrees) (Russo et al., 2012). To ensure that the experiments are relatively well distributed, not affected by single studies, and to deal with the within-group effects (Turkeltaub et al., 2012).

2.8.8. Behaviour Data Analysis and Assessment of Publication Bias

To analyse the behaviour data we performed a multilevel random effect meta-analysis in *R* using the package metafor (Viechtbauer, 2010). This approach was chosen for its ability to manage

within- and between-study variances, which is crucial for our diverse dataset. In a case where a study included different chronic pain samples compared to the same control group, we treated it as two studies (e.g., study 1: chronic pain group 1 versus pain-free, study 2: chronic pain group 2 versus pain-free). A forest plot was created to summarise pain rating effect sizes and confidence intervals. Additionally, we report prediction intervals which indicate the range of effects in future similar studies (Nagashima et al., 2019). To assess publication bias we used Egger's test, ensuring robustness in our meta-analytical conclusions (Dowdy et al., 2022; Sterne and Egger, 2001). Finally, we explored the moderating effects of age, gender, depression, and anxiety on pain perception between patients and pain-free.

2.9. Results

This meta-analysis included 48 articles comprising a total of (k = 75), of which (k = 39) within-subjects and (k = 36) between-subjects experiments. The combined sample size was (n = 2,052 participants), including (n = 1,206 patients and (n = 846 pain-free). Following chronic primary pain classification, the number of studies of chronic pain conditions included in this review were IBS; k = 16, MI; k = 14, FB; k = 11, and chronic lower back pain; k = 7.
We conducted 13 meta-analyses across the within-subjects and between-subjects experiments using two correction methods: cFWE and vFWE. Seven meta-analyses were performed for the within-subjects, which included analyses of chronic primary pain (k = 21), pain-free (k = 18), conjunctions, and contrasts (k = 39). For the between-subjects, we performed six meta-analyses of patients (k = 21), pain-free (k = 15), and pooled (k = 36).

2.9.1. Neural data: Chronic primary pain Clusters Summary

The ALE analysis revealed significant clusters identified in the within-subjects experiments when cFWE and vFWE corrections were applied. The highest contributing structures being the Ins and CG. No significant clusters were found in the between-subjects analyses. Figure (10) illustrates the contribution (%) of each structure within a cluster. The Ins consists of several gyri (i.e., anterior, middle, and posterior gyri), while the posterior Ins comprises two long gyri

(Myoraku et al., 2022). Hence, although Ins includes multiple gyri, the table represents information about the identified clusters in terms of specific structures (e.g., Ins; see Table 11). For the clusters identified in the conjunction meta-analysis and contrast meta-analyses of the within-subjects experiments using cluster-level correction, see Table 8.

Cluster	Region	(%) Foci	Max ALE Value	Foci / Exp. (*k*)
Conjunction Analysis				
1	CG (BA 32)	93.6% (61.7%)	0.017	9 / 8
2	Ins (BA 13)	81.8% (81.8%)	0.012	5 / 5
Contrast Analysis (Pain-free > Patients)				
1	MFG (BA 6)	44.4% (44.4%)	0.005	3 / 3
Contrast Analysis (Patients > Pain-free)				
1	Ins (BA 13)	81.4% (81.4%)	0.001	2 / 2
2	Ins (BA 13)	45.5% (45.5%)	0.006	1 / 1

Table 8: Summary of within-subjects Clusters, Conjunction and Contrast meta-analyses (cluster-level)

For the clusters identified in the single meta-analyses of the within-subjects experiments using cluster-level correction, see Table 9. For the clusters identified in the within-subjects and between-subjects experiments using voxel-level correction, see Table 10. A more detailed description of all the identified clusters can be found in Table 11.

Cluster	Region	(%) Foci	Max ALE Value	Foci / Exp. (k)
Patients Meta-Analysis of within-subjects				
1	Ins (BA 13)	57.2% (57.2%)	0.020	16 / 13
2	CG (BA 32)	95.4% (77.8%)	0.023	10 / 8
3	Ins (Ins) (BA 13)	77.5% (73.8%)	0.020	11 / 7
Pain-free Meta-Analysis of within-subjects				
1	CG (BA 24)	71.9% (53.9%)	0.025	10 / 7
2	Ins (BA 13)	93.5% (80.6%)	0.014	6 / 6
Between-subjects experiments				
No clusters identified				

Table 9: Summary of within-subjects Clusters, Single meta-analyses chronic primary pain and pain-free (cluster-level)

Cluster	Region	(%) Foci	Max ALE Value	Total Foci (k) / Exp. (k)
Pain-free Meta-analysis of within-subjects				
1	CG (BA 24)	73.7% (73.7%)	0.025	4 / 4
Patients, Conjunction, Contrast of within-subjects				
No clusters identified				
Patients, Pain-free, Conjunction, Contrast of between-subjects				
No clusters identified				

Table 10: Summary of Clusters, voxel-level meta-analyses

Table 11: **ALE meta-analyses clusters identified using cFWE and vFWE**

ALE	N	# Foci	# Exp	Cluster	x	y	z	Vol. thresh-old	Chosen min. cluster size	Region	Max. ALE value
Within-subjects cFWE (Conj)	494	450	39	2	1.6	8.2	37.7			CG/MFG	0.017
					33.6	12.3	8			Ins/ Claus	0.012
Within-subjects cFWE (Contrast P>C)	494	450	39	2	38.7	0.9	10.8	1240 mm³	200 mm³	Ins/Claus	0.0017
					-34.2	10.9	-1.7			Ins/Claus/IFG	0.0068
Within-subjects cFWE (Contrast C>P)	494	450	39	1	-.6	4.6	47.2	512 mm³	200 mm³	MFG/CG/SFG	0.0055
Within-subjects cFWE (Patients)	264	260	21	3	36.5	5.9	9.4	8008 mm³	936 mm³	Ins/Claus/LN/PreG	0.020
					2.3	11.4	37.5			CG/MFG	0.023
					-37.4	8.6	1.6			Ins/Claus/IFG/ PreG	0.020
Within-subjects cFWE (Pain-free)	230	190	18	2	1.3	5.6	41.3	3952 mm³	1016 mm³	CG/MFG/SFG	0.025
					36.5	10.7	2.4			Ins/ Claus	0.014
Within-subjects vFWE (Patients)	264	260	21	NONE				0 mm³	200 mm³		
Within-subjects vFWE (Pain-free)	230	190	18	1	1.4	4.2	44.1	376 mm³	200 mm³	CG/MFG	0.025
Between-subjects cFWE (Patients > Pain-free)	259	108	21	NONE				0 mm³	1072 mm³		
Between-subjects cFWE (Pain-free > Patients)	255	45	15	NONE				0 mm³	776 mm³		
Between-subjects cFWE (Pooled)	550	153	36	NONE				0 mm³	888 mm³		
Between-subjects vFWE (Patients > Pain-free)	295	108	21	NONE				0 mm³	200 mm³		
Between-subjects vFWE (Pain-free > Patients)	255	45	15	NONE				0 mm³	200 mm³		
Between-subjects vFWE (Pooled)	550	153	36	NONE				0 mm³	200 mm³		

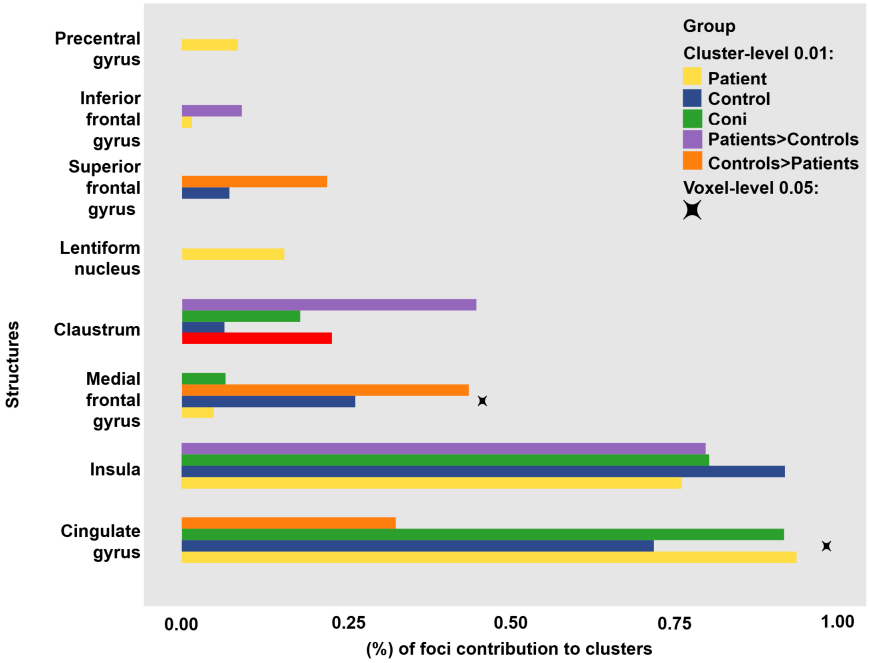

Figure 10: Frequency of reported brain structures across meta-analyses of spatial convergence. Data reflect cluster-level and voxel-level results from within-subject experiments. Each cluster indicates the contribution of a specific brain structure across different groups (e.g., patients or controls). Blue represents controls, yellow represents patients, green represents conjunction, purple represents patient control, orange represents control patient. A star at the end of a bar indicates voxel-level results that survived a threshold of P

2.9.2. Neural results: cFWE, within-subjects experiments

We present the main effects of within-subjects using cFWE and vFWE correction methods in the following sections. For detailed results, including peaks and Z-score images associated with each experiment, please refer to our OSF repository titled "Clusters.docx". Additional materials, including uncorrected image results, supplementary peak files, cluster statistics, and complete data history, are available at https://osf.io/xjbg2/.

The main effects of within-subjects, analysed using cluster-level correction, revealed significant convergences in response to provoked pain. The conjunction analysis, conducted at our preregistered statistical threshold of $p < 0.01$, demonstrated spatial convergence in the daIns and MCC. These convergence patterns are illustrated in Figure 11.

Contrast analyses revealed significant differences between pain-free and patients. Specifically,

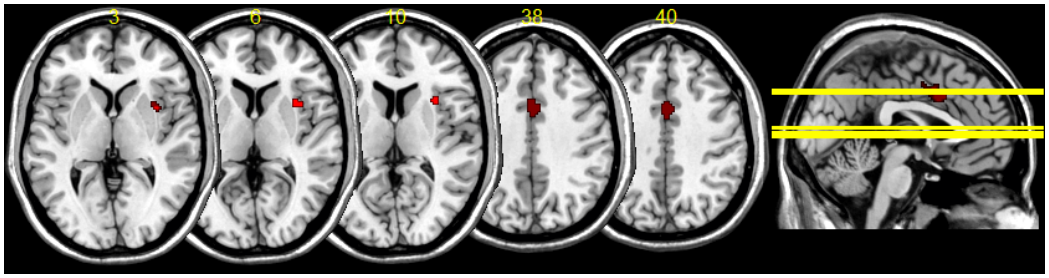

Figure 11: Conjunction map peak coordinates of the within-subjects meta-analysis. Spatial convergence identified in patients and Pain-free during provoked pain in the MCC (0, 12, 34) and daIns (40, 8, 4). Images were thresholded at $p < 0.01$ (cluster-level correction) (Lobo et al., 2023). *Abbreviations*: MCC, mid-cigulate cortex; dorsal anterior Insula, daIns

patients showed greater activation than pain-free in the dorsal anterior insula (daIns) at $p < 0.007$ (see Figure 12) and in the ventral anterior insula (vaIns) at $p < 0.01$. Pain-free partivipants exhibited greater activation than patients in the superior frontal gyrus (SFG) at $p < 0.005$ (see Figure 13).

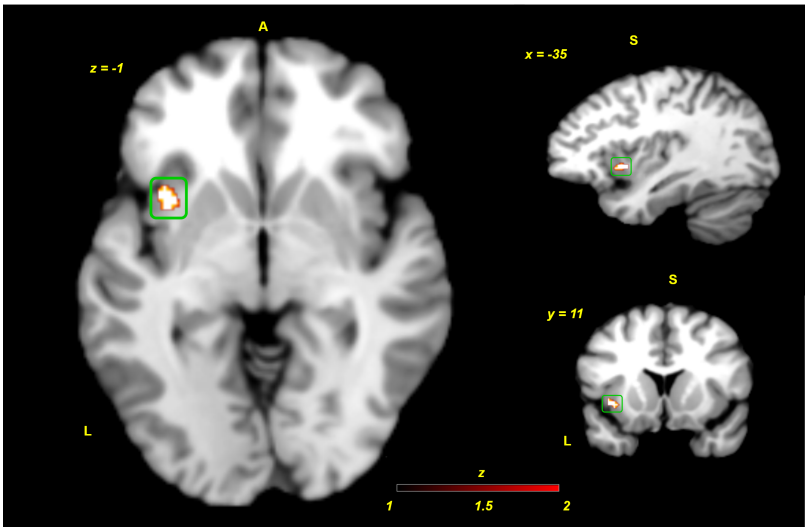

Figure 12: Contrast maps of patients and pain-free (within-subjects). Patients greater than pain-free in the daIns (-35, 11, -1). Images were thresholded at $p < 0.01$ (cluster-level corrected FWE). *Abbreviations*: daIns, dorsal anterior Insula

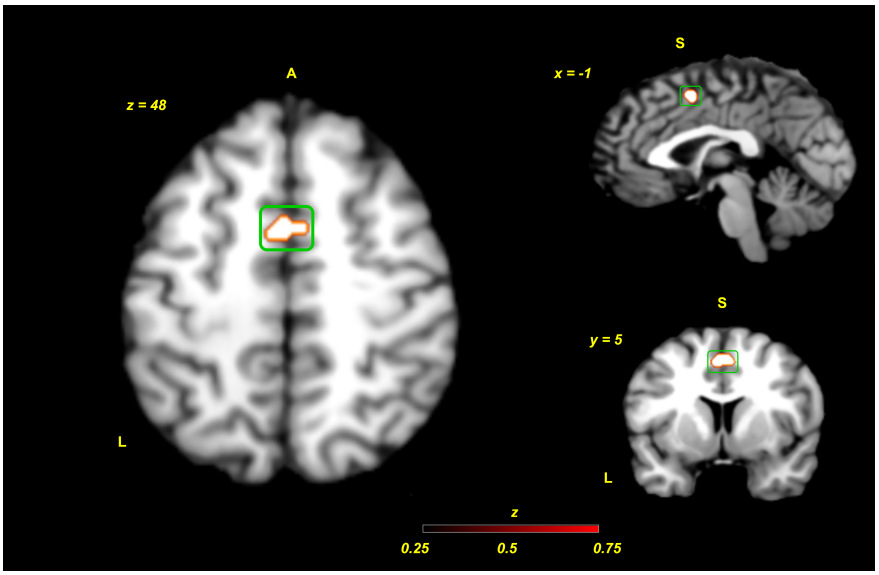

Figure 13: Contrast maps of patients and pain-free (within-subjects). Pain-free greater than patients in the SFG (-1, 5, 48), in green. Images were thresholded at $p < 0.01$ (cluster-level corrected FWE). *Abbreviations*: SFG, superior frontal gyrus

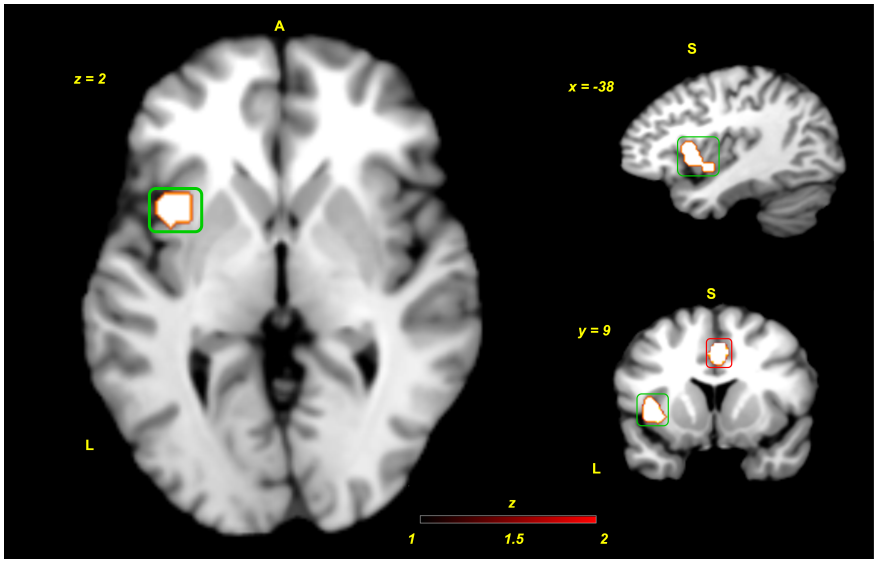

Figure 14: Thresholded images of within-subjects for patients. Coordinate-based meta-analysis of neural response to pain vs rest showing convergences in the vdaIns (-38, 9, 2) in green, ACC and MCC (2, 10, 38) in red (cluster-level corrected FWE). *Abbreviations*: daIns, dorsal anterior insula; vdaIns, ventral and dorsal anterior insula; ventral daIns; MCC, mid-cingulate cortex; ACC, anterior cingulate cortex

A single meta-analysis of patients revealed spatial convergence in the following structures, ACC and MCC at $p < 0.001$, vdaIns at $p < 0.001$ (see Figure 14). For pain-free, spatial convergence was identified in the daIns at $p < 0.001$ (see Figure 15 and Table 11).

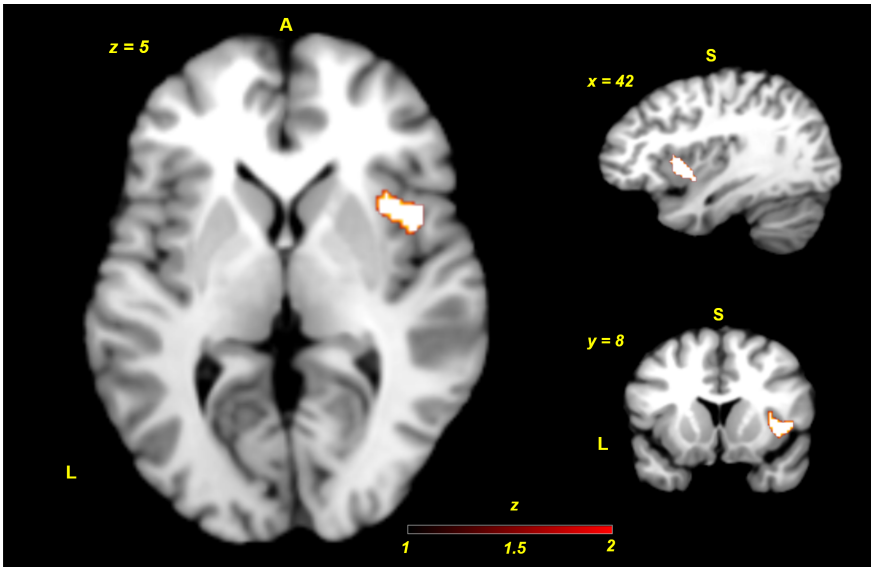

Figure 15: Thresholded images of within-subjects for pain-free. Coordinate-based meta-analysis of neural response to pain vs rest showing convergences in the daIns (32, 16, 14) and Claus (40, 10, 2) (cluster-level correction). *Abbreviations*: daIns, dorsal anterior insula; vdaIns, ventral daIns

2.9.3. Neural results: vFWE and within-subjects experiments

The conjunction analysis of within-subjects, conducted at our preregistered statistical threshold of $p < 0.05$, revealed no spatial convergence. Contrast analyses showed an overlap in WS using vFWE correction, indicating no significant differences observed between patients and pain-free, and vice versa.

A single meta-analysis of patients showed no spatial convergence. In contrast, spatial convergence was identified in the MCC for pain-free at $p < 0.001$ (see Figure 16 and Table 11 for a full list of structures identified in each meta-analysis).

2.9.4. Neural results: cFWE, vFWE, and between-subjects experiments

The main effects of between-subjects using voxel-level correction and cluster-level correction, revealed no spatial convergence in all six meta-analyses.

2.9.5. Within-subjects analysis of chronic primary pain

These results encouraged us to conduct a post-hoc analysis to examine the variations within chronic primary pain conditions and identify which chronic primary pain condition mostly

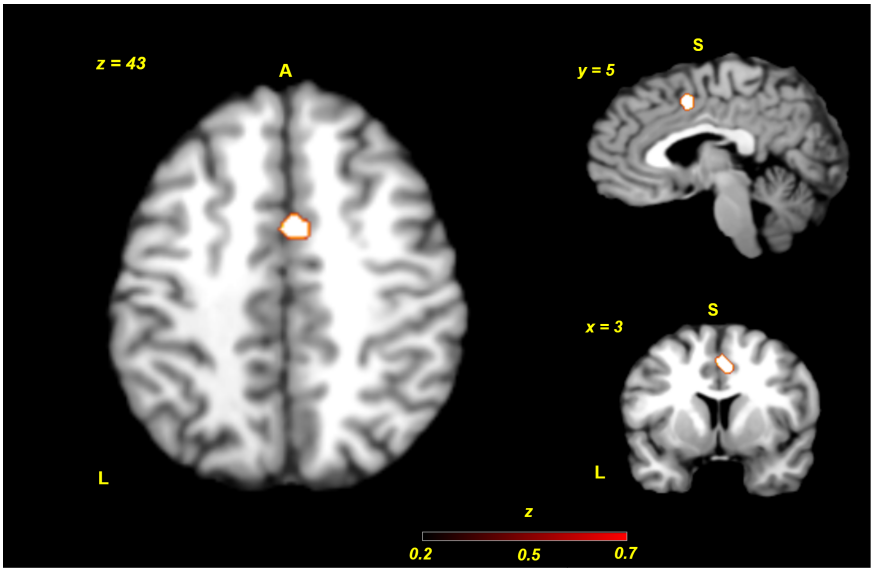

Figure 16: Thresholded images of within-subjects for pain-free. Coordinate-based meta-analysis of neural response to pain vs rest showing convergences in the MCC (1, 5, 45). Images were thresholded at $p < 0.05$ (voxel-level correction). *Abbreviations*: MCC, mid-cingulate cortex

contributed to these results. We chose to focus our analysis on conditions with the highest number of identified studies. The total number of studies of the experiments identified within-subjects was IBS ($k = 5$), fibromyalgia ($k = 5$), migraine ($k = 4$), and chronic lower back pain ($k = 5$). However, this limited number was insufficient, restricting us to conduct a cFWE analysis within subjects within the chronic primary pain conditions. Notably, the number of experiments between subjects was significantly lower than that within subjects.

2.9.6. Behavioural data results

The multi-level random effects meta-analysis estimated effect size for the pain rating between patients and pain-free individuals shows Hedges' $g = 0.71$, 95%-CI [0.29, 1.14], 95%-PI[-1.16, 2.56], $SE = 0.21$, p-value < 0.001, with patients showing higher ratings compared to pain-free, the heterogeneity as assessed by I^2 was 85.39% (see Figure 17). Moreover, the behavioural findings suggest a high heterogeneity between groups and across studies pain ratings (Figure 17).

The Forest plot shows that most effect sizes are positive (Figure 17). Thus, chronic pain patients

experienced more pain during experimental pain, compared to pain-free. Some studies did not provide pain rating scores or did not collect any pain rating (k = 19). Egger's regression test for publication bias indicated no evidence of publication bias, $p < 0.38$ [Kendall's tau = 0.10].

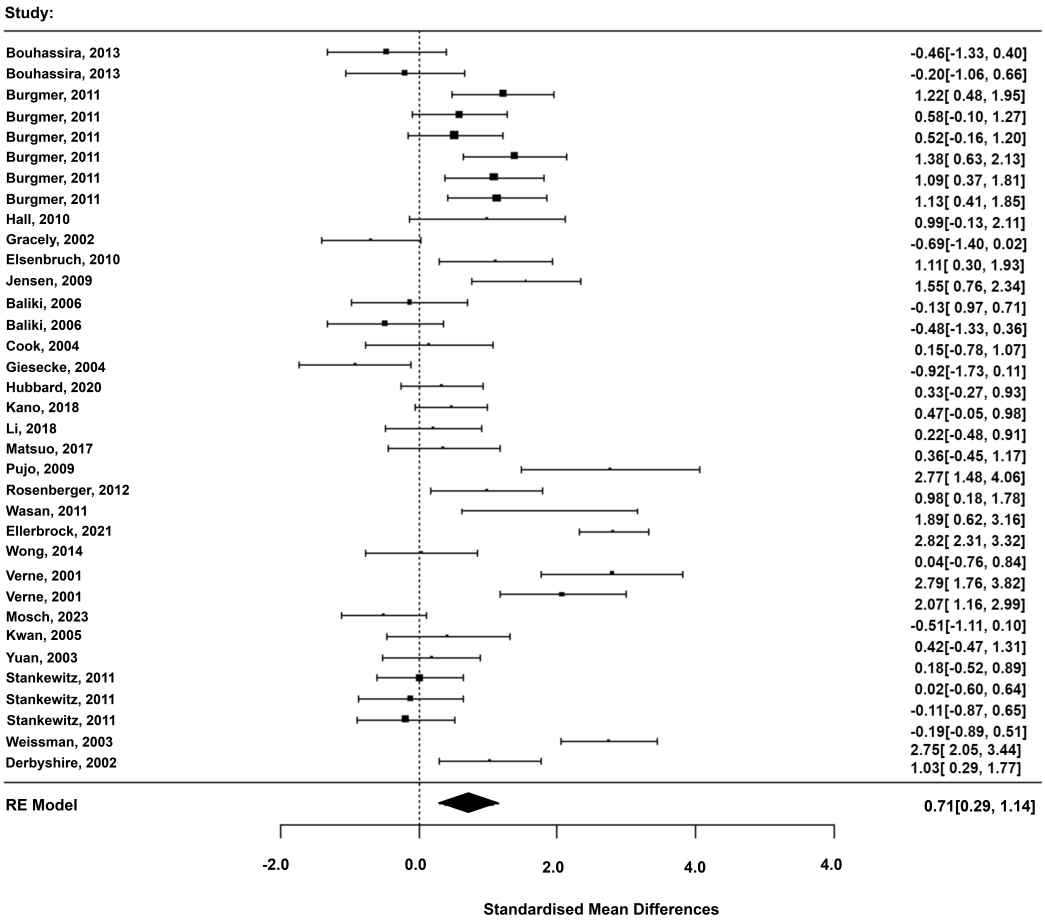

Figure 17: Pain rating effect size between patients and pain-free. Forest plot displaying the effect size(s) of pain ratings per study. Positive effect size indicate higher pain reporting in patients compared to pain-free.

2.9.7. Moderators, confounds, and covariates

The extent of heterogeneity across studies motivated post-hoc analysis of moderator effects. To assess whether psychological, demographic, or methodological differences influence the experience of pain across studies, we tested moderating effects such as age, B = -0.03, SE = 0.02, $p < .18$, 95%-CI [-0.08, 0.01], gender: female, B = 0.03, SE = 0.03, $p < .36$, 95%-CI [-0.03, 0.09], male: B = -0.007, SE = 0.07, $p < .92$, 95%-CI [-0.15, 0.14]. For psychological moderator, depression, B = -0.002, SE = 0.04, $p < .94$, 95%-CI [-0.08, 0.08], anxiety, B = 0.01, SE = 0.03, $p < .69$, 95%-CI [-0.05, 0.07].

For methodological differences, electric stimuli and mechanical stimuli, B = -0.53, SE = 0.40, $p < .18$, 95%-CI [-1.33, 0.25], thermal and mechanical painful stimuli, B = -0.05, SE = 0.41, $p < .90$, 95%-CI [-0.87, 0.76], and painful intensity, B = 0.63 SE = 0.47, $p < .18$, 95%-CI [-0.29, 1.56]. Moderator analysis consistently did not show significant differences that affected pain rating scores.

Together, our findings are robust across a range of potential moderators. The number of sessions of painful stimuli being administered per study showed no significant differences across studies, B = -0.39, SE = 0.25, $p < .12$, 95%-CI [-0.89, 0.11]. Methodological differences, such as days, B = 0.10, SE = 0.13, $p < 0.44$, 95%-CI [-0.16, 0.36], and contrasts (experiments) B = -0.31, SE = 0.31, $p < 0.31$, 95%-CI [-0.94, 0.30], did not moderate pain ratings. Therefore, we found no evidence that psychological variables, demographics, and methodological differences influenced pain scores.

We used the confounding variable extracted from the checklist by Downs and Black (1998) to assess the quality of the included studies by addressing *"The adequacy of adjustment for confounding in the analyses from which the main findings are drawn"*. We tested moderating effects of the confounding variable, B = 0.31, SE = 0.44, $p < 0.48$, 95%-CI [-0.55, 1.17]. In addition, we tested for moderating effects of the year of study publication, B = -0.01, SE = 0.03, $p < .72$, 95%-CI [-0.07, 0.05].

2.10. Discussion

This research investigates the consistent brain responses associated with provoked pain in chronic primary pain. It extends previous meta-analyses by addressing key factors that contribute to the challenge of identifying consistent patterns in chronic pain conditions (Tanasescu et al., 2016; Friebel et al., 2011; Xu et al., 2021; Lanz et al., 2011).

Methodologically, we followed a three-fold strategy. First, we adopted the recent framework of chronic primary pain classification to enhance study inclusivity (Scholz et al., 2019; Nicholas et al., 2019). Second, we conducted separate meta-analyses for within-subjects and between-subjects experiments to improve sample representation (Müller et al., 2018). Third, we

unravelled the spatial convergences by applying rigorous statistical controls for multiple comparisons (Eickhoff et al., 2016).

We controlled for Type I error by using rigorous statistical significance thresholds, employing the cFWE inference approach as the primary method and the more conservative vFWE approach to ensure robust findings (Lobo et al., 2023; Eickhoff et al., 2016). By employing greater methodological rigour than previous analyses (Xu et al., 2021), we enhanced the reliability of our outcomes. Using both method, we did not observe the expected spatial convergence in the pIns among patients (Tanasescu et al., 2016; Horing and Büchel, 2022; Isnard et al., 2011; Garcia-Larrea, 2012).

2.10.1. Summary of Findings

Our findings for the between-subjects meta-analyses suggest a lack of evidence of consistent convergences in patients and pain-free, when applying vFWE and cFWE. Pooled results from between-subjects experiments revealed no convergence differences between groups, using both corrections (Müller et al., 2017). These null results are unlikely due to insufficient statistical power (>17 experiments) or dominance by single studies (Eickhoff et al., 2016). A possible explanation is that neural patterns differentiating groups are widely distributed, or that methodological heterogeneity among studies obscured consistent patterns. These findings underscore the need for more between-subjects experiments in chronic primary pain research using standardised methodologies (Müller et al., 2018).

Moreover, according to Eickhoff et al. (2016), for the vFWE 8 experiments are sufficient to ensure that the average contribution of the dominant experiments are lower than 50%, while the two most dominant represent more than 90%. On the other hand, cFWE requires 17 experiments with the two most dominant represent less than 80% (Eickhoff et al., 2016). We calculated pooled analysis across experiments (k = 36) independent of reporting increase or decrease (e.g., pain greater than rest, and vice-versa) (Müller et al., 2017). Instead, the pooled analysis indicated consistent aberrant activation, while providing the best summary of the findings (Müller et al., 2017). The advantage of this approach is that it ensures the coverage is not driven by single experiments while providing higher power for smaller effects (Eickhoff

et al., 2016). However, this approach may also compromise the homogeneity of the experiments included within the pooled meta-analyses and their quality (Müller et al., 2017).

The heterogeneity surfaced in our meta-analyses across different experiment types (i.e., within- and between-subjects) and methodologies (i.e., cFWE and vFWE). Factors such as methodological differences, pain paradigm (Gao et al., 2022), unequal distribution of chronic primary pain conditions experiments, may have introduced confounding variables contributing to the lack of convergences (Xu et al., 2021). Pinpointing the precise reasons behind the lack of convergences in the between-subjects experiments poses a considerable challenge. The complexity of interpreting these results underscores the need for further research, leveraging the new chronic primary pain diagnosis to ensure findings hold broader meaning and applicability.

In line with previous research, within-subjects findings obtained with the cFWE method showcased patient convergences in various key brain structures, such as the right vdaIns, MCC, ACC, Claus, PreG, MFG, and LN (Xu et al., 2020; Friebel et al., 2011; Duerden and Albanese, 2013; Tanasescu et al., 2016; Jensen et al., 2016; Lanz et al., 2011; Tillisch et al., 2011; Pujol et al., 2009; Melzack, 2001). Nevertheless, we did not observe convergent activity in the pIns, caudate, Striatum, and Thal (Garcia-Larrea, 2012; Friebel et al., 2011; Wang et al., 2022; Duerden and Albanese, 2013). These results may reflect differences in methodological approaches (e.g., task versus rest or statistical methods) (Wang et al., 2022). On the other hand, pain-free demonstrated convergence in distinct regions, such as the right MFG and MCC, using both methods. While cFWE detected additional convergent activity in the SFG, daIns, and Claus. This finding supports the generalised involvement of these structures in pain processing.

We conducted conjunction analyses that revealed overlaps between patients and pain-free, with notable convergences in the right MCC, MFG, daIns, and Claus, challenging previous findings (Xu et al., 2021). Contrast analyses showed differences between patients and pain-free during provoked pain. For patients, we identified greater spatial convergence than pain-free, where two clusters reported in the vdaIns, Claus, and IFG (Peyron et al., 2000). For pain-free individuals, we observed one cluster in the MFG, MCC, and SFG. These findings suggest differences in the vdaIns and MCC between patients and pain-free in pain processing. The contrast and

conjunction findings do not rule each other out. The differences detected in the contrasts—such as stronger patient convergence in the daIns, vdaIns, and Claus—appeared in two clusters compared to pain-free, which showed one cluster in the daIns. Conversely, we only detected the SFG in pain-free, with no activity observed in patients.

Furthermore, while single meta-analyses identified MCC convergence for both groups, we found this activity to be stronger in pain-free, as shown in the contrast meta-analysis ($p < 0.001$). These findings contradict previous research (Xu et al., 2021). One reason for this discrepancy may be our adoption of a stricter sample population, where chronic pain conditions followed a specific chronic primary pain criterion and the specification of experiment-type. Whereas, previous meta-analysis (Xu et al., 2021) included both within-subjects (Bouhassira et al., 2013), and between-subjects (Guleria et al., 2017) in their meta-analysis.

The within-subjects of patients using the vFWE method revealed a lack of consistent convergence (Xu et al., 2021). Nevertheless, we identified convergence in the MCC and MFG for pain-free. When we employed the cFWE method, pain-free demonstrated activity in the MFG, MCC, and SFG. The MFG identified in pain-free during noxious stimuli, aligns with previous ALE meta-analyses (Duerden and Albanese, 2013). Also, we identified the CG, previously suggested as a pain-related activation in prior meta-analyses consistent with these findings (Tanasescu et al., 2016; Xu et al., 2020; Friebel et al., 2011; Duerden and Albanese, 2013). Although earlier research reported convergences in the SI and cerebellum, we did not observe these in the current work (Derbyshire et al., 1997). Moreover, our conjunction and contrast analyses did not reveal any convergent activity.

These results highlight the complexity of understanding pain processing mechanisms when employing conservative methods such as vFWE, which may risk missing key structures (Eickhoff et al., 2016). However, vFWE provides certainty regarding the specific structures that survive the set threshold. These findings underscore and confirm the methodological differences between vFWE and cFWE, raising the question of whether specific regions are truly associated with pain processing or represent noise.

Overall, these findings indicate distinct brain activity patterns altered pain processing

mechanisms in chronic primary pain compared to pain-free. In the cluster summary (see Tables 8 and 9), we identified the Ins (the anterior portion) and MCC as key regions involved in pain processing. The prominence of these structures suggests their critical role in chronic primary pain during provoked pain. When we compared the groups, we observed differences in how each group processes pain. Patients showed greater convergent activity in the Ins, while pain-free exhibited activity in the CG. Both structures are part of the pain matrix (Legrain et al., 2011). The lack of convergence in the between-subjects analysis may indicate that the differences between groups are either subtle or require a larger sample size to detect an effect. These findings contribute to understanding the neural mechanisms underlying pain perception in chronic primary pain patients and may guide future research.

2.10.2. Comparison with Existing Literature

Our findings indicate the necessity to assess the structures linked to pain processing in patients in structures such as the ACC, MCC, IFG, vdaIns, MFG, Claus, LN, and PreG (Segerdahl et al., 2015). Hence, suggesting an abnormal activity in pain processing (Liberati et al., 2016; Mouraux and Iannetti, 2018; Lieberman and Eisenberger, 2015; Wang et al., 2022). Ongoing debates regarding the roles of the Ins, anterior and dorsal posterior Ins, and ACC, in pain perception shed light to the problem of heterogeneous findings in the literature. Several studies have highlighted the role of the ACC in pain processing or selective pain-related processes among patients and pain-free (Lieberman and Eisenberger, 2015; Peyron et al., 2000; Tracey and Mantyh, 2007; Bushnell and Apkarian, 2005; Garcia-Larrea et al., 2003; Baliki et al., 2006; Duerden and Albanese, 2013). Some researchers have suggested that this involvement is not specific to pain generation (Lieberman and Eisenberger, 2015).

A recent review by Labrakakis (2023) summarised human studies exploring the neuronal mechanisms of the insula in pain perception. The ongoing debate regarding the brain regions involved in pain—particularly when comparing clinical and healthy samples—centres on the anterior insula and posterior insula.

For example, studies on chronic back pain or chronic low back pain highlight the role of the anterior insula (Kim et al., 2019; Hashmi et al., 2013). In contrast, conditions such as

fibromyalgia, irritable bowel syndrome, and migraine have been linked to the involvement of the posterior insula (Harris et al., 2009; Motaghi et al., 2024; Benison et al., 2011; Hougaard et al., 2017; Maya-Casalprim et al., 2020; De Simone et al., 2022). Additionally, the posterior insula has also been implicated in pain (Galhardoni et al., 2019). These findings suggest potential points of convergence within the insula across chronic pain populations, aligning with the concept of a primary pain matrix (Xiang et al., 2018).

Our results for pain-free revealed spatial convergence in the right daIns and Claus, which support the notion of a more general involvement of these regions in pain processing (Gandolfi et al., 2017), challenging the specificity of the so-called "pain matrix". Instead, this finding dovetails with the neuromatrix concept proposed by Melzack, suggesting a complex network of brain structures generating pain neurosignatures (Melzack, 2001; Califf, 2018). Although our findings do not support the notion that the Thal is involved in pain in pain-free, other structures, such as the CG and the aIns, align with our findings (Wager et al., 2013).

Similarly, another meta-analysis reveals abbarent activity in the right Ins with chronic pain patients during provoked pain (Jensen et al., 2016). On the other hand, Tanasescu et al. (2016) identified spatial convergence in the left putamen, right mid and pIns and left middle frontal gyrus when comparing the administration of painful stimuli to a painful location in the body in patients. Their findings may partially differ from the current meta-analysis due to the FCDR method, which is less strict method compared with FWE (Eickhoff et al., 2016). Therefore, using a strict correction method across studies is crucial to reduce false positives and loss of true positives to ensure consistent and reliable results.

Another meta-analysis reported in patients with neuropathic pain, bilateral activity in the SII, PFC, cerebellum, ipsilateral aIns and pIns, contralateral Thal, basal ganglia, and the brainstem during evoked pain. Compared with pain-free, in the ipsilateral SI, bilateral anterior and pIns, contralateral ACC, bilateral CC, bilateral PFC, bilateral IPL, ipsilateral Thal, and bilateral cerebellum (Lanz et al., 2011). Though, most of the identified regions do not support our findings. Possible reasons, the clinical sample population included in their review primarily concentrated on hyperalgesia and allodynia, excluding individuals with conditions such as

headaches, backaches, and fibromyalgia. Consequently, this restriction narrows our ability to confirm and contrast our results to their findings (Lanz et al., 2011). Nevertheless, it offers valuable insights into the role of the aIns and ACC, which may serve as a potential neural marker for chronic pain populations with neuropathic pain during stimulus-evoked pain.

Our findings for the conjunction and contrast analyses using vFWE of between-subjects align with a meta-analysis finding (Xu et al., 2021). In the current work, chronic primary pain and pain-free show no spatial convergence. However, prior work included various types of clinical chronic pain population (Xu et al., 2021) and included within- and between-subjects experiments in their meta-analysis. Their findings align with our between-subjects findings, suggesting increased heterogeneity in the results. This is important as it underscores that the potential heterogeneity may stem from the between-subjects rather than within-subjects meta-analysis.

The conflicting implications in the literature underscore the need for future research to reduce variability by standardising methodological approaches, thereby increasing the power of future meta-analyses to produce more meaningful and generalisable findings. Additionally, careful selection of clinical populations in future meta-analyses may reduce any unknown confounding variables contributing to heterogeneity. Ultimately, validating and confirming the neural substrates associated with chronic primary pain with similar characteristics and criterion definition (Nicholas et al., 2019), see Tables 3 and 4.

2.10.3. Challenges and differences when comparing patients to pain-free individuals

Challenges arise when comparing patients and pain-free, primarily due to significant variability (Xu et al., 2021; Davis et al., 2017) and concerns about specificity, including factors unrelated to pain itself (Davis et al., 2017). These challenges increase the difficulty of interpreting results. However, between-subjects pooled meta-analysis proves useful by examining the overall direction of group differences. At the same time, conducting between-group comparisons (patients versus pain-free) remains critical for establishing baseline distinctions and gaining a deeper understanding of pain processing mechanisms. Therefore, researchers must carefully account for variability, specificity, and causality—such as recognising that observed group

differences may not necessarily be linked to provoked pain.

A meta-analysis by Apkarian et al. (2005) explored the neural mechanisms involved in the representation and modulation of experimental pain in clinical pain conditions compared to pain-free. The study identified key brain structures, including the Ins, ACC, and Thal, which align with findings from the current chronic primary pain single meta-analysis. However, some distinctions emerged. For instance, the PFC showed the highest agreement among patients (81%) and less prominent in pain-free (55%). Similarly, the Thal appeared in 80% of studies reviewed by Apkarian et al. (2005), this finding does not align with the results of the current work. Another review by Yang and Chang (2019) examined neural areas associated with chronic pain and reported structural and functional changes within corticolimbic regions, including the PFC, ACC, hippocampus, NAc, and PAC. These findings may help explain the lack of convergence in the current between-subjects meta-analyses, and underscores the potential role of the ACC in experimental pain processes within chronic pain conditions.

Some structures identified in previous meta-analyses may represent pain-related activations in the current findings, however they did not survive the threshold as strong convergence activation (Apkarian et al., 2005; Yang and Chang, 2019). Alternatively, some of these regions may not be related to pain, however they may influence the experience of pain leading to aberrant activity (Blackburn-Munro and Blackburn-Munro, 2001; Surah et al., 2014; Genoese et al., 2022). Consequently, it is essential to explore both types of experiments—between-group and within-group analyses—to identify convergent differences. Additionally, integrating qualitative assessments (e.g., evaluating the chronic primary pain pain experience in terms of medication effects, psychological well-being, and physical activity) with more extensive quantitative assessments that focus on classification can help address existing discrepancies in chronic pain research. This comprehensive approach may provide a clearer understanding of the mechanisms underlying chronic pain and advance effective treatments.

2.10.4. Inconsistencies in the literature

Although provoked pain does not directly reflect the neural substrates associated with ongoing chronic pain in the current sample population, numerous studies have reported a consistent

association between pain matrix areas and nociceptive input (e.g., thermal, mechanical, or visceral balloon inflation) (Geha and Waxman, 2016). Moreover, this activity has also been observed in pain-free individuals (Wager et al., 2013). This suggests that these structures are more closely related to nociceptive input rather than ongoing pain in chronic primary pain. Interestingly, a meta-analysis examining grey matter differences between chronic primary pain patients and pain-free individuals during resting-state found results that align with the present meta-analysis. Specifically, they identified shared structural differences, including increased grey matter activity in the MFG and decreased activity in the ACC, MCC, and Ins (Wang et al., 2022). These findings suggest that specific structures within the pain matrix may be implicated in chronic primary pain, both during provoked and ongoing pain.

Furthermore, some of the discrepancies identified in previous studies may arise from the activation of specific types of fibres, leading to spinal segregation that influences central pain processing. Many meta-analyses lack a well-distributed mix of noxious stimuli, possibly due to strict inclusion criteria. Aiming for a well-balanced pain paradigms increases the risk of heterogeneity between experiments and chronic pain conditions (Müller et al., 2018; Xu et al., 2021; Tanasescu et al., 2016; Xu et al., 2020). This limitation restricts the generalisability of the findings, increasing the bias towards specific noxious stimuli. Consequently, the results represent a particular nociceptor pain pathway, reflecting unique mechanisms involved in pain perception. This highlights the need to incorporate other, less-studied pain paradigms in chronic primary pain to better understand the mechanisms involved in provoked pain and to determine whether shared neural substrates underlie different nociceptors in chronic primary pain.

Moreover, the moderator analysis indicated the overall perception of painful stimuli did not significantly influence pain ratings. This aligns with findings from a meta-analysis by Tanasescu et al. (2016), which observed notable similarities across three types of painful stimuli: electrical, mechanical, and thermal. However, the omnibus test results reveal differences between mechanical and thermal stimuli compared to mechanical and electrical stimuli (Tanasescu et al., 2016). Specifically, mechanical and thermal stimuli exhibit stronger effects than electrical and mechanical stimuli. This discrepancy may arise from the higher number of

studies employing mechanical and thermal pain paradigms (Tanasescu et al., 2016).

In addition, the neural representation of pain differs across chronic primary pain conditions with varying pathophysiologies. Previous research showed that fibromyalgia patients exhibit heightened activation in pain-related regions, including the operculo-Ins cortex, ACC, basal ganglia, and parietal cortex, while pain-free display activation in motor cortices, the SMA, and the cerebellum (Pujol et al., 2009). In contrast, studies on IBS report partial overlap in activation between patients and pain-free, specifically in the Thal, Ins, and MCC (Tillisch et al., 2011). These findings partially align with our results, where consistent convergences emerged in within-subjects findings particularly in the ACC, MCC, and Ins in chronic primary pain, and in the Ins and MCC in pain-free. Therefore suggesting these activity may be related to pain processing within specific conditions.

2.10.5. Methodological Considerations

The within-subjects meta-analyses identified one cluster that survived both inferences: the CG and MFG in pain-free (Duerden and Albanese, 2013). Compared to vFWE correction, cFWE identified several additional clusters with sufficient power for detecting moderate effects (Eickhoff et al., 2016). Notably, cFWE is more permissive, offering a balance between correcting for multiple comparisons and maintaining sensitivity. However, this comes with the increased risk of false positives, particularly when clusters are small or widely dispersed. While both methods control the FWE rate, vFWE provides greater protection against false positives by independently correcting each voxel, thereby reducing the likelihood of overlooking smaller activity clusters (Eickhoff et al., 2016). However, its conservativeness can result in missed true positives. Despite this limitation, vFWE highlights clusters that may prove crucial for future research on pain processing.

Evidence from a meta-analysis on neuropathic pain identified bilateral activity during evoked pain in brain regions such as the SII, PFC, cerebellum, Ins, Thal, and brainstem (Lanz et al., 2011). While the Ins was identified in the current work, the clinical population in prior work primarily included patients with hyperalgesia and allodynia, excluding those with conditions such as headaches, backaches, or fibromyalgia.

In addition, methodological differences may have contributed to this variability (Lanz et al., 2011). For instance, they employed FDR correction and two ALE methods, whereas cFWE correction offers higher sensitivity (Chumbley and Friston, 2009; Eickhoff et al., 2012, 2016). These methodological variations limit direct comparisons between our findings and those from previous meta-analyses. By addressing these methodological inconsistencies, future research can reduce heterogeneity in the literature and gain deeper insights into the neural substrates associated with chronic primary pain during provoked pain.

2.10.6. Behavioural data implications

Previous studies suggest that prolonged exposure to fibromyalgia-related pain leads to significant volumetric, structural, and functional alterations in brain regions (Jensen et al., 2013). This aligns with current behavioural and neural findings, where patients reported substantially greater pain than pain-free. Consequently, patients exhibited a higher number of clusters compared to pain-free. These findings, together with prior research, underscore the need for further investigation into how disease duration influences brain alterations in chronic primary pain.

Pain rating scores can vary by condition, gender, and age (Adeyemo et al., 2010; Goubert et al., 2017). However, our findings do not align with this, moderator analyses revealed no evidence that age, gender, or psychological variables (e.g., depression and anxiety) significantly influenced participants' pain ratings. Additionally, chronic pain conditions may co-occur with unrelated or undiagnosed secondary conditions, which could affect pain perception (Cole et al., 2006). For instance, fibromyalgia patients often display heightened sensitivity to painful stimuli, manifesting as hyperalgesia and allodynia.[8] Understanding these co-occurring comorbidities or symptoms with chronic primary pain conditions may provide insights into the pathophysiological mechanisms contributing to the neural representation of pain.

The non-significance of all examined moderators and predictors indicates the consistency of our findings across experimental designs and demographics (Adeyemo et al., 2010; Goubert et al.,

[8]Hyperalgesia refers to increased sensitivity to painful stimuli, while allodynia involves sensitisation to non-painful stimuli.

2017). Moderator analyses revealed no evidence that the depression, anxiety, gender, age, and methodological differences influenced participants' pain rating scores. This indicates the consistency of our findings across experimental designs and demographics. However, moderator analysis suggested that the number of pain sessions influenced pain rating scores across studies. Particularly, an increased number of sessions appeared to not affect pain ratings, suggesting repetitive exposure did not intensify. This supports previous research showing that repeated painful stimulation reduces pain-related responses due to habituation (Savitha et al., 2022). It is important to note that these findings pertain to subjective pain ratings and do not reflect the neural representation of pain.

2.10.7. Limitations and Future Perspectives

Our review identified key limitations within the literature, which are essential for guiding future research. While the sample size and diversity of conditions provided a preliminary understanding, they fell short of adequately representing the full spectrum of chronic primary pain. In the current study, migraine and IBS contributed the most to the findings, while fibromyalgia and chronic lower back pain contributed the least. The unequal number of experiments for each condition raises concerns about the representation of chronic primary pain. Additionally, comparing patients with chronic primary pain to those with other classifications (e.g., chronic secondary MSK pain) may reveal distinct and valuable shared neural patterns related to pain processing. However, as the concept of chronic primary pain diagnosis is relatively recent, such comparisons may only become possible in the future, once more primary studies examining BOLD signals during provoked pain across different conditions within specific classifications are conducted, excluding pain-free individuals.

Given the complexity of chronic primary pain, further studies are imperative to improve the accuracy and reliability of conclusions. Although this study encompassed various chronic primary pain conditions, it is important to recognise the distinct pathophysiological differences among these conditions and how they may shape pain experiences.

Our findings highlighted the potential value of subgroup analyses to explore the neural characteristics specific to each condition. However, this was hindered by the limited number of

within-subjects experiments available for individual conditions, see section 2.9.5. Additional research on specific chronic primary pain conditions is necessary to enable thorough meta-analyses for each condition, thereby facilitating comparisons of shared neural substrates across the chronic primary pain classification.

Meta-analysis inherently involves trade-offs between the number of experiments (power), study quality, and heterogeneity (Müller et al., 2018). These trade-offs are critical as they influence the homogeneity and statistical power of included studies (Radua and Mataix-Cols, 2012). Variability within studies can arise from unobserved factors, diagnostic heterogeneity, statistical methods, or random noise, all of which can increase inconsistency in the literature and reduce the likelihood of identifying robust findings (Müller et al., 2018; Radua and Mataix-Cols, 2012). This study could not account for all these factors due to existing variability across studies and conditions. Addressing these variables would risk excluding a substantial portion of studies, compromising the statistical power of the findings.

Different types of noxious stimuli elicit varied responses from skin nociceptors (Molokie et al., 2020; Murrell et al., 2007). In this meta-analysis, mechanical stimuli were the most common (k = 26), followed by thermal stimuli (k = 18). However, the number of experiments was further reduced depending on whether studies provided neural coordinates for both groups (patients and pain-free). This reduction disproportionately affected the representation of some stimuli types, potentially biasing the neural responses towards specific painful stimuli. As a result, biases or variability in outcomes compared to prior meta-analyses may reflect on the different noxious stimuli used (Xu et al., 2021; Jensen et al., 2016; Tanasescu et al., 2016; Duerden and Albanese, 2013).

An additional problem in the selection of experimental types. In this study, comparing within-subject and between-subject designs aimed to address two distinct questions:

1. What structures are involved in pain processing within a specific group (within-subject)?
2. What structures are involved in pain processing in patients compared to pain-free (between-subject)?

The within-subjcts meta-analysis revealed consistent spatial convergences within groups, whereas the between-subject meta-analysis showed no evidence of convergent activity. This lack of convergence, observed across both correction methods, may stem from variability in patients' neural responses compared to pain-free, as seen in the pooled meta-analysis. Alternatively, it could reflect the conservative nature of the vFWE method, which reduces the likelihood of detecting true effects (Mirman et al., 2018). However, this does not fully explain the absence of convergence with cFWE between-subjects results. Identifying the precise cause of this heterogeneity remains challenging, however it aligns with prior meta-analyses that combined within- and between-subjects experiments (Xu et al., 2021).

Another limitation is the reliance on self-reported pain scales, which may fail to capture the full complexity of the pain experience. This highlights the need for more sophisticated, multidimensional tools to assess the intricate relationship between subjective pain and neural activity. Additionally, variability in pain rating scales restricted the comparability of findings. Many studies either did not report or did not include pain ratings (n=21), making it difficult to draw definitive conclusions about chronic primary pain's subjective experiences. Standardised approaches to collecting behavioural data are essential to enhance the analysis and interpretation of behavioural for chronic primary pain conditions.

Future studies should employ longitudinal designs to track the progression of chronic primary pain and the associated neural changes over time, potentially identifying early markers for timely intervention. A more classification-driven meta-analysis is essential to better understand the mechanisms underlying the chronic primary pain population. Future primary studies should focus on conditions such as fibromyalgia and chronic lower back pain, using whole-brain analysis to validate these findings and enhance the interpretability of meta-analytic results on the chronic primary pain population. Increasing sample sizes and ensuring greater diversity among participants (e.g., in terms of gender and ethnicity) will improve the representation of the clinical population and the generalisability of the findings. Additionally, such diversity will offer valuable insights into how chronic pain impacts individuals across different countries, considering socio-economic or genetics factors. Adopting this comprehensive approach

promises to advance our understanding of the neural mechanisms underlying chronic primary pain.

2.11. Conclusion

This meta-analysis represents a significant advancement in our understanding of the neural mechanisms underlying chronic primary pain during provoked pain. By synthesising quantitative findings, it clarifies the association between BOLD signals in chronic primary pain patients and pain-free. Employing both cFWE and vFWE corrections, the dual-method approach revealed spatial convergence in within-subjects experiments, as well as non-significant convergence differences in between-subjects comparisons.

At the cFWE level, conjunction analysis revealed consistent spatial convergence in the MCC, daIns, and Claus. In patients, convergent activity was observed in the vdaIns, ACC, and MCC, while vFWE analysis highlighted the MCC and MFG in pain-free. These findings underscore the significance of structures such as the daIns and MCC in pain processing across chronic primary pain conditions. This work addresses some of the heterogeneity in the field and provides a foundation for future research to build upon the identified neural substrates, further advancing our understanding of the mechanisms underlying chronic primary pain conditions.

3. Exploring Chronic Secondary MSK Pain: A Focused Analysis of Two Conditions within the ICD-11 Framework

3.1. Literature Review

Chronic pain syndromes exhibit diverse manifestations, necessitating a comprehensive understanding of their underlying pathophysiological processes. Musculoskeletal (MSK) pain is a prominent form of chronic pain that can evolve into neuropathic and/or visceral pain syndromes (El-Tallawy et al., 2021). In diseases affecting the central nervous system (CNS), such as Parkinson's disease and multiple sclerosis, shared symptoms include neuropathic or MSK pain, impaired balance, difficulty walking, sleep disturbances, and speech impairments (Beitz, 2014; Blaney and Lowe-Strong, 2009; Tai and Lin, 2020; Nurmikko et al., 2010; Perrot et al., 2019). MSK pain in such conditions arises from persistent nociception in MSK structures (Perrot et al., 2019). While multiple sclerosis affects individuals across all age groups, Parkinson's disease primarily impacts older adults (Alroughani and Boyko, 2018; Pachana et al., 2013). Consequently, MSK pain may emerge in both conditions however at different ages or stages of disease progression.

MSK pain is a prevalent condition that affects individuals of all ages and genders (ShayestehAzar et al., 2015). In the United States alone, approximately one million people are diagnosed with multiple sclerosis, with women (76%) and young adults showing a significantly higher prevalence (Hittle et al., 2023; Wallin et al., 2019). Multiple sclerosis is divided into four distinct categories: Clinically Isolated Syndrome, Relapsing-Remitting multiple sclerosis (RRMS), Secondary Progressive multiple sclerosis (SPMS), and Primary Progressive multiple sclerosis. These categories, discussed further in section 3.2, reflect the different stages of the condition.

Each type of multiple sclerosis can contribute to MSK pain (Bernardini et al., 2016; Nurmikko et al., 2010), which often manifests as painful muscle spasms, lower back pain, or general muscle discomfort (O'Connor et al., 2008; Nurmikko et al., 2010). clinically isolated syndrome is characterised by an initial episode of inflammation and demyelination in the CNS (Miller et al., 2005, 2012). Notably, the majority of multiple sclerosis patients (85%) are diagnosed with RRMS, typically between the ages of 20 and 30 (McGinley et al., 2021; Buhse, 2008). Primary progressive multiple sclerosis, in contrast, is associated with a continuous decline in

neurological function, with symptoms typically appearing from the age of 35 (Bashir and Whitaker, 1999). Over time, many patients with RRMS transition to SPMS, which is marked by fewer relapses and an increase in the severity of pain (Pontieri et al., 2024; Becker et al.). Understanding the interplay between these multiple sclerosis categories, along with their associated symptoms and varying degrees of severity, is crucial for effective diagnosis and management.

Conversely, the Parkinson's Disease Foundation estimates that approximately 1 million people in the U.S. are diagnosed with Parkinson's disease before the age of 50, with a predominantly male demographic (Parkinson's, 2018; Marras et al., 2018). Parkinson's disease, the second most common neurodegenerative disease, is projected to affect 1.2 million people by 2030, with an annual economic burden of 41£ billion in the U.S. alone due to treatment costs, care, and lost income (Willis et al., 2022). MSK pain is one of the most prevalent non-motor symptoms in Parkinson's disease, experienced by approximately 61–75% of patients (Parkinsons Foundation, 2024; Galhardoni et al., 2019). It is often linked to rigidity and decreased mobility, with variations in prevalence and pain characteristics influenced by factors such as ethnicity and disease type (Mukhtar et al., 2018; Ha and Jankovic, 2011). For instance, a study in Pakistan reported that 30% of Parkinson's disease patients experienced pain unrelated to the MSK system (Mukhtar et al., 2018), while an Ethiopian study found that 68% of children experienced MSK pain (Delele et al., 2018), highlighting the potential role of ethnicity, age, and environmental factors in MSK pain development.

The differences between multiple sclerosis and Parkinson's disease are evident and have been well-documented (Riazi et al., 2003). As mentioned earlier, multiple sclerosis is characterised as a chronic inflammatory demyelinating disease and is classified as a chronic autoimmune disorder that affects the CNS (Korn, 2008). Patients with multiple sclerosis may experience symptomatic episodes that vary over time and affect different anatomical locations (Tafti et al.). The condition involves recurrent inflammation within the CNS, leading to damage to axons and their surrounding myelin sheaths. While the exact mechanisms of this inflammation are not fully understood, it is speculated that an autoimmune response directly targets CNS antigens

(Hersh and Fox, 2018; Hubbard and Hodge Jr, 2019; Hersh and Fox). Consequently, individuals with multiple sclerosis may experience a range of variable neurological symptoms that can impact the optic nerve, brain, and spinal cord (Hersh and Fox, 2018). Researchers have proposed that multiple sclerosis is both an autoimmune and neurodegenerative disorder(Korn, 2008). One study suggests that autoreactive CD4+ T cells play a pivotal role in triggering multiple sclerosis by activating the peripheral immune system (Korn, 2008). This aberrant immune response leads to an attack on the CNS, resulting in myelin damage that disrupts the normal flow of information within the brain, as noted by the National Multiple Sclerosis Society (O'Connor et al., 2008). However, despite these insights, the precise aetiology of pain associated with multiple sclerosis remains elusive (Kenner et al., 2007).

Moreover, Parkinson's disease is characterised as a progressive neurodegenerative disorder (Cairns et al., 2004), with neurodegeneration primarily occurring in the midbrain (Bartels and Leenders, 2009). Consequently, both motor and cognitive functions, as well as various skill performances, are significantly impacted by Parkinson's disease. In advanced stages of the disease, pathological changes in the limbic loop occur (Rüb et al., 2002). Previous investigations have elucidated anatomical markers for Parkinson's disease, including the presence of α-synuclein pathology in periadrenal tissues and the adrenal gland; these markers have been linked to orthostatic hypotension in Lewy body diseases (Jellinger, 2014).

Importantly, research suggests a potential link between MSK pain in Parkinson's disease and dopaminergic depletion in the caudate nucleus, positing that the pain may not solely be a motor symptom (Rukavina et al., 2024; Carlsson, 1959). Specifically, dopamine depletion in targeted areas of the brain may underlie these pain experiences (Hornykiewicz, 2006). Understanding the impact of neurodegeneration on brain function in Parkinson's disease and multiple sclerosis can provide valuable insights into the mechanisms underlying MSK pain.

While, MSK is prevalent in both multiple sclerosis and Parkinson's disease (Tseng and Lin, 2017; Perrot et al., 2019; ShayestehAzar et al., 2015; Buhmann et al., 2020; Parkinsons Foundation, 2024). Its expression in Parkinson's disease seems to vary depending on its underlying causes (Gandolfi et al., 2017; Ford, 2010; Buhmann et al., 2020). For instance, the

aetiology of pain in Parkinson's disease can be complex and multi-causal, sometimes involving factors that may not be directly related to the condition itself, such as depression or spinal arthrosis (Buhmann et al., 2020). Additionally, periods of heightened parkinsonism can lead to increased MSK pain, reflecting the dynamic nature of symptom expression in this population (Goetz et al., 1986). In the case of MS, MSK pain may be caused by the demylination (unrelated to neuropathic pain), thus a nerve damage not affecting the somatosensory pathways (McBenedict et al., 2024a). Consequently, this leads to weakness, muscle spasm, reduced mobility. Therefore the underlying disease leads to the development of secondary MSK pain in the lower back (McBenedict et al., 2024a; Perrot et al., 2019). Given the intricate nature of pain in both diseases, further research is warranted to investigate specific pain aetiologies within these diseases. Particularly, to address the variations and complexities associated with MSK pain experienced among patients. This knowledge is crucial for enhancing our understanding of pain mechanisms, developing targeted interventions that can effectively alleviate discomfort, and improve the QoL of patients.

3.2. Subtypes symptoms, and comorbidity

MSK pain is commonly reported across most subtypes of both Parkinson's disease and multiple sclerosis patients (Brola et al., 2014; Buhmann et al., 2020). Notably, MSK is the most common type of pain reported in Parkinson's disease, occurring in 40% to 90% of all cases (Wasner and Deuschl, 2012). A recent study found that MSK pain impacts 61-80% of Parkinson's disease patients (Rukavina et al., 2024; Galhardoni et al., 2019). In Parkinson's disease, pain can be detected as an early symptom (Schrag et al., 2015; Ford, 2010). Notably, tremor or shaking in the hands, arms, or leg, when patient is awake, sitting or standing is often the first symptom of Parkinson's disease (Saikia et al., 2020). Particularly, 50% of Parkinson's disease patients experience chronic low back pain, contributing to MSK pain (Galazky et al., 2018). Though pain may arise from secondary motor disability (e.g., MSK pain), in the early stages of Parkinson's disease approximately 43% of patients experience "primary pain" when motor symptoms are not detected (Giuffrida et al., 2005; Tseng and Lin, 2017).

Moreover, MKS pain involves pain in the head, neck, upper and lower extremities, and trunk

(Galhardoni et al., 2019). Notably, shoulder pain is the most common complaint, often leading to a Parkinson's disease diagnosis several months or even years before the onset of initial motor symptoms (i.e., pain unrelated to disease) (Schrag et al., 2015). One contributing factor to MKS pain may be the postural changes associated with Parkinson's disease (Li et al., 2022). Despite this prevalence, pain (i.e., non-motor symptoms) are often overlooked in Parkinson's disease diagnosis because they are not obvious as motor symptoms (e.g., lack of movement or shaking of hands) (Rathore and Ilavarasi, 2023). Hence, non-motor symptoms can be difficult to detect resulting in missed early diagnosis of Parkinson's disease.

The aetiology of Parkinson's disease is complex and pain may be related or unrelated to disease. The manifestations of pain in Parkinson's disease can be pain of neuropathic, MSK, or psychomotor restlessness (Mylius et al., 2015; Nègre-Pagès et al., 2008; Lee et al., 2006). Previous literature highlighted that compared to the general population, Parkinson's disease experiences more MSK pain (Beiske et al., 2009). MSK pain associated with Parkinson's disease affects muscles, bones, ligaments, and nerves (Perrot et al., 2019). In some cases, MSK pain may occur independently of Parkinson's disease however it can be exacerbated by other motor or non-motor symptoms, such as akinesia or depression (Buhmann et al., 2020).

In other cases, pain may not be directly related to Parkinson's disease. Hence, it can be influenced by motor and non-motor symptoms, such as hyposmia, rapid eye movement sleep behaviour disorder, depression, constipation, excessive daytime sleepiness, and akinetic rigidity (Buhmann et al., 2020; Schapira et al., 2017). Previously, subtypes of Parkinson's disease with MSK origins included multiple system atrophy, pain is predominantly reported in the back, neck, and shoulders (Ford, 1998). Episodes of freezing of gait have been associated with an increase in pain severity in joints of muscles fatigue, especially as abnormal gait patterns become prolonged and severe (Vitorio et al., 2020; Misu et al., 2022; Nutt et al., 2011). Consequently, this leads to postural changes or misalignment due to back, shoulder, or neck pain. Pain severity tends to fluctuate with the motor state of Parkinson's disease, particularly during OFF medication periods (Schapira et al., 2017).

Extensive research has shown that Parkinson's disease is primarily linked to the loss or death of

dopamine-producing cells in the substantia nigra (Trist et al., 2019). Dopamine acts as a neurotransmitter that coordinates motor functions, and the substantia nigra is a critical structure in the brain associated with Parkinson's disease. This degeneration leads to MSK pain arising from various disease symptoms, including limb rigidity and radicular-neuropathic disorders such as restless legs syndrome, dystonia, akathisia, neck pain, and headaches (Ford, 1998; Waseem and Gwinn-Hardy, 2001). Previously, it was suggested that MSK disorders are positively correlated with the risk of dementia and this may be used as biomarker for early detection of dementia in MSK disorders (Wang et al., 2023). Moreover, higher prevalence of patients with dementia subtypes suffered from MSK pain-related to diagnosis, compared to vascular dementia (Lin et al., 2018). Particularly, patients with dementia with lewy bodies showed significantly lower motor performance than Alzheimer's disease (Fritz et al., 2016). Therefore, this reduced movement leads to more difficulties in walking with lewy bodies and Parkinson's disease population (Lin et al., 2018).

However, some symptoms and their underlying pathophysiologies remain incompletely elucidated (Rahimpour et al., 2021; Appeadu and Gupta, 2020). Research indicates that the prevalence of MSK pain increases in advanced stages of the disease which may be linked to higher severity of motor symptoms (Frontera and Silver, 2018). Hence, MSK pain in Parkinson's disease may be related or unrelated to the disease, however it is often aggravated by the disease presence (i.e., MSK or neuropathic pain). Therefore, Parkinson's disease patients' experience of MSK pain is multifactorial and heterogeneous reflecting variety of clinical features, symptoms, and underlying mechanisms, which may pose a challenge in diagnosing.

In MS, pain is a common symptom that can occur at any stage of the disease, early signs of neuropathic pain burning sensations painful responses to nonpainful stimuli (allodynia) or increased sensitivity to painful stimuli (hyperalgesia) (Solaro et al., 2013). Nociceptive pain (MSK pain) includes painful tonic, spasm, pain secondary to spasticity (i.e., abnormal muscle tightness or poor posture) (Solaro et al., 2013; Nurmikko et al., 2010). Or a combination of both neuropathic and non-neuropathic pain, resulting in headache (O'Connor et al., 2008). MSK pain is linked to a tissue damage which activates nociceptors. Similar to Parkinson's disease,

multiple sclerosis symptoms lead to the development of MSK pain (McBenedict et al., 2024a). Therefore, pain may arise from MSK conditions (nociceptive pain) or nerve damage (neuropathic pain) (Mandloi et al., 2023; Truini et al., 2013, 2012).

Furthermore, RRMS is characterised by sudden immune attacks, or relapses, during which symptoms "flare up" (Fymat, 2023). While the exact cause of these attacks remains unclear, research has identified several risk factors (Waubant et al., 2019; Amor et al., 2010). Following each relapse, a recovery phase known as remission occurs (Patzold and Pocklington, 1982). These repeated attacks cause nerve inflammation and permanent damage, leading to pain associated with nerve damage, spasticity, and other factors (Ben-Zacharia, 2011). In the context of MSK pain, this damage may be less related to neuropathic pain and more to demyelination (McBenedict et al., 2024a). Moreover, MSK pain in multiple sclerosis patients often presents as postural abnormalities and lower back pain (McBenedict et al., 2024a; Truini et al., 2013).

Characteristic	**Details and References**
Disease Type	Neurodegenerative conditions that significantly impact the normal functioning of the CNS, leading to motor dysfunction and alterations in sensation (Fymat, 2023; Khan et al., 2019; Magrinelli et al., 2016).
Pain Types	Pain originates from neuropathic or nociceptive (i.e., MSK) sources—or often a combination of both (Waseem and Gwinn-Hardy, 2001; Svendsen et al., 2003; Archibald et al., 1994; Perrot et al., 2019; Kramis et al., 1996).
Disease Progression	Disease typically begin with mild symptoms that progressively worsen over time.
Common Symptoms	Back pain, poor balance, numb or weak limbs, uncontrollable spastic movements, and depression, among others (Vaswani and Wilkinson, 2024; Kennedy-Malone, 2018; Schapiro, 2014; Ben-Zacharia, 2011; McBenedict et al., 2024a; Galazky et al., 2018).

Table 12: Commonalities of MS and PD Characteristics. *Abbreviations*: MS, Multiple Sclerosis; PD, Parkinson's disease

Importantly, research has shown that both Parkinson's disease and multiple sclerosis, when free from cognitive impairment, significantly increase the likelihood of experiencing pain in various forms (Scherder et al., 2005). Others suggest in Parkinson's disease patients with cognitive

impairment, pain levels tend to be lower, while those with multiple sclerosis exhibit a stable pain perception that may increase as cognitive decline progresses (Scherder et al., 2005). This highlights the role of comorbidities and disease stage in shaping pain perception, as well as the impact of cognitive function in both conditions. Despite substantial differences in the pathophysiology of Parkinson's disease and multiple sclerosis, both conditions share MSK pain as a common symptom, suggesting potential shared mechanisms. Understanding the pathophysiology of both diseases related pain remains limited, as pain experiences vary significantly between patients, creating challenges in effective pain management and therapeutic approaches (Nick et al., 2012; Gandolfi et al., 2017; Ford, 2010; Buhmann et al., 2020).

3.3. Pain mechanisms of Parkinson's Disease and Multiple Sclerosis

Both Parkinson's disease and multiple sclerosis present peripheral and central mechanisms (Brola et al., 2014). Central sensitisation (Mylius et al., 2021; Mirabelli and Elkabes, 2021), neuroinflammation (Musella et al., 2018; Hirsch and Hunot, 2009; Hirsch et al., 2003; Healy et al., 2022), abnormal pain processing, and MSK strain. In the case of Parkinson's dopaminergic dysfunction is one of the main contributor (Viseux et al., 2023). While, multiple sclerosis shows demyelination playing a major role influencing these mechanisms (Truini et al., 2013), particularly with nerve injury multiple sclerosis ephatic transmission is observed leading to the development of neuropathic pain (McAllister and Calder, 1995), see Table 13.

3.4. Musculoskeletal Pain Classification

One issue with certain classifications is their reliance on subjective factors, such as patient-reported symptoms, which can introduce uncontrolled variability into the diagnosis process (Poser, 1965; Eshaghi, 2021). Moreover, the lack of clearly defined objective boundaries for conditions affects clinical practices and patients' health outcomes (Eshaghi, 2021).

The pain of multiple sclerosis can manifest as neuropathic pain (e.g., Lhermitte's phenomenon/signs), nociceptive pain (e.g., MSK pain), or a mixed presentation (e.g., spasms) (Brola et al., 2014). Essentially, MSK pain in multiple sclerosis is caused by irritation of

Mechanism	Parkinson's Disease (PD)	Multiple Sclerosis (MS)
Dopaminergic Dysfunction	Yes (loss of dopamine increases pain sensitivity)	No
Demyelination & Nerve Damage	No	Yes (leads to neuropathic pain)
Central Sensitisation	Yes (lower pain threshold, increased pain perception)	Yes (altered pain modulation)
Neuroinflammation & Glial Activation	Yes (chronic neuroinflammation affects pain pathways)	Yes (immune-mediated inflammation contributes to pain)
Peripheral Neuropathy	Yes (nerve damage contributes to pain)	Yes (small fiber neuropathy in some cases)
Spasticity & MSK Pain	Yes (rigidity, dystonia, postural strain)	Yes (spasticity, immobility, joint pain)

Table 13: Comparison of Pain Mechanisms in Parkinson's Disease and Multiple Sclerosis. *Abbreviations*: PD, Parkinson's Disease; MS, Multiple Sclerosis.

peripheral system damage in the nociceptive system (Brola et al., 2014). Similarly, pain of Parkinson's disease is classified into neuropathic and nociceptive types (Nègre-Pagès et al., 2008; Lee et al., 2006; Lien et al., 2017). With Parkinson's disease, the origins of MSK pain stem from an overlap between Parkinson's disease symptoms and/or comorbidities (Rukavina et al., 2024).

3.4.1. Parkinson's disease Classifications

Parkinson's disease is categorised by the Hoehn and Yahr scale into five stages (I–V), with stages I–III considered early-stage and stages IV–V classified as advanced-stage (Zhao et al., 2010). In the early stage, the nociceptive disruption and abnormal process were linked with central and peripheral deafferentation (Tseng and Lin, 2017). However, it is unclear in early-stage Parkinson's disease, when motor symptoms are not prominent, whether nociceptive processing is dysfunctional (Tai and Lin, 2020). As Parkinson's disease progresses to late stages, motor dysfunction severity increases gradually, accompanied by motor and non-motor symptoms (Zhao et al., 2010; Krüger et al., 2017). This stage overlaps with syndromes such as multiple system atrophy (MSA) or progressive supranuclear palsy with Parkinson's disease (PSP-PD) (Ashour and Jankovic, 2006; Kurz et al., 2016; Petrovic et al., 2012). Notably, MSK pain is often present in subtypes such as MSA patients with 60% of patients reporting pain,

possibly due to the joint and skeletal deformities in approximately 68% of MSA patients (Ashour and Jankovic, 2006). Previous research suggested that advanced Parkinson's disease reflects broad and diverse distinct phenotypes of Parkinson's disease (e.g., motor, non-motor, psychosocial aspects) rather than fully reflecting the disease progression (Krüger et al., 2017). Focusing solely on Parkinson's disease stages may not capture the full complexity of the condition, as it involves multidimensional phenotypes encompassing motor, non-motor, and/or psychosocial which influences Parkinson's disease. Instead, viewing Parkinson's disease from the lens of multidimensional phenotypes may offer a more holistic view with enhanced precision.

Ford (2010) introduced a structured classification consisting of five categories of the pain of Parkinson's disease: (1) MSK pain, (2) radicular or neuropathic pain, (3) dystonia, (4) central or primary pain, and (5) akathisia pain. This classification offered detailed clinical features associated with MSK pain (e.g., myalgic sensation in joints or muscles related to postural abnormalities and limited joint movement). However, criticisms around the classification was reported regarding the over-complexity of it for non-specialists in pain and movement disorders (De Andrade et al., 2022). Notably, pain was classified according to diseases or aetiologies, mixing different pain types. For instance, pain may originate as MSK or radicular-related pain. However, it is based on syndromes such as (e.g., neuropathic pain) and motor symptoms (e.g., dystonia) (De Andrade et al., 2022). Importantly, De Andrade et al. (2022) highlighted that conflating terms such as 'primary pain' and 'central pain' in Ford's classification can create confusion in clinical practices, potentially leading to misdiagnosis or inappropriate treatment strategies. Suggesting precise terminologies in Parkinson's disease classifications referring to central diseases of the CNS and primary pain, as chronic pain that stands alone (De Andrade et al., 2022; Nicholas et al., 2019). Particularly when these two cannot exist together, and shared mechanistic backgrounds within different pain aetiologies may exist (De Andrade et al., 2022). Another limitation of this classification is the lack of a clear explanation of the mechanistic approach of the anatomical pathway of Parkinson's disease with pain (Nardelli et al., 2024). Hence, there is an incomplete understanding of the aetiology and underlying

pathophysiological mechanisms of MSK pain in Parkinson's disease.

Another taxonomy based on aetiology proposed by Wasner and Deuschl (2012), Parkinson's disease pain classification system (PD-PCS), consisted of three categories: nociceptive, neuropathic, and miscellaneous pain and the characterisation into subcategories. Notably, nociplastic pain was added as a third mechanistic descriptor (Wasner and Deuschl, 2012). This system provided a classification where Parkinson's disease is divided into subgroups, Parkinson's disease-related and Parkinson's disease-unrelated pain. Followed by the distinction between the three types of pain, based on pathophysiological differences. This classification categorised Parkinson's disease-related pain into three primary mechanistic types: neuropathic, nociceptive, and nociplastic, each with distinct pathophysiological bases (Nardelli et al., 2024; Mylius et al., 2021), see Table 14. Therefore, although this classification accounts for several pathophysiological mechanisms, it neglects non-motor psychological symptoms in Parkinson's disease that may contribute to nociceptive pain (Trist et al., 2019; Waseem and Gwinn-Hardy, 2001; Ford, 1998; van der Heeden, 2016; Nardelli et al., 2024).

PD-unrelated pain	**PD-related pain**
Pain does not begin with the onset symptom of PD, worsens due to PD or motor complications	Pain starts or aggravated by PD and/or symptom, it increases when patients medication wear off or is improved when patients receive medication
	Nociceptive Due to discharge of peripheral nociceptors (MSK pain)
	Neuropathic Due to lesions at the peripheral or central pain sensory system (peripheral nerves compression, compromission of basal ganglia-thalamo-cortical system)
	Nociplastic Due to overactivity of the pain processing system (dopaminergic fluctuations associated with non-motor cognitive and behavioural symptoms)

Table 14: PD pain classification system (Mylius et al., 2021; Nardelli et al., 2024). *Abbreviations*: PD, Parkinson's disease; MSK, Musculoskeletal.

3.4.2. Multiple Sclerosis Classification

In 1965, Poser (1965) introduced an objective scoring system based on the clinical signs and symptoms of multiple sclerosis. This system utilised a survey to develop a "core" group of symptoms, aiming to standardise comparisons across investigators in different countries. However, challenges arose in capturing patients' verbal descriptions of symptoms (e.g., "blurring vision"), which led to the categorisation of multiple symptoms under broader headings (e.g., "vision") (Poser, 1965). As a result, the classification was limited by its reliance on subjective and simplified categories, failing to address aetiological differences and focusing on clinical features such as pain, rather than distinguishing the various types of pain.

Given the lack of objective biomarkers for multiple sclerosis, recent research has employed a machine-learning-based decision tree classifier to predict multiple sclerosis phenotypes using clinical data, such as the Expanded Disability Status Scale (EDSS) score and patient age (Ramanujam et al., 2020). This model was trained on large datasets from Swedish and Canadian cohorts to predict whether multiple sclerosis patients had SPMS or RRMS. The classifier achieved 85% accuracy based on patient history ($(n = 100)$, compared to 84.3% accuracy from neurologists ($(n = 3)$ (Ramanujam et al., 2020). This approach provides a novel, standardised classification system that reduces individual biases and offers consistent performance in contrast to variability in neurologist assessments (Eshaghi, 2021).

Despite its utility, this classification system has limitations, including an over-reliance on subjective assessments by neurologists, which risks overlooking critical transitions in disease progression and leading to misdiagnosis or misinterpretation of symptoms (Eshaghi, 2021). Furthermore, it does not elucidate the biological mechanisms underlying multiple sclerosis subtypes or consider non-motor symptoms such as pain, focusing instead on motor function as reflected in EDSS scores.

In contrast, Truini et al. (2013) proposed a mechanism-based classification for multiple sclerosis, identifying nine distinct types of multiple sclerosis-related pain, including neuropathic and nociceptive pain. They found that the most published categories of multiple sclerosis pain were neuropathic pain ($n = 7{,}759$) and inflammatory or nociceptive pain ($n = 2{,}247$). One such

category is MSK pain, caused by postural abnormalities secondary to motor disorders or disruption (Truini et al., 2013). This classification highlights the importance of accurately characterising multiple sclerosis pain. However, its limitation lies in oversimplifying the mechanisms involved in MSK pain, possibly due to insufficient research on its underlying mechanisms (Truini et al., 2013).

These classifications underscore the existing gaps in understanding MSK pain mechanisms and the factors influencing it (e.g., biopsychosocial). Such gaps can lead to misclassification and suboptimal patient treatment. Therefore, a more comprehensive classification system is needed to address MSK pain in depth and explore its relationship with multiple sclerosis and Parkinson's disease, to better understand the aetiology and underlying mechanisms involved in pain processing.

3.4.3. Pain Classification in Parkinson's disease and Multiple Sclerosis

A most recent classification, proposed by the IASP for International Classification of Disease 11th edition , categorises chronic secondary MSK pain as pain arising from an underlying disease (Perrot et al., 2019). This classification creates a distinction between pain as a symptom arising from a disease (e.g., pain associated with stiffness in Parkinson's disease) leading to chronic MSK pain, and chronic pain which stands as a condition in its own right (i.e., chronic primary MSK pain) (Perrot et al., 2019).

Cause	Description
1	Persisting local or systemic inflammatory illnesses caused by infection, crystal deposition, or autoimmune and autoinflammatory processes.
2	Local structural MSK changes.
3	Diseases of the nervous system that are not MSK conditions themselves but can cause MSK problems, such as muscular hypertonicity in Parkinson's disease.

Table 15: Main causes of chronic secondary MSK pain reflected in the classification (Perrot et al., 2019).

This classification categorises pain based on site, disease category and mechanisms, particularly MSK pain. Essentially, three main causes reflect this classification, see Table 15. Moreover, it addresses the aetiological aspects of diseases within chronic secondary MSK pain. Therefore, chronic secondary MSK pain entails conditions arising from nociception originating in joints

and bones and related to soft tissues such as local or systemic aetiologies and deep somatic lesions.

Category	PD	MS
Definition	Regional or diffuse MSK pain, primarily in joints and muscles, not directly caused by PD.	MSK pain primarily in muscles and joints, not directly caused by MS.
Cause of Pain	Altered motor function, altered sensory function, and altered biomechanical function activating nociceptors.	Nociceptive pain arising from postural abnormalities secondary to motor disorders; originating from MSK structures not related to MS.
Pain Mechanism	Nociceptive pain.	Nociceptive pain, MSK pain may coexist with neuropathic pain.
Common Challenges	- Pain can occur at any stage of PD and any type of PD. - Cognitive and depressive symptoms complicate assessment and require adapted evaluation.	Pain may occur with any type of MS. - MSK pain can coexist with neuropathic pain, which should be coded separately.

Table 16: Summary of chronic secondary MSK pain in PD and MS (Perrot et al., 2019). *Abbreviations*: PD, Parkinson's disease; MS, Multiple sclerosis; MSK, Musculoskeletal.

The chronic secondary MSK pain framework adopts a comprehensive approach by integrating the biopsychosocial model, which acknowledges non-motor symptoms challenges and how they may influence pain (Perrot et al., 2019). The underlying diseases play a significant role in the pain experience; however, biopsychosocial can be self-perpetuating, reflecting the interaction between these factors. Conditions within this classification include multiple sclerosis and Parkinson's disease, these nervous system diseases are not MSK conditions; however, they cause MSK problems.

3.5. Meta-analytic Evidence of Specific Neural Substrates Involved in Pain Processing in Parkinson's disease and Multiple Sclerosis

Adopting a standardised classification system is crucial for advancing our understanding of the pathophysiological mechanisms and neural substrates associated with pain processing in chronic secondary MSK pain. In Parkinson's disease, early pathological hallmarks, such as abnormalities in the substantia nigra, vagus nucleus, and locus coeruleus, implicate the basal

ganglia in pain processing (Wasner and Deuschl, 2012). Later studies report increased amygdala activity, contributing to the pain matrix (Braak et al., 2003; Wakabayashiº, 1997). Additionally, positron emission tomography studies in early-stage Parkinson's disease highlight the involvement of the medial pain pathway, including the medial thalamus, anterior cingulate cortex (ACC), and anterior insula, particularly during provoked pain (Gerdelat-Mas et al., 2007; Mylius et al., 2009; Brefel-Courbon et al., 2005).

Despite consistent evidence of basal ganglia involvement, the direct relationship between these structures and Parkinson's disease-associated MSK pain remains unclear (Chudler and Dong, 1995; Borsook et al., 2010). Abnormal nociceptive processing was linked to dopamine depletion which is a characteristic feature of Parkinson's disease (Sung et al., 2018; Potvin et al., 2009). Previous meta-analyses of FC studies (k = 30) using CBMA found decreased activity in the left pre- and post-central gyrus in idiopathic Parkinson's disease compared to heathy controls, indicating the post-central gyrus as a key marker during resting-state conditions (Ji et al., 2018a). Furthermore, increased FC activity was observed in medication-naive Parkinson's disease patients versus those on medication (Ji et al., 2018a; Tahmasian et al., 2017), suggesting that treatment modulates neural substrates associated with pain. Moreover, resting-state meta-analyses highlight aberrant activity in the inferior parietal lobule (IPL) in unmedicated Parkinson's disease patients (Tahmasian et al., 2017; Wang et al., 2017).

Functional changes in the cerebellum, which plays a role in motor control and balance, was observed in early-stage Parkinson's disease, with implications for both motor and non-motor symptoms (Pietracupa et al., 2024). In Parkinson's disease subtypes with gait features, cerebellar locomotor regions show consistent activation (Gilat et al., 2019), emphasising the cerebellum's role in pain and movement disorders. Moreover, prior work do not often report the specific subtypes of Parkinson's disease and whether they are diagnosed with a specific type of pain. Therefore, this suggests that the variability across these studies may be due to the differences in underlying mechanisms that exist within different subtypes.

Another study investigating alterations in spontaneous brain activity in Parkinson's disease patients with and without pain identified regions such as the SFG, SMA, left paracentral lobule,

and PreG, previously implicated in chronic pain modulation (Zou et al., 2023; Di Pietro et al., 2013; Saavedra et al., 2014). Moreover, structures such as the SMA which is implicated in motor and sensory processes (Chung et al., 2005). These findings raises the question between the link between motor functions and pain processing, particularly in the context of movement disorders.

Similarly, the pathophysiological mechanisms underlying MSK pain in multiple sclerosis remain poorly understood (Truini et al., 2013). One study using rs-fMRI in RRMS revealed greater FC in the DMN, sensorimotor, and visual networks compared to healthy controls (Wu et al., 2016). There was heightened activation in the right caudate and dorsal PFC, with reduced activity in the left insula and PreG, highlighting the involvement of multiple networks in executive and sensory processing (Wu et al., 2016).

In contrast, research on FC abnormalities in thalamic subregions in multiple sclerosis revealed activity reductions in the ipsilateral caudate nucleus (d'Ambrosio et al., 2017), aligning with this finding, suggesting potential involvement of the caudate and Parkinson's disease with MSK pain (Rukavina et al., 2024). However, distinguishing MSK pain driven by nociceptive versus central mechanisms remains poorly understood (Brola et al., 2014). As such, improved reporting of subtypes, pain types (Truini et al., 2013), comorbidities, and symptoms is vital for accurate interpretation of meta-analyses for MSK pain.

A quantitative CBMA investigating brain structures involved in multiple sclerosis with and without fatigue symptoms revealed variable convergence in the thalamus, post-central gyrus, ACC, and cerebellum (Tanasescu et al., 2014). These findings underscore the heterogeneity among patients, with factors such as medication, symptoms, subtypes, and methodological differences potentially contributing to variability. This highlights the need for better reporting and accounting for these variables in future research to enhance our understanding of the neural substrates associated with MSK pain.

3.6. Rationale of the present study

Neurological disorders such as Parkinson's disease and multiple sclerosis, both classified under chronic secondary MSK pain as diseases of the nervous system that can present with MSK pain

(Perrot et al., 2019; Gandolfi et al., 2017). These disorders involve nociceptive pain mechanisms, which stem from disease-related symptoms contributing to MSK pain (Buhmann et al., 2020; Perrot et al., 2019; Brola et al., 2014; Perrot et al., 2019). Although the underlying pathophysiology of these diseases remains incompletely understood, their shared symptoms, characteristics, and pain mechanisms suggest the involvement of common neural substrates linking these conditions to MSK pain (Truini et al., 2013; Buhmann et al., 2020; Racke et al., 2022; Schapira et al., 2017).

To our knowledge, this work represents the first attempt to meta-analyse rs-fMRI data for chronic secondary MSK pain as a newly recognised diagnosis. The objective of this chapter is to identify consistent neural substrates associated with spontaneous pain in patients with Parkinson's disease and multiple sclerosis, as well as patterns linked to MSK pain processing. We conducted a systematic review and meta-analysis exploring spontaneous BOLD signals associated with chronic secondary MSK pain conditions. Specifically, we performed ten whole-brain CBMA using ALE and applied dual-method inference corrections for multiple comparisons: cluster-level and voxel-level corrections, adhering to the Preferred Reporting Items for systematic review and meta-analysis guidelines and best practices in neuroimaging research (Moher et al., 2015; Müller et al., 2018). A stringent statistical threshold was applied to control for Type I errors, ensuring high sensitivity (Eickhoff et al., 2016).

We examined differences between chronic secondary MSK pain conditions and pain-free individuals. In addition, we compared chronic secondary MSK pain patients without symptoms (P1) to those with symptoms (P2). We anticipate observing spatial convergence in the pIns, a key region implicated in pain processing (Christopher et al., 2014; Blanchet and Brefel-Courbon, 2018; Neumann et al., 2023; Barboza et al., 2024; Labrakakis, 2023; Truini et al., 2013; Ellis et al., 2023). This meta-analysis is critical for addressing inconsistencies in the literature and advancing our understanding of the neural mechanisms underlying chronic secondary MSK pain (Tseng and Lin, 2017; Perrot et al., 2019; ShayestehAzar et al., 2015).

3.7. Methods

3.7.1. Pre-registered feasibility study

We conducted a systematic review and meta-analysis that followed the Preferred Reporting Items for systematic review and meta-analysis and neuroimaging meta-analyses, reporting guidelines (Müller et al., 2018; Page et al., 2021). The following procedures and analyses conducted in this meta-analysis were pre-registered on PROSPERO (ID: CRD42023475942), completed on 22 Feb 2024. We ran a lenient threshold on a pilot study, p-value < 0.05, without applying correction to have a sense for what size results are in the convergent maps. This helped us gain a list of the cluster volumes which are the largest. For instance, in the between-subjects experiments of patients (single dataset) indicated the largest cluster was 93344 mm^3 in the LN, which was below $p < 0.05$.

The Preferred Reporting Items for systematic review and meta-analysis flowchart depicting the process for the literature search and screening see 18, and following inclusion criteria. In total, we identified 28 studies and a total of 62 experiments. Furthermore, by making our data accessible in the Open Science Framework (OSF) repository, we embrace open science principles and fostering reproducibility `https://osf.io/vaphx/`.

3.7.2. Literature search and selection

Literature search included all the fMRI studies on Parkinson's disease and Multiple sclerosis before 22 Feb 2024, performed by KA. We conducted a literature search for functional magnetic resonance imaging and pain research on 26 Oct 2023. These studies were obtained through five databases (i.e., APA PsychArticles, APA PsychInfo, CINAHAL, MEDLINE, and Scopus). No date limit was set. Hand searching, forward and backward searching was conducted to maximise the inclusion possibilities of most relevant studies that were not found in the mentioned databases.

Given the extensive range of our search terms, detailed in Supplements (see SEARCH_STRATEGY.pdf in OSF: `https://osf.io/v7taf`). In total, we identified (k= 236) Parkinson's disease articles and (k= 368) multiple sclerosis articles. We included corrected

images, if we had to choose between corrected (1) and uncorrected (2) in a single study (see column corrected images, 17 and 18). This decision was made based on the fact that the majority of the included studies were corrected. Additionally, we included studies that compare between two patients groups, patient 1 represents Parkinson's disease or multiple sclerosis without any known symptoms and patient 2 represents Parkinson's disease or multiple sclerosis with known symptoms (e.g., depression or freezing of gait). The cut-off date for our search (22 Feb 2024) was strategically chosen to include the most recent studies while allowing sufficient time for analysis.

Eligibility process was similar to section 2.8.2. The full-text screening of the final studies were performed by authors. Any disagreements were managed resolved a discussion.

Inclusion Criteria

Adhering to recent guidelines for neuroimaging meta-analysis (Müller et al., 2018), inclusion criteria were as follows:

1. The study was peer-reviewed and in English.
2. The study assessed BOLD activity with rs-fMRI and reported the specific coordinated of activated brain region as (*x, y, z*.
3. The study focused on Parkinson's disease or MS, hereby targeted due to their reported association with MSK pain.
4. The study provided between-group experiments (e.g., Patients greater than pain-free OR Patients 1 greater than Patients 2).
5. The study only included participants 18 years or older.
6. The study analysed the whole-brain or almost complete brain coverage (missing only one or two slices) (Müller et al., 2018).

Exclusion Criteria

1. The study did not directly focus on the experience of pain *tout court* but instead investigated the effects of an independent variable (e.g., social pain, anticipation of pain, painful stimuli, or pharmacology) on pain.
2. The study applied masks to the images, seed-based approach, ROI, or volumes of interest.
3. The study applied volume correction instead of no correction.

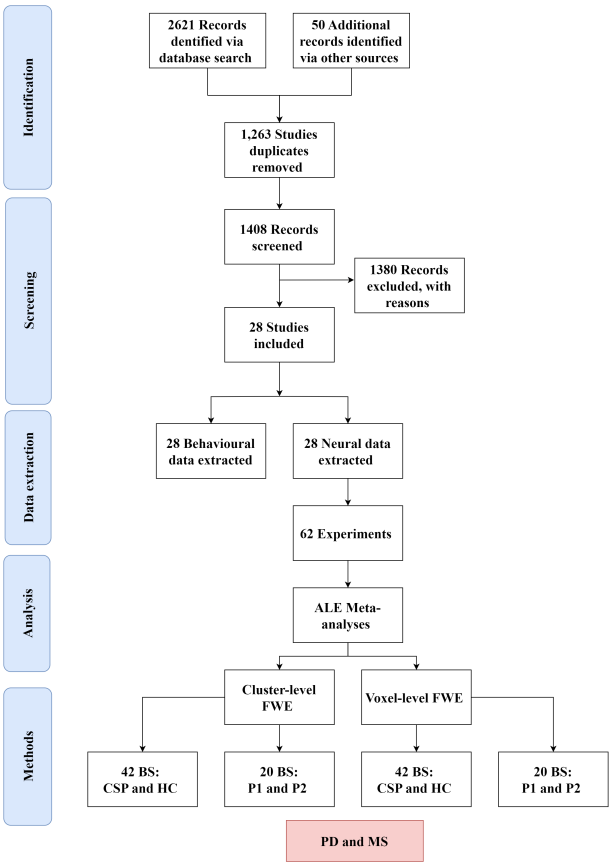

Figure 18: PRISMA flowchart detailing the screening process and meta-analyses methods. In total, we 62 experiments from 28 articles were included in the meta-analysis. **Abbreviations:** PRISMA, Preferred Reporting Items for systematic review and meta-analysis; ALE, Activated likelihood estimation; FWE, Family wise error; PD, Parkinsons; MS, Multiple Sclerosis.

3.7.3. Inter-rater Reliability

The above databases returned titles and abstracts screened by at least four reviewers for initial eligibility (KA, AG, and AK) through full-text screening for potential article inclusion (KA). To assess IRR to ensure objectivity, consistency, and reliability of the study selection (Belur et al., 2021). The IRR was performed during full-text screening stage of the potential studies that were considered to be included (n =63) (Belur et al., 2021). Each rater independently full-text screened the selected studies to measure the agreement or consistency among different raters. Sixty-three were assessed for IRR with details of reasons of exclusion (see Raters_IRR.docx in

https://osf.io/nxhmg). The consistency of raters' responses between three raters from the initial selected articles, resulted in a Fleiss' Kappa of 0.21, indicating "poor agreement". Most disagreements arose from confusion regarding incomplete reporting of neural coordinates (e.g., within-subjects experiments) or uncertainty about whether a study used whole-brain coverage. To address this, a BrainMap team member (JD) reassessed the disagreements to confirm which studies met the BrainMap criteria (https://brainmap.org/taxonomy/criteria.html). For studies that did not provide complete coordinates, I contacted the authors of the respective study. All discrepancies were resolved through discussions among the authors (KA, PH, and EV).

Once the studies were finalised, data extraction and quality assessment were performed, in the next section.

3.7.4. Data Extraction and Quality Assessment

Data was manually extracted by at least one author (KA) and independently checked by a third party (PH), ensuring all included studies met the inclusion criteria. Disagreements during this phase were also resolved by involving a third or fourth evaluator. The decisions made were documented in a report which was reviewed and discussed among the authors (KA, PH, EV). The extracted information for analysis included imaging results as coordinated clusters [*x, y, z*] in voxels, which were used for analyses.The details extracted from the articles encompassed key elements: study title, authors, number of patients and healthy participants, age, gender, diagnosis, disease duration, psychological well-being score (i.e., depression), and medication (see Table 17 and 18). We contacted authors to ask for unpublished results, data clarification, and verification (Meursinge Reynders et al., 2017).

When one study included different conditions such as rapid eye movement and freezing of gait, these were treated as separate data entries. In total, we identified several diagnoses for Parkinson's disease, cognitive impaired (CI), mild cognitive impairment (MCI), cognitively unimpaired (CU and noMCI), dementia lewy bodies (DLB), Parkinson's disease normal cognition (NC), Freezing of gait (FOG), multiple system atrophy-cerebellum type (MSA-c) -Parkinson's diseases type (MSA-p), resting essential tremor (rET), tremor-dominant

Parkinson's disease (tPD), impulsive control disorder (ICD), excessive daytime sleepiness (ESD), Parkinson's disease dementia (PDD), without ESD (NoESD), postural instability/ gait difficult (PIGD), akinetic rigidity (AR), no depression (NoDep), depression (Dep), Parkinson's disease left onset (LPD), and Parkinson's disease right side (RPD). For multiple sclerosis, relapsing remitting multiple sclerosis (RRMS), cognitively impaired multiple sclerosis (CI MS), cognitively preserved multiple sclerosis (CP RRMS), clinically isolated syndrome (CIS), Primary progressive multiple sclerosis (PPMS), and Secondary progressive multiple sclerosis (SPMS) (see Table 17, 18). For medication, total number of studies involved antiparkinsons medication (AR, k = 1), L-Dopa (k = 9), LEDD (k =3), authors reporting medication included, however they did not reporting medication name (k = 2), and authors that did not include medication in their study (k = 15) (see OSF https://osf.io/wvdu4). Total number of (k =15) studies included patients undergoing medication or treatment during the experiment, and (k = 14) no medication reported. The number of studies increased if a group condition included both (medicated vs. unmedicated), treating them as separate entries.

For each selected study, we assigned a score according to the Downs and Black checklist for quality assessment (Downs and Black, 1998). This tool assesses the methodological quality of different studies. We used one item of the checklist: *"Was there an adequate adjustment for confounding in the analyses from which the main findings were drawn?"* As it was the only question that showed significant discrepancies across studies. Thus, confounding variables should be described and taken into account in the each study included. Some of the confounding variables that are relevant for this meta-analysis include whether they applied multiple comparisons correction, employing robust statistical methods. Additionally, we assessed whether the study adjusted for confounding variables such as psychological factors, medication, age, and gender. The scores are either 0 = "No or Unable to determine", if the study does not report taking into account these confounding variable. Or, " 1 = "Yes", with the highest score suggesting good quality of external and internal validity (Ayoub et al., 2018; Raimo et al., 2021) for details on the scores see Supplements (Black_Downs2.xlsx in Supplements https://osf.io/vaphx/.

Table 17: **Study Information About Articles and contrasts Included in The Meta-analyses.**

Study	**# of CSMP (Pain-free)**	**gender of CSMP and Pain-free (F/M)**	**M age CSMP (Pain-free)**	**Diagnosis**	**Disease duration**	**Depression scale**	**M CSMP (Pain-free)**	**SD CSMP (Pain-free)**	**Method**	**Corrected images**	**P-value**
Borroni 2015	34(10)	11/23(7/3)	66.3(62.2)	MCI,noMCI,DLB	91.6mo	None	None	None	vFWE	2	0.005
Cui 2021	24,13	19/19	55.68	MSA-c,MSA-p	N/A	Dep scale	None	None	cFWE	1	0.05
Harrington 2017	31(30)	9/22(19/11)	67.4(68.6)	PD	Nona	None	None	None	Alpha	1	0.05
Li 2019	35(35)	18/17(24/11)	60(63)	PD	50.28mo	Dep scale	None	None	GRF,vFWE,cFWE	1	0.005,0.05
Liu 2019	68(35)	36/32(16/19)	65.75(59.57)	FOG- and FOG+	39.6mo	None	None	None	GRF,vFWE,cFWE	1	0.05,0.05
Wen 2016	16,60	6/10,15/45	60.3, 62.29	PD:ESD,noESD	5.24mo	HAMD	2.08,2.81	1.9,2.8	Regional homogeneity	2	0.001
Wen 2013	33(21)	18/15(8/13)	62.55(55.4)	PD,Dep,noDep	72.54mo	HAM-D	15.2,4.4	7.8,4.4	Regional homogeneity	2	0.005
Zhu 2022	53(15)	23/30(9/6)	64.46(63.4)	PD,NC,MCI,PDD	32mo	HAMD	12.36,15.64,18.18	9.43,8.26,10.44	FDR	1	0.05
Zi 2022	21,22	8/13,13/9	58.64	PD:ESD,NESD	47.46mo	HAMD	9.19,7.55	6.49,6.8	AlphaSim	1	0.05
Li 2020	43(19)	35/8(21/4)	50.72(49.12)	rET,tPD	99mo	None	None	None	AlphaSim	1	0.05
Li 2016	20(9)	12/11(9/11)	63(65.3)	PD	84mo	None	None	None	AlphaSim,vFWE	1,2	0.05,0.01
Sheng (2014)	41(25)	15/26(9/16)	56.6(56.7)	PD:Dep,NoDEP	44.4mo	HAMD	19.3,6.4(5.6)	5,2.1(1.9)	AlphaSim	1	0.05
Luo (2015)	51(51)	24/27(24/27)	52.83(52.24)	PD	20.16mo	None	None	None	cFWE,vFWE	1	0.001,0.005
Zhang (2015)	47(26)	21/26(15/11)	58.96(59.31)	AR,TD	55.02mo	None	None	None	AlphaSim	1	0.05

Table 18: **Study Information About Articles and contrasts Included in The Meta-analyses.**

Study	**# of CSMP (Pain-free)**	**gender of CSMP and Pain-free (F/M)**	**M age CSMP (Pain-free)**	**Diagnosis**	**Disease duration**	**Depression scale**	**M CSMP (Pain-free)**	**SD CSMP (Pain-free)**	**Method**	**Corrected images**	**P-value**
Hu (2019)	39(28)	26/25(6/10)	60.10(59.12)	TD,PIGD	100.37	None	None	None	AlphaSim	1	0.05
Li (2020)	50(25)	25/25(12/13)	61.26(61.76)	PD-MCI,PD-NC	46.44mo	None	None	None	Bonferroni (cluster)	1	0.05
Mi (2017)	31,31(32)	34/28(17/15)	59.45(58.34)	FOG,noFOG	23.4mo	None	None	None	AlphaSim	1	0.05
Li (2020)	57(32)	28/29(16/16)	64.24(62.41)	LPD,RPD	81.6mo	None	None	None	cFWE,vFWE	1	0.05,0.001
Liu 2016	18(18)	13/5(14/4)	35(35.17)	RRMS:CIS	28.52mo	None	None	None	AlphaSim	1	0.05
Zhou 2016	34(34)	21/13(21/13)	42.1(41.8)	RRMS	27.1 mo	None	None	None	AlphaSim	1	0.05
Bonavita 2011	36 (10)	21/15(10/8)	40.7(39)	CI MS,CP RRMS	136.6mo	None	None	None	N/S	2	0.001
Carotenuto 2022	1942(330)	1248/994(186/144)	44.58(41.2)	MS,CIS,RRMS,SPMS,PPMS	124.8mo	None	None	None	cFWE	1	0.05
Dogonowski 2013	87(30)	44/40(15/15)	45(45)	MS,RRMS,SPMS	243mo	None	None	None	FWE	1	0.05
Chen 2015	31(22)	15/16(10/12)	63.7(65.1)	PD:PIGD,tPD	78.36mo	None	None	None	3DClustSim	1	0.05
Choe 2013	22(25)	12/10(15/10)	58.3(58.3)	PD	40.8mo	BDI	14.9	1.4	Regional homogeneity	1	0.05
Hou 2014	101(102)	42/59(42/60)	59.84(59.91)	PD	86.76mo	None	None	None	FWE	1	0.05
Zhang 2013	72(78)	47/35(46/31)	59.7(58.6)	PD	84.6mo	None	None	None	FDR	1	0.05
Gan 2021	54(37)	22/32(12/25)	60.35(62)	PD:ICD,no ICD	96.6mo	HAMD24	12.6,9.5	8.2,7	VMHC	N/A	N/A

3.7.5. Coding and Data Preparation

One coder (KA) independently coded the data using the BrainMap software. The coding went through three software processes provided by BrainMap, similar step as section 2.8.5. We used GingerALE (version 3.0.2) to perform ALE meta-analysis on coordinates in MNI space. We will use ANIMA to publish our results, thus fostering transparency and sharing of analytical tools to enable others to replicate or build on our research (Reid et al., 2016a).

3.7.6. Activated Likelihood Estimation

Using GingerALE software, we converted the neural coordinates from TAL to MNI space. We conducted multiple comparisons of cluster-level corrected $p = 0.05$ for FWE, cluster-forming $p = 0.001$ (Müller et al., 2017; Eickhoff et al., 2012). For vFWE, and threshold of $p = 0.05$ (Eickhoff et al., 2016). Both methods used threshold permutation of 1000 and minimum volume of 200. Single and contrasts datasets analysis strategy was performed similarly to section 2.8.6, notably, the threshold and experiments types used was the main differences. We computed contrast datasets of patients and pain-free to create an analysis mask and identify structures that spatially converge, and ensure relevant structures are not missed or overlooked in both groups, see section 2.8.6.

We calculated ten meta-analyses across using two methods (i.e., cFWE and vFWE). Four BS, chronic secondary MSK pain ($k = 21$) and pain-free ($k = 21$). Six between-subjects experiments of chronic secondary MSK pain patients without symptoms (P1) ($k = 8$) and patients with symptoms (P2) ($k = 12$). Pooled datasets of P1 and P2 ($k = 20$).

3.7.7. Different Meta-analytic Groupings

We followed similar strategy of meta-analyses grouping, used in section 2.8.7, with P1 and P2 datasets due to insufficient experiments number. For multiple contrasts to avoid negatively impacting the results (i.e., inflating the results), we combined experiments as one experiment, if they were reported as 2 or more (Müller et al., 2018).

3.8. Results

This meta-analysis included 28 articles comprising a total of (k = 62 experiments), all of which were between-subjects experiments, consisting of between-subjects representing: 1) chronic secondary MSK pain and pain-free, 2) chronic secondary MSK pain without symptoms (P1) and chronic secondary MSK pain with symptoms (P1). The combined sample size (n = 4,296 participants), including (n = 3217 patients, and n = 1079 pain-free). Following chronic secondary MSK pain classification, the number of studies of chronic pain patient conditions included in this review were Parkinson's disease k = 23 and multiple sclerosis k = 5) (Nicholas et al., 2019).

We conducted 10 meta-analyses consisting of between-subjects using two correction methods: cFWE and vFWE. Five meta-analyses were performed, chronic secondary MSK pain (k = 21), pain-free (k = 21), P1 (k = 8), P2 (k = 12), and pooled (k = 20).

3.8.1. Neural data: chronic secondary MSK pain Clusters Summary

We report the highest structure that contributed to the identified clusters in the between-subjects meta-analyses, using cFWE corrections. Using both methods, no clusters was identified in conjunction analyses. No clusters was identified when comparing chronic secondary MSK pain versus pain-free and P1 versus P2, using vFWE.

For the clusters identified in the single meta-analyses of between-subjects experiments (chronic secondary MSK pain and pain-free individuals) using cluster-level, see Table 19. For the clusters identified in the single meta-analyses of between-subjects experiments (P1 and P2) using cluster-level, see Table 20. A more detailed description of all the clusters identified can be found in (Table 21).

Cluster	Region	(%) Foci	Max ALE Value	Foci / Exp. (k)
Patients Meta-Analysis of between-subjects				
1	ScG	45.5	0.018	5 / 4
	IFG	31.8		
	(BA 47)	(54.5%)		
	(BA 25)	(36.4%)		
	(BA 11)	(4.5%)		
Pain-free Meta-Analysis of between-subjects				
No clusters identified				

Table 19: Summary of Clusters, Single meta-analyses chronic secondary MSK pain and pain-free (cluster-level)

Cluster	Region	(%) Foci	Max ALE Value	Foci / Exp. (k)
P1 Meta-Analysis of between-subjects				
1	Para	57.1%	0.014	2 / 2
	Fusiform gyrus	42.9%		
	(BA 19)	(65.7%)		
	(BA 37)	(34.3%)		
2	SG	100%	0.015	2 / 2
	(BA 21)	(100%)		
3	STG	42.9%	0.009	2 / 2
	IFG	28.6%		
	Claus	28.6%		
	(BA 38)	(42.9%)		
	(BA 13)	(28.6%)		
P2 Meta-Analysis of between-subjects				
1	CT	75.0%	0.015	3 / 2
	ISLL	13.0%		
	Tu	7.6%		
	Pyr	4.3%		
	(No BA reported)			
Pooled Meta-Analysis (P1 and P2)				
1	CT	76.2%	N/A	3 / 2
	ISLL	13.1%		
	Tu	6.0%		
	Pyr	4.8%		
	(No BA reported)			
2	SG	66.7%	N/A	3 / 3
	Para	33.3%		
	(BA 21)	(66.7%)		
	(Amygdala)	(33.3%)		

Table 20: Summary of cFWE Clusters, Single meta-analyses P1 and P2 (cluster-level)

Table 21: **ALE meta-analyses clusters identified using cFWE and vFWE**

ALE	N	# Foci	# Exp	Cluster	x	y	z	Vol. thresh-old	Chosen min. cluster size	Region	Max. ALE value
Between-subjects cFWE (Patients > Pain-free)	928	194	21	1	15.1	20.6	-20	872 mm³	624 mm³	Subcallosal gy, IFG, MFG	0.0186
Between-subjects cFWE (Pain-free > Patients)	929	217	21	NONE				0 mm³	672 mm³		
Between-subjects cFWE (P1 > P2)	133	20	8	3	32.3	-53.7	-6.2	1928 mm³	528 mm³	Para , Fusiform gy	0.0149
					-39.7	-8.4	-16.3			Sub-gyral	0.015
					36.7	4.3	-16.7			STG, IFG, Claus	0.0097
Between-subjects cFWE (P2 > P1)	236	52	12	1	40.9	-66.6	-36.1	736 mm³	648 mm³	CT, ISLL, Tu, and Pyr	0.0155
Between-subjects cFWE (P1 and P2; pooled)	369	72	20	2	40.7	-66.7	-36.1	1312 mm³	608 mm³	CT, ISLL, T, and Pyr	0.0155
					-37.8	-8.1	-16.1			Sub-Gyral, Para	0.0153
Between-subjects vFWE (Patients > Pain-free)	928	194	21	NONE				0 mm³	200 mm³		
Between-subjects vFWE (Pain-free > Patient)	929	217	21	NONE				0 mm³	200 mm³		
Between-subjects vFWE (P1 > P2)	133	20	8	NONE				0 mm³	200 mm³		
Between-subjects vFWE (P2 > P1)	236	52	12	NONE				0 mm³	200 mm³		
Between-subjects vFWE (P1 and P2; pooled)	369	72	20	NONE				0 mm³	200 mm³		

3.8.2. Neural results: cFWE, vFWE, and between-subjects experiments (chronic secondary MSK pain versus pain-free)

We present the main effects of between-subjects using the cFWE and vFWE correction methods in the following sections. For detailed results, please refer to the OSF repository, titled "Clusters.docx," which includes peaks and Z images associated with each experiment. Additionally, the uncorrected image results, supplementary files for peaks, cluster statistics, and data history are available on OSF at the following link: https://osf.io/vaphx/.

The main effect of between-subjects, analysed using cluster-level correction, revealed significant convergences during spontaneous pain at the preregistered threshold of $p < 0.05$. A single meta-analysis of patients identified convergence in the MFG, as shown in Figure 19. In contrast, pain-free did not exhibit any spatial convergence.

When applying voxel-level FWE correction, neither of the two meta-analyses (patients and pain-free) revealed any significant convergence (see Table 21).

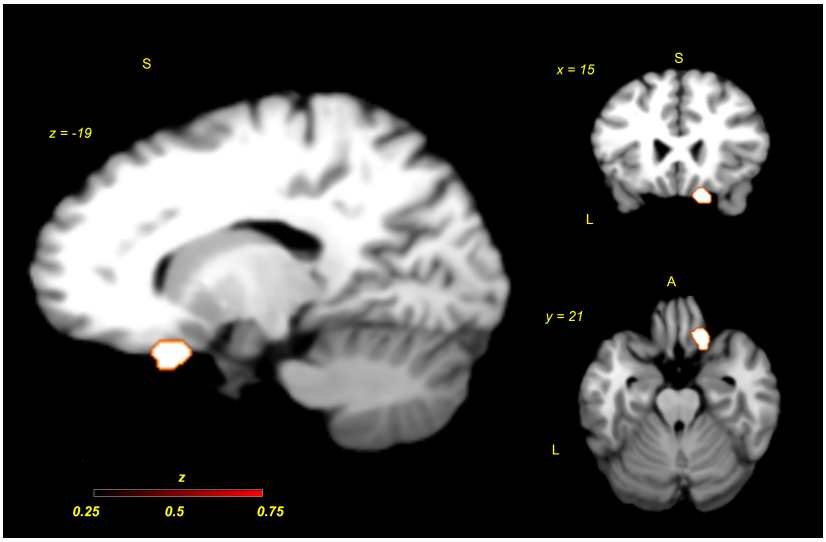

Figure 19: Thresholded images of between-subjects for patients and pain-free. Coordinate-based meta-analysis of neural response during SP, patients > pain-free in the MFG (15, 21, -19). Images were thresholded at $p < 0.05$, cluster-forming threshold of $p < 0.001$. (cluster-level corrected FWE). *Abbreviations*: MFG, Medial frontal gyrus

3.8.3. Neural results: cFWE, vFWE, and between-subjects experiments (P1 versus P2)

The main effects of between-subjects experiments using both cluster-level and voxel-level correction methods, revealed convergences in response to SP.

Single meta-analyses revealed distinct patterns, P1 group demonstrated convergent activity in the sub-gyral at $p < 0.001$, STG at $p < 0.001$ (see Figure 20). P2 group showed activity in the CT at $p < 0.001$ (see Figure 21).

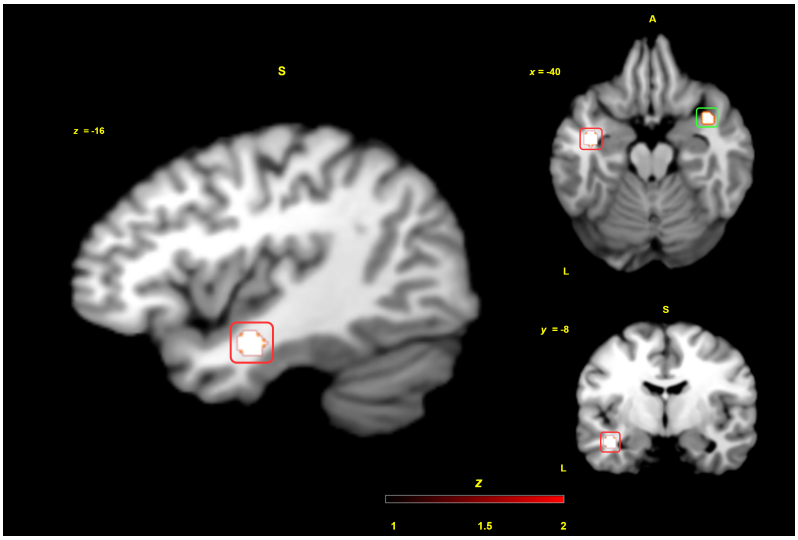

Figure 20: Thresholded images of between-subjects for P1 > P2. Coordinate-based meta-analysis of neural response during SP, P1 in the SG (-40, -8, -16; red) and the STG (36, 5, -16; green) Images were thresholded at $p < 0.05$, cluster-forming threshold of $p < 0.001$. (cluster-level corrected FWE). *Abbreviations*: SG, sub-gyral; STG, Superior temporal gyrus

The combined meta-analysis of both groups revealed significant activity in the sub-gyral and Para, both at $p < 0.001$ (see Figure 22). When applying voxel-level correction, direct comparisons between P1 and P2 groups (in both directions) revealed no significant convergences.

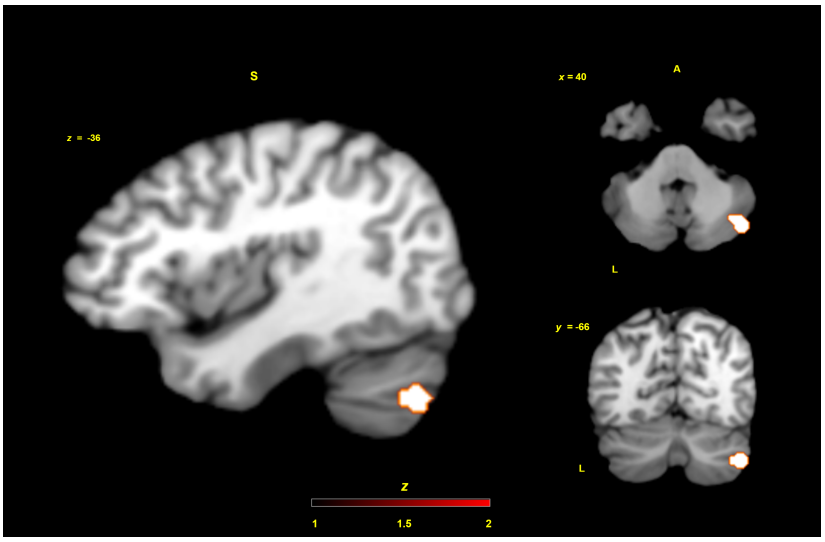

Figure 21: Thresholded images of between-subjects for P2 > P1. Coordinate-based meta-analysis of neural response during SP, P2 in the CT (40, -66, -36) (cluster-level corrected FWE). *Abbreviations*: CT, Cerebellar Tonsil; FWE, Family wise error.

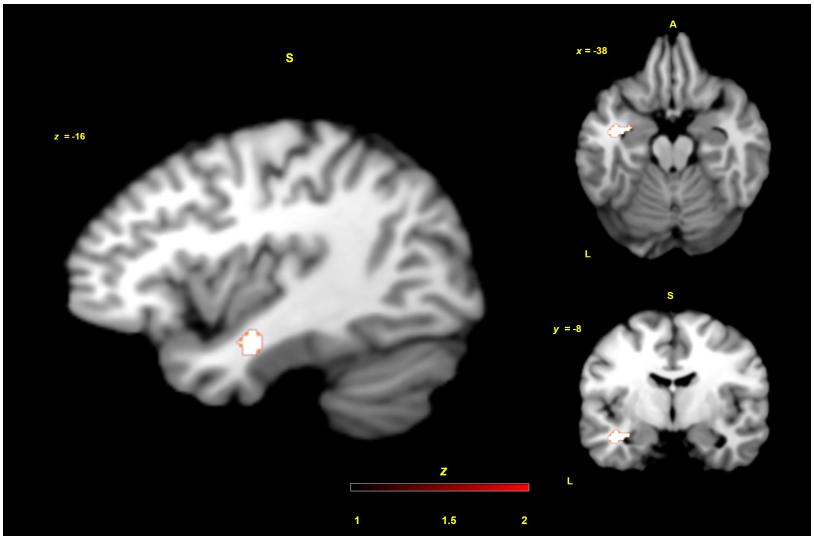

Figure 22: Thresholded images of combined between-subjects meta-analysis for P1 and P2. Coordinate-based meta-analysis of neural response during SP, P1 in the SG (-38, -8, -16) (cluster-level corrected FWE). *Abbreviations*: SG, sub-gyral; FWE, Family wise error.

3.8.4. Neural results: Follow-up sub-group analysis on Parkinson's disease

We conducted a follow-up 12 meta-analyses to account for the sub-group differences examining convergences with Parkinson's disease during SP, using the cFWE and vFWE methods. Notably, multiple sclerosis studies were insufficient. For Parkinson's disease versus pain-free we identified total of (k =34) experiments, and Parkinson's disease without symptoms (PD1) versus Parkinson's disease with symptoms (PD2) (k = 18).

3.8.5. Neural results: cFWE, vFWE, and between-subjects experiments (Parkinson's disease versus pain-free)

We conducted six between-subjects meta-analyses comparing patients with Parkinson's disease versus pain-free, employing both cFWE and vFWE, correction methods.

Single meta-analysis of Parkinson's disease group showed convergence patterns identical to those in Figure 19, at cluster-level correction. However, pain-free group demonstrated convergence in the LN (see Figure 23)

Contrast analysis results of pain-free versus Parkinson's disease comparison revealed, greater activation in the LN at $p < 0.006$. While, Parkinson's disease versus pain-free comparison showed greater activation in the ScG at $p < 0.02$ (see Figure 24)

Consistent with our primary results, voxel-level correction analyses comparing Parkinson's disease versus pain-free (and vice versa) revealed no significant convergences.

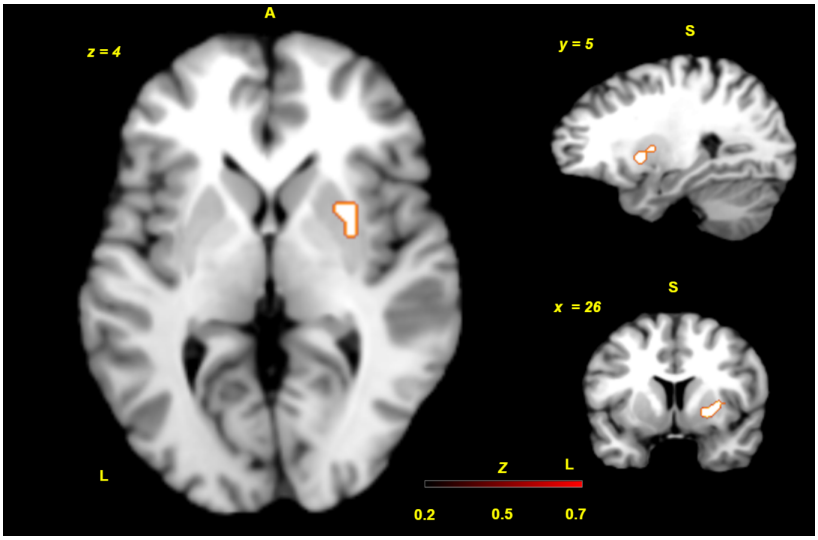

Figure 23: Contrast maps of pain-free and PD of between-subjects. Pain-free greater than PD in the LN (26, 4, 5) (cluster-level corrected FWE). *Abbreviations*: PD, Parkinson's disease; LN, Lentiform nucleus

3.8.6. Neural results: cFWE, vFWE, and between-subjects experiments (PD1 versus PD2)

We conducted six between-subjects meta-analyses comparing PD1 versus PD2, using both methods. Single meta-analysis results of PD1 and PD2 replicated the activation patterns shown in Figures 20 and 21, respectively. Similarly, the combined analysis revealed significant activity in the sub-gyral and Para (see Figure 22)

Contrast analysis results of PD1 showed greater activation than PD2 in the Para and fusiform gyrus both at $p < 0.04$ (see Figure 25). PD2 versus PD1 comparison revealed overlapping activation patterns, indicating no significant differences.

Using voxel-level correction, bidirectional comparisons (PD1 versus PD2 and vice versa) showed no significant convergences.

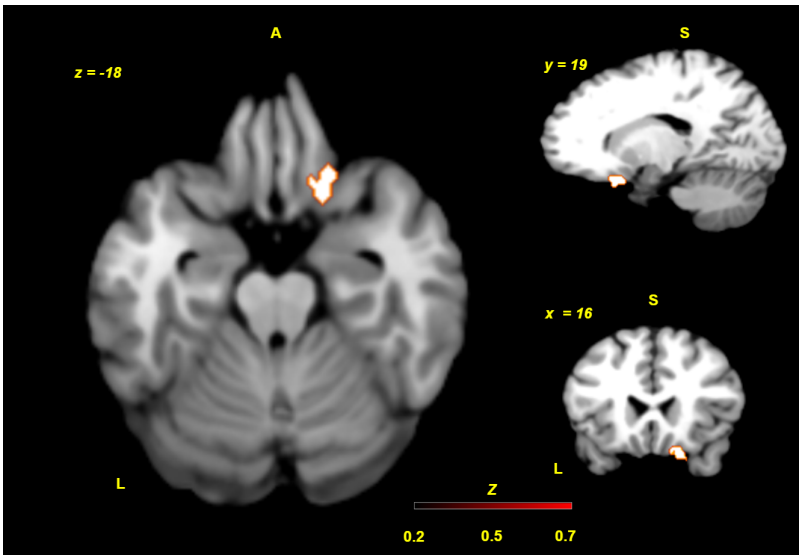

Figure 24: Contrast maps of PD and pain-free of between-subjects. PD greater than pain-free in the subcallosal gyrus (16, 19, -18) (cluster-level corrected FWE). *Abbreviations*: PD, Parkinson's disease; ScG, subcallosal gyrus

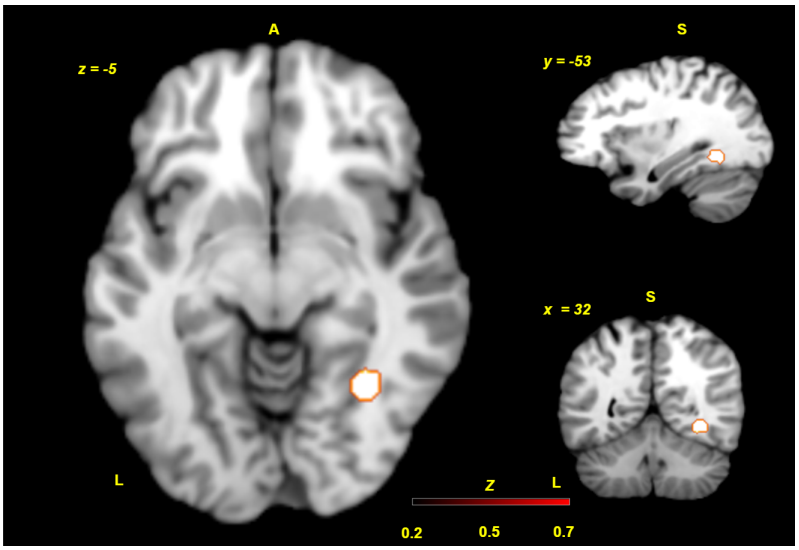

Figure 25: Contrast maps of PD1 and PD2 of between-subjects. PD1 greater than PD2 in the Para (32, -53, -5). Images were thresholded at $p < 0.05$ (cluster-level corrected FWE). *Abbreviations*: Para, Parahippocampus

3.9. Discussion

The present research explores consistent neural patterns of MKS pain associated with chronic secondary MSK pain conditions during SP. Previous ALE whole-brain meta-analyses, demonstrated considerable heterogeneity in their findings related to multiple sclerosis or Parkinson's disease (Kollndorfer et al., 2013; Tanasescu et al., 2014; Wang et al., 2018; Tahmasian et al., 2017; Gilat et al., 2019), due to several reasons which will be discussed in the section 3.9.4.

In this work, we employed cFWE and vFWE within the latest framework for classifying chronic secondary MSK pain (Perrot et al., 2019). We meta-analysed two types of between-subjects experiments for chronic secondary MSK pain, specifically, we focused on comparisons between patients and pain-free, and patients without symptoms (P1) and those with symptoms (P2). We applied a recommended statistical threshold to control for Type I error resulting from multiple comparisons to ensure high sensitivity (Eickhoff et al., 2016). We anticipated observing spatial convergence in the pIns (Barboza et al., 2024; Labrakakis, 2023; Truini et al., 2013; Blanchet and Brefel-Courbon, 2018; Ellis et al., 2023). However, our findings did not meet this expectation.

3.9.1. Summary of Findings

The between-subjects meta-analyses revealed a lack of consistent convergences when applying vFWE corrections. This inconsistency may be attributed to the conservative nature of vFWE or foci were widely distributed across experiments (Eickhoff et al., 2016; Xu et al., 2021). Although previous recommendations suggested that a minimum of (k = 8) experiments is sufficient for vFWE to ensure adequate controlling for excessive contribution of single experiments, additionally it provides protection from reporting incidental significant overlap (Eickhoff et al., 2016). With the current work, we meta-analysed P1 and P2, consisting of less than 13 experiments for each group, and a relatively large number of participants in P1 (n = 133) and P2 (n = 236). This means the burden of few experiments may have led to less data points contributing to the overall null-distribution (Eickhoff et al., 2012). In this case, the results would reflect a tighter Gaussian distribution and higher ALE score (Eickhoff et al., 2009).

Moreover, when these datasets were combined (k = 20) we identified similar results of non-signficant convergences, at voxel-level correction. Therefore, using vFWE we were not able to observe any differences in convergent activity with larger number of experiments, possibly due to high variability. In contrast, cFWE, as the most sensitive and optimal inference approach compared to vFWE and voxel-FDR (Eickhoff et al., 2016), we identified several structures which will be discussed in this section.

The findings from the between-subjects meta-analyses, cFWE correction, comparing patients without symptoms to those with symptoms indicated a high ALE in several brain structures. Specifically, we identified the Para, fusiform gyrus, sub-gyral, STG, IFG, and Claus (Shura et al., 2014). Previously, these structures were implicated in findings related to multiple sclerosis and the DMN, particularly the Para (Wu et al., 2016). Moreover, the Para was associated with pain modulation and sensitivity in chronic pain (Grant et al., 2010). Recent research has highlighted the Claus as a significant node in pain processing (Faig et al., 2024; Shura et al., 2014). However, no convergences were identified in the Thal, postcentral gyrus, ACC, or cerebellum among multiple sclerosis patients with fatigue, as previously demonstrated (Tanasescu et al., 2014).

In the context of Parkinson's disease, a decrease in the amplitude of low-frequency fluctuation was observed in the left putamen (Wang et al., 2018). Another ALE meta-analysis indicated convergent activity in the bilateral IPL and supramarginal gyrus (Tahmasian et al., 2017). Notably, when Parkinson's disease was accompanied by symptoms such as freezing of gait, activity was detected in the cerebellar locomotor region (CLR) (Gilat et al., 2019). Hence, suggesting this activity may be associated with symptoms of Parkinson's disease, rather than pain. These findings go against our findings, possibly due to the methodological differences where seed-based FC and amplitude of low-frequency fluctuation was utilised. Interestingly, when comparing P2 to P1, we found that the CT contributed significantly to the cluster, accounting for 75%, while the Pyr contributed the least at 4.3% (Kollndorfer et al., 2013; Gilat et al., 2019). In addition, the activity in the IFG, MFG, STG, and Pyr have been suggested to be associated with working memory and attention in multiple sclerosis patients (Kollndorfer et al.,

2013). This may suggest this activity was linked to cognitive and motor processes, rather than MSK pain processes.

The between-subjects meta-analysis revealed that patients exhibited greater convergences in the subcallosal gyrus, IFG, and MFG compared to pain-free (Ruppert et al., 2021; Amunts et al., 1999; Costafreda et al., 2006; Henssen et al., 2019; Gandolfi et al., 2017). Previous findings indicated activity in the subcallosal gyrus with Parkinson's disease during resting state (Ruppert et al., 2021). However, it contradicts recent findings (Ellis et al., 2023; Zou et al., 2023). In contrast, the control group showed a lack of convergence of differences which may suggest high level of variability.

Interestingly, follow-up subgroup meta-analysis, pain-free demonstrated convergent activity in the LN, compared to Parkinson's disease. While, Parkinson's disease showed activity in the ACC, in line with previous research suggesting this area link to pain processing (Konno and Sekiguchi, 2018; Fuchs et al., 2014). These heterogeneous findings can be attributed to the complex nature of multiple sclerosis and Parkinson's disease as neurodegenerative diseases. Nevertheless, when comparing between the primary meta-analyses and the subgroup meta-analysis we can see high overlap across the identified convergences, with few differences. This may mean multiple sclerosis studies did not significantly contribute to the overall neural representation in the primary meta-analyses. Moreover, factors that can potentially contribute to these findings may be the Parkinson's disease shared onset and progression of the disease, and symptoms such as MSK pain (Buhmann et al., 2020; Perrot et al., 2019).

3.9.2. Comparison with Existing Literature

Pain disorders of Parkinson's disease are evident on the established phase of the disease (Buzas and Max, 2004). In stage 4 of Braak's timeline for Parkinson's disease, lewy pathology is identified in the Claus and amygdala (Hawkes et al., 2010; Braak et al., 2003). This aligns with our findings when comparing patients without symptoms convergent activity to those with symptoms. Interestingly, the Claus is located directly medial to the pIns (Shura et al., 2014), which was associated with sensations of warmth and pain (Stephani et al., 2011).

Moreover, disease in the amygdala has been associated with impairment of emotion (Hawkes

et al., 2010). Notably, the number of included Parkinson's disease studies (k =23) was significantly higher than that for multiple sclerosis studies (k =5), which may further explain this trend. Importantly, stages 5 and 6 of Braak's for Parkinson's disease is prevalent and characterised by motor dysfunction, including impaired balance and frequent falls (Hawkes et al., 2010). This stage may be more relevant to MSK pain, where secondary motor disability is evident (Galazky et al., 2018; Giuffrida et al., 2005; Tseng and Lin, 2017).

These later stages highlight the need to consider the onset, severity, and transitions of Parkinson's disease and Parkinson's disease-related MSK pain. As symptoms vary across stages and significantly contribute to pain perception. However, the literature remains unclear regarding the type of pain (neuropathic or nociceptive) Parkinson's disease is experiencing (Mylius et al., 2021). Clarifying these uncertainties by establishing more objective criteria for pain types could enhance the interpretation of future findings.

The cerebellum and Claus, while not directly implicated in pain processing, may contribute to a pain matrix related to Parkinson's disease. The cerebellum's involvement in motor control and cognitive functions has been observed in early Parkinson's disease (Pietracupa et al., 2024; Li et al., 2023), as well as in multiple sclerosis patients with fatigue (Tanasescu et al., 2014). This supports our findings of convergent activity in the cerebellar structures when comparing chronic secondary MSK pain patients with symptoms to those without. Suggesting, the inferior part of the cerebellum role in in Parkinson's disease or multiple sclerosis early symptoms, possibly influenced by MSK pain (Schrag et al., 2015; Ford, 2010; Galazky et al., 2018; Giuffrida et al., 2005; Tseng and Lin, 2017).

The complex aetiology of pain in Parkinson's disease is multifactorial and may be influenced by factors such as depression and Rapid eye movement sleep behaviour disorder, which impact motor and non-motor symptoms such as MSK pain (Buhmann et al., 2020; Schapira et al., 2017). Although, the pathophysiologies of these symptoms remain unclear (Rahimpour et al., 2021; Appeadu and Gupta, 2020; Schapira et al., 2017; Truini et al., 2013; Kenner et al., 2007). Both diseases secondary MSK pain is associated to peripheral or central neurological disorders which are classified elsewhere (Perrot et al., 2019). Nevertheless, the mechanisms underlying

secondary MSK pain in Parkinson's disease and multiple sclerosis remain poorly understood, as some pain types require further classification to inform clinical interpretation (Kenner et al., 2007; Truini et al., 2013; Perrot et al., 2019). Pathways linking the substantia nigra (part of the basal ganglia) to pain processing have been described, and key regions such as the ACC, PFC, amygdala, Thal, Ins, S1 and S2, and the spinal cord (Wasner and Deuschl, 2012). These findings partially align with our subgroup meta-analysis of Parkinson's disease, which identified activity in the ACC and Para (located in the amygdala). Despite previous research detecting basal ganglia involvement in both Parkinson's disease and multiple sclerosis (Tona et al., 2014), the specific role in nociceptive pain remains unclear.

Our findings in chronic secondary MSK pain and Parkinson's disease indicated convergent activity in the frontal cortex, specifically the IFG. Neuroimaging studies have previously demonstrated associations between the PFC and abnormal pain-induced activity in Parkinson's disease (Gandolfi et al., 2017; Brefel-Courbon et al., 2005). Similarly, the Ins is implicated in pain processing across Parkinson's disease, multiple sclerosis, and pain-free populations (Kollndorfer et al., 2013; Blanchet and Brefel-Courbon, 2018; Labrakakis, 2023). However, an ALE meta-analysis revealed decreased spontaneous Ins activity in Parkinson's disease patients (Wang et al., 2018), suggesting variability influenced by pain subtypes and accompanying symptoms. These variations highlight the need to categorise pain types in Parkinson's disease and multiple sclerosis subgroups for improved understanding. The heterogeneity among Parkinson's disease and multiple sclerosis studies is evident, particularly regarding pain-specific neural substrates associated with MSK pain. Therefore, contributing factors such as differences in subtype, disease stage, and medication effects, which can exacerbate or alleviate pain symptoms (Li et al., 2022; Perrot et al., 2019; Buhmann et al., 2020). Addressing these factors in future research may reduce this variability and enhance our understanding of the neural substrates underlying specific conditions that experience secondary MSK pain.

3.9.3. chronic secondary MSK pain subgroups link to neural activity

The MSK pain is the most common type of pain associated with Parkinson's disease, affecting the muscles, bones, and skeleton, contributing to rigidity and reduced mobility (Engels et al.,

2018; Tinazzi et al., 2010). However, other classification systems categorised pain to be related or unrelated to disease, suggesting Parkinson's disease related pain can develop as nociceptive pain (Mylius et al., 2021). The current classification used in this work, emphasises secondary MSK pain is considered Parkinson's disease-related pain. This means pain arises from disease associated with motor dysfunction (i.e., stiffness) (Mylius et al., 2021; Perrot et al., 2019). For instance, Parkinson's disease disorders such as idiopathic or atypical parkinsonism are categorised as movement disorders and associated with MSK pain (Avenali et al., 2017; Goetz et al., 1986). However, drawing this distinction or related and unrelated MSK pain, through diagnosis and reporting these differences in research may be challenging.

Studies included in this meta-analysis investigated subtypes such as EDS, Rapid eye movement, and sleep behaviour disorder, previously been linked to the coeruleus/subcoeruleus complex and reticular nuclei (Hawkes et al., 2010). However, these prior findings disagree with the current findings. Pain-related brain structures have been extensively examined in Parkinson's disease. For instance, the N2 is associated with bilateral SII and Ins activity, while the P2 is involved with the ACC (Xia et al., 2016). These structures are suggested components of the pain matrix (Ingvar, 1999; Peyron et al., 2000; Tracey and Mantyh, 2007). A study assessing late event-related potentials (LEPs) in response to shoulder stimulation in Parkinson's disease patients with unilateral bradykinetic-rigid syndrome suggested similar N2/P2 latencies across groups. However, N2/P2 amplitudes were significantly lower in Parkinson's disease, indicating reduced activity in the ACC and Ins associated with attention to noxious stimuli (Tinazzi et al., 2008, 2009; Khan et al., 2024).

A follow-up study of hemiparkinsonian Parkinson's disease patients with MSK shoulder pain revealed further reductions in N2/P2 amplitude during noxious stimulation compared to pain-free patients (Tinazzi et al., 2010). These findings indicate abnormal nociceptive processing in Parkinson's disease, independent of motor clinical signs or medication status (Tinazzi et al., 2008, 2009, 2010). Moreover, this finding may suggest the activity in the pain matrix is pronounced during noxious stimuli, rather than spontaneous pain. By contrast, during rest, our findings show only the ACC activity with Parkinson's disease. This sheds light on

dynamic alterations in brain activity with Parkinson's disease patients, potentially implicating the ACC in MSK pain processing.

Functional connectivity (FC) studies explored pain-related connectivity in Parkinson's disease. They identified increased FC in the postcentral gyrus in Parkinson's disease during rest, with activity observed in both medication-naive patients and those off medication, suggesting medication-independent findings (Ji et al., 2018a). Decreased connectivity was identified in the Ins, basal ganglia, and between the accumbens and hippocampus in Parkinson's disease with non-motor symptoms such as pain (Filippi et al., 2019; Tan et al., 2015; Polli et al., 2016). These findings suggest a complex "pain matrix" involvement with Parkinson's disease, predominantly within the default mode network (DMN) (Filippi et al., 2019). However, such results often stem from seed-based approaches, which may bias findings towards specific structures and hinder whole-brain comparisons.

Activity in regions such as the IFG, STG, and fusiform gyrus identified in this study aligns with previous findings of altered resting-state amplitude of low-frequency fluctuations in Parkinson's disease (Zhang et al., 2013). Similarly, cerebellar activity observed in regions such as the posterior lobe, including the CT, supports its involvement in non-motor manifestations of Parkinson's disease (Wu and Hallett, 2013). These findings suggest aberrant activity in these regions may reflect underlying disease mechanisms, rather than MSK pain specifically.

A large-scale ALE meta-analysis examined brain abnormalities in Parkinsonian disorders and identified shared neural substrates across different subgroups, such as progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS) (Ellis et al., 2023), that share similar symptoms that lead to MSK pain (Chang et al., 2021). Their findings highlighted the Thal, IFG, and middle temporal gyrus as key areas (Ellis et al., 2023; Shao et al., 2014). While, their MRI findings did not align with our findings, the positron emission tomography findings corroborated IFG involvement (Ellis et al., 2023). While, these shared neural substrates across Parkinsonian syndromes may be identified, they do not provide a clear identification of the specific structures responsible for MSK pain. Particularly, whether pain is unrelated, or related to Parkinson's disease; secondary to disease processes (Perrot et al., 2019; Mylius et al., 2021).

Additionally, variability in included syndromes may reflect the type of pain (i.e., neuropathic or nociceptive pain), further complicating interpretation. Interestingly, the activity in the MFG, STG, and Claus align with a previous CBMA meta-analysis of multiple sclerosis studies (Chiang et al., 2019). However, this activity was not diminished in subgroup analyses, suggesting shared neural mechanisms between Parkinson's disease and multiple sclerosis, potentially reflecting motor functions or MSK pain processing.

Overall, these findings emphasise the importance of recognising methodological heterogeneity in neuroimaging studies. While FC and amplitude of low-frequency fluctuation are commonly employed approaches in Parkinson's disease studies (Ji et al., 2018a; Tahmasian et al., 2017), coordinate-based ALE analyses focus on consistency across activated foci rather than connectivity between nodes (Yu et al., 2024; Tench et al., 2020). Differences in methodological approaches, such as ALE and voxel-based methods, may explain the discrepancies in findings (Chiang et al., 2019; Klawiter, 2013). In addition, the limited number of whole-brain studies examining Parkinson's disease and multiple sclerosis further underscores the need for more research to consolidate pain-related activity, while minimising bias, and to better understand the neural substrates associated with chronic secondary MSK pain during rest.

3.9.4. Methodological Considerations and Broader Implications

A recent study investigated cortical morphometric alterations in Parkinson's disease patients with severe and mild hyposmia [9] using surface-based morphometry (Li et al., 2024). The study employed cFWE inference correction to control for false positives and adjust for multiple comparisons ($p < 0.05$). Structural changes were identified in the superior temporal cortex for both mild and severe hyposmia, aligning with our STG findings (P1 > P2). Similarly, this activity was observed with MS,in an ALE meta-analysis with FDR (correction) (Kollndorfer et al., 2013).

Although, the studies included in P1 did not report non-motor symptoms in Parkinson's disease or MS, unlike P2, where these symptoms were reported. Motor dysfunction typically drives

[9]Hyposmia, a non-motor symptom of Parkinson's disease characterised by a reduced sense of smell, has been suggested as a potential predictive marker for neurological diseases such as Parkinson's disease (Sui et al., 2019)

clinical Parkinson's disease diagnosis (Tolosa et al., 2009), these findings suggest a potential role of the STG in non-motor symptoms rather than MSK pain processing (Tan et al., 2015; Shah-Basak et al., 2018). Other findings indicate STG involvement in shaping biased pain-related memories and emotional processing. For instance, exaggerated pain responses were mitigated when single-pulse transcranial magnetic stimulation when applied over the STG (Houde et al., 2020). This highlights its role in modulating emotional and cognitive processes.

A CBMA study examining resting-state activity in Parkinson's disease using signed difference map analysed 15 amplitude of low-frequency fluctuation studies, 11 regional homogeneity studies, and combined studies of both methods (Wang et al., 2018). Using an uncorrected threshold of $p < 0.001$ for FDR, they found increased regional homogeneity in the SFG and middle frontal gyrus and decreased amplitude of low-frequency fluctuation activity in the fusiform gyrus compared to pain-free. Our chronic secondary MSK pain (no symptoms) findings partially align, as we observed fusiform activity that diminished in the pooled findings. Moreover, we identified activity in the IFG and MFG, consistent with previous ALE meta-analyses (Henssen et al., 2019; Jia and Yu, 2017), however no activity detected in the SFG and middle frontal gyrus. The discrepancies may stem from methodological differences, such as signed difference map's uncorrected FDR threshold, which has been criticised for yielding spurious clusters (Eickhoff et al., 2012). Corrected FDR thresholds, while addressing false positives, may also underperform (Laird et al., 2005a). These methodological variations contribute to the heterogeneity and limit the accuracy of findings.

In MS, resting-state FC has been reported in the DMN (Bonavita et al., 2011; Rocca et al., 2010) and sensorimotor network (Lowe et al., 2008), with alterations influenced by disease stage and cognitive functions (Faivre et al., 2012; Sumowski et al., 2013; Loitfelder et al., 2012). Studies have also highlighted the fronto-parietal network's role in cognitive function during rest (Tommasin et al., 2020; Meijer et al., 2017; Riccitelli et al., 2020). In the current work, we identified abbarent activity in the IFG, MFG, and STG, aligning with multiple sclerosis ALE meta-analysis (Kollndorfer et al., 2013). However, in line with previous findings, this activity may be implicated with working cognitive functions (i.e., memory and attention

task), rather than MSK pain during rest.

Despite the growing interest in resting-state FC, the field lacks sufficient whole-brain rs-fMRI studies in multiple sclerosis, with most research focused on task-based or network-specific FC approaches (Rocca et al., 2022). This limitation hindered the inclusion of enough multiple sclerosis studies for a balanced whole-brain meta-analysis representing both Parkinson's disease and multiple sclerosis, equally. Addressing this would improve the current understanding of the neural mechanisms underlying MSK pain in chronic secondary MSK pain conditions.

3.9.5. Behavioural data implications

Overall, the gender ratio of participants from the extracted studies indicated a higher number of females than males experiencing MS. This is in line with previous evidence showing greater prevalence of this condition among women (Hittle et al., 2023; Wallin et al., 2019). Moreover, a cross-sectional study in Saudi Arabia suggested higher MSK pain prevalence in females, with 229 out of 360 participants (mean age of 34.9) reporting discomfort (Amer et al., 2022). Among these, 28.9% were diagnosed with RRMS, and 34.4% reported high levels of disability. Notably, 55.6% experienced MSK pain, while 21.1% reported neuropathic pain. Although, the current meta-analyses do not fully capture the complexity of MS, these findings highlight the prevalence of MSK pain with female RRMS patients. However, it also underscores neuropathic pain and its possible contribution in the current findings, particularly, when coexisting with MSK pain (Perrot et al., 2019). Therefore, it is crucial to distinguish between the two types of pain—or their coexistence—in order to clarify any ambiguities that may influence the underlying pathophysiology.

A study investigating MSK pain in Parkinson's disease patients (n = 260) found that 45.58% experienced MSK pain, with a higher prevalence among older females (Li et al., 2022). Of those reporting MSK pain, 77.67% experienced pain in the lower limbs, followed by pain in the upper body and back (n = 93, 45.15%). Other studies suggested MSK pain can arise anytime during the disease course (Perrot et al., 2019). Our findings revealed a total of 534 female and 591 male patients with Parkinson's disease, with an average age of 61.17 (Li et al., 2022; Marras et al., 2018). Although the gender differences in Parkinson's disease were less

pronounced than in multiple sclerosis, they align with previous findings suggesting multiple sclerosis is present with younger age groups (McGinley et al., 2021; Buhse, 2008; Bashir and Whitaker, 1999), while Parkinson's disease with older adults (Parkinson's, 2018; Marras et al., 2018). Despite, Parkinson's disease prevalence with males (Parkinson's, 2018; Marras et al., 2018), these findings may suggest that the neural substrates associated with MSK pain observed in the current meta-analysis reflect mostly the female sample population.

The average disease duration across studies for Parkinson's disease and multiple sclerosis was 6.4 years (76.8 months). According to Braak's Parkinson's disease hypothesis, this duration corresponds to stages 4–5 of disease progression, which precede the Hoehn and Yahr classification and occur after clinical onset (i.e., diagnosis) (Hawkes et al., 2010). Notably, various types of pain are recognised as early as stage 1 (Schrag et al., 2015; Ford, 2010). Recognising pain in Parkinson's disease as early as stage 1 suggests it could serve as an early marker of disease onset.

Moreover, the current work included fourteen studies, where unmedicated patients for at least six hours before the rs-fMRI session. A review showed that patients on treatments such as levodopa experienced a 30% reduction in MSK pain over a short period (Blanchet and Brefel-Courbon, 2018), although 17.48% of patients showed no improvement, and some reported worsening pain. Research suggests dopamine deficiencies may correlate with MSK pain (Blanchet and Brefel-Courbon, 2018), indicating Parkinson's disease off or on medication may either increase or suppress pain-specific activation associated with MSK pain.

Furthermore, we identified twenty-three studies published in Asia and five from Western countries. Additionally, fifteen studies included patients on medication, while fourteen unmedicated. Some studies treated medicated and non-medicated groups as separate entities, raising questions about how medication, socioeconomic status, and cultural influences contribute to MSK pain. In lower-income countries, limited access to treatment may exacerbate MSK pain, as patients may lack financial resources and proper medical services (Petrova et al., 2022; Umeh and Feeley, 2017). Understanding how medication accessibility varies across countries and how it influences the onset of MSK pain and disease duration in chronic

secondary MSK pain could provide valuable insights into the impact of healthcare systems and socioeconomic status on MSK pain.

Furthermore, non-motor symptoms such as MSK pain was previously linked to depression (Tai and Lin, 2020). Others suggested, depression and anxiety are prevalent in MSK pain populations (Boeschoten et al., 2017; Sagna et al., 2014). In the current work, seven Parkinson's disease studies reported depression scores (M=10.77, SD=5.8), two studies reported anxiety (M=16.41, SD=9.96), and no studies included these measures for MS. Importantly, depression is a common symptom of chronic pain conditions, and the severity often depends on the management of physical well-being, including physical therapy, sleep quality, and diet. Risk factors for developing lower back pain include older age, rigidity, and poor posture, which may increase depression levels (Tai and Lin, 2020). These findings highlight the need for more comprehensive reporting on depression and anxiety in patients with chronic secondary MSK pain conditions to better understand the relationship between psychopathologies and MSK pain. Improved reporting can help develop targeted treatment strategies that address the specific symptoms of MSK pain (Buhmann et al., 2020).

3.9.6. Limitations and Future Perspectives

The limitations of this study highlight several important considerations. Whole-brain studies reporting peak coordinates are scarce, with most research focusing on ROI, seed-based analyses, or FC—particularly in multiple sclerosis. Similarly, studies on Parkinson's disease predominantly utilise seed-based or FC methods (Ji et al., 2018a; Pan et al., 2017; Tahmasian et al., 2017; Pietracupa et al., 2024), reflecting a similar trend in multiple sclerosis research (Wu et al., 2016; d'Ambrosio et al., 2017; Liu et al., 2015; Tona et al., 2014). Additionally, we included both corrected and uncorrected images due to the limited number of experiments available, which may have influenced our findings and their interpretability. This underscores the need for more whole-brain ALE meta-analyses utilising consistent correction statistical methods to increase the reliability of the pain-specific convergences linked to chronic secondary MSK pain.

An issue identified during the full-text screening was the inadequate reporting of neural

coordinates in studies, particularly in within-subjects experiments. A significant number of studies fitting the inclusion criteria were excluded due to missing or incomplete coordinate data, such as reporting results as "patients and pain-free" without specifying coordinates, or omitting them entirely (Engels et al., 2018; Filippi et al., 2021; Hou et al., 2018; Dogonowski et al., 2013; Seixas et al., 2016). Adherence to recommended neuroimaging guidelines (Müller et al., 2018) is crucial for enhancing transparency and reproducibility in chronic secondary MSK pain research, particularly in within-subjects experiments employing whole-brain analyses.

Our findings are more representative of Parkinson's disease literature, with only a limited number of five studies for multiple sclerosis; however, a greater sample size (n = 2414) compared with Parkinson's disease. While sufficient for initial exploration, this limits the generalisability of the results and the ability to fully capture Parkinson's disease and multiple sclerosis from a well-distributed number of studies and samples. Comorbidities associated with Parkinson's disease and multiple sclerosis further complicate interpretation, as they may be accompanied by symptoms or disease related- or unrelated-pain (Mylius et al., 2021). Consequently, directly or indirectly influencing MSK pain (Perrot et al., 2019). Previously, Perrot et al. (2019) reported pain assessment in Parkinson's disease patients is challenging when cognitive or depressive symptoms are present.

MSK pain is the most common type of pain in Parkinson's disease, with its intensity often increasing during periods of heightened (Buhmann et al., 2020; Goetz et al., 1986). Notably, medication also contributes to the pain experience, as patients off medication tend to experience greater pain severity (Schapira et al., 2017). In the current study, due to our strict criteria, excluding medication would have reduced the number of relevant studies. As a result, we included studies involving patients both on and off medication, which may have influenced the findings. Furthermore, MSK pain in Parkinson's disease can stem from both motor and non-motor symptoms, suggesting nociceptive origins that are not directly linked to the disease itself (Buhmann et al., 2020; Perrot et al., 2019). Similarly, in multiple sclerosis, pain often originates from MSK structures unrelated to the disease (Perrot et al., 2019). However, some studies suggest that MSK pain is directly related to Parkinson's disease (Mylius et al., 2021;

Nardelli et al., 2024). Therefore, it remains unclear in the present study whether the presence of MSK pain is solely associated with motor symptoms linked to the disease or if MSK pain developed prior to the onset of motor dysfunctions associated with the disease.

Moreover, there are uncertainties regarding whether patients were formally diagnosed with MSK pain, as this was not reported in the included studies, despite its prevalence in both conditions (Rukavina et al., 2024; ShayestehAzar et al., 2015). MSK pain is documented across all multiple sclerosis subtypes (Brola et al., 2014; Bernardini et al., 2016), which may result from symptoms such as muscle spasms, low back pain, and general muscle discomfort (O'Connor et al., 2008; Nurmikko et al., 2010). Multiple sclerosis, including subtypes such as PPMS and SPMS, shares some symptoms that may gradually lead to MSK pain (e.g., spasticity, rigidity, postural imbalance, mobility issues such as joint stiffness) (Perrot et al., 2019; McBenedict et al., 2024a; Truini et al., 2012). However, some of these symptoms may be related to neuropathic pain rather than nociceptive pain. The included studies lacked explicit reporting of pain types and the onset of pain, so we inferred MSK pain diagnoses based on subgroup characteristics. However, a more transparent reporting system is necessary to draw meaningful conclusions regarding MSK pain in chronic secondary MSK pain populations.

Furthermore, cognitive impairment in attention, memory, learning, and decision-making has been reported in one-third of chronic pain patients (Moriarty et al., 2011). The link between MSK pain and cognitive impairment, as well as the influence of non-motor symptoms such as depression or anxiety in Parkinson's and multiple sclerosis, requires further research. This underscores the need for more detailed reporting of pain types, pain onset, and symptoms within these clinical populations to deepen our understanding of the relationship between pain and these diseases.

These limitations suggest several promising directions for future research. Whole-brain investigations should be prioritised, particularly with MS. This will ensure the results are not biased toward a specific ROI and provide a well-balanced representation of chronic secondary MSK pain meta-analyses. The within-subjects may enhance our understanding of individual variability. Studies should also report MSK pain characteristics—such as duration, intensity,

and location—alongside comorbidities or symptoms. This would facilitate a clearer understanding of how these factors can influence chronic secondary MSK pain's underlying pathophysiological mechanisms.

Future research should further investigate the relationship between MSK pain and sleep disturbances in Parkinson's disease, as a study involving 300 participants identified a moderate to high correlation between the two and highlighted MSK pain as a significant predictor of sleep problems (Martinez-Martin et al., 2019). This finding underscores the interconnected nature of Parkinson's disease symptoms, emphasising the need to explore the mechanisms that link MSK pain and sleep disturbances.

Moreover, cross-sectional studies could offer valuable insights into demographic and geographical variations in the occurrence of chronic secondary MSK pain. For example, investigating whether patients in low-income countries experience prolonged MSK pain compared to those in high-income countries—while considering treatment accessibility as a moderating factor—could help clarify the influence of genetic and socio-economic factors on disease onset or duration.

In summary, these findings underscore the necessity of exploring and reporting pain types, particularly MSK pain, to establish the neural substrates associated with chronic secondary MSK pain. Future research should address these gaps to provide accurate findings that inform clinicians and researchers, enabling more targeted interventions and comprehensive meta-analyses.

3.10. Conclusion

This meta-analysis provides valuable insights into the neural mechanisms associated with chronic secondary MSK pain diseases. The primary objective was to identify BOLD signal patterns linked to the spontaneous pain within the chronic secondary MSK pain population. By employing cFWE and vFWE methods, we observed notable differences in spatial convergence patterns. Specifically, using cFWE inference correction, patients exhibited significant convergences in the subcallosal gyrus, IFG, and MFG compared to pain-free, whereas no convergence differences were detected with vFWE correction.

When examining chronic secondary MSK pain patients with and without symptoms, variable neural activity was identified in regions such as the sub-gyral, Para, and CT. Parkinson's disease patients exhibited neural activity patterns similar to chronic secondary MSK pain patients but showed distinct differences in the ACC and LN compared to pain-free. Further subgroup variability emerged: Parkinson's disease patients without symptoms displayed differences in the Para and fusiform gyrus, while those with symptoms showed overlapping activity in the cerebellum.

These findings underscore the intricate variability of chronic secondary MSK pain conditions, potentially influenced by differences in symptoms, treatment, or methodological approaches. They highlight the complexity of identifying MSK pain as a shared neural mechanism underlying chronic secondary MSK pain, particularly between symptomatic and asymptomatic patients. This emphasises the critical importance of thoroughly reporting pain types and symptoms in future studies to advance the understanding and diagnostic framework for chronic secondary MSK pain.

4. General Discussion

4.1. General Literature Review

Conditions within classifications such as chronic primary pain and chronic secondary MSK pain have a complex and multifaceted aetiology, often involving unknown underlying pathomechanisms and pathophysiological mechanisms (Sagredo et al., 2024; Dorsey et al., 2024; Censi et al., 2024; Di Rosa et al., 2023; Patil et al., 2024; ALMohiza et al., 2023; Dizner-Golab et al., 2023). As a result, there exists a notable deficiency in empirical evidence that clarifies the aetiological origins of numerous chronic pain conditions (Woolf and Doubell, 1994; Do et al., 2023; Meylakh and Henderson, 2022; Enck et al., 2016; Kenner et al., 2007; Buhmann et al., 2020; Schapira et al., 2017; Rahimpour et al., 2021). This ambiguity regarding the distinct pathophysiological and psychophysiological mechanisms underlying chronic pain is reflected in the heterogeneity of the empirical literature (Wang et al., 2022; Xu et al., 2021; Friebel et al., 2011; Tanasescu et al., 2016; Giesecke et al., 2004; Russo et al., 2012; Burgmer et al., 2012; Bouhassira et al., 2013; Gerdelat-Mas et al., 2007; Mylius et al., 2009; Brefel-Courbon et al., 2005; Ji et al., 2018a; Tahmasian et al., 2017; Wu et al., 2016; Liu et al., 2015; Tona et al., 2014; Tanasescu et al., 2014; Scholz et al., 2019). Consequently, there is an urgent need for researchers and clinicians to reconsider some of these differences present with chronic pain conditions for the advancements of pain research and the development of treatment.

Previous taxonomies approached diagnosis of chronic pain from a narrow, evidence-based perspective, overlooking its intricate and multifaceted nature. The implementation of the International Classification of Disease 11th edition Revision, was essential to address the variability among chronic pain conditions, as it introduces a new framework that positions *Pain* at different hierarchical levels based on the underlying disease. This system acknowledges the diverse pathophysiological mechanisms contributing to the experience of chronic pain while integrating the biopsychosocial framework (Nicholas et al., 2019; Perrot et al., 2019).

This thesis aims to achieve several objectives:

1. To evaluate the consistency of neuroimaging findings while accounting for these classifications.

2. To identify reliable pain-specific patterns associated with each classification during provoked or spontaneous pain.

3. To examine the effectiveness of the diagnostic taxonomies for chronic primary pain *(Pain as a stand-alone condition)* and chronic secondary MSK pain *(Pain as a symptom of an underlying condition)* in the context of neuroimaging research.

4.2. Summary of overall findings

With chronic primary pain, we examined the relationship between BOLD signals and provoked pain in chronic primary pain patients compared to pain-free. We used this taxonomy and conducted an fMRI meta-analysis, finding that only one meta-analysis explored chronic primary pain classification in the context of resting state (Wang et al., 2022). The primary analysis, encompassing 75 within-subjects experiments, aimed to identify neural substrates within patient and control groups. However, to our knowledge, no prior meta-analysis has explored neural correlates of chronic secondary MSK pain during rest.

With chronic secondary MSK pain, we included 62 between-subjects experiments to assess differences in spatial convergences link to spontaneous pain between chronic secondary MSK pain patients and pain-free during resting state. Additionally, we investigated differences between chronic secondary MSK pain patients with symptoms and those without (Müller et al., 2018). While findings indicated distinct convergences between chronic primary pain and chronic secondary MSK pain, some shared patterns emerged. In the current work, only one meta-analysis of pain-free individuals employing vFWE correction revealed spatially convergent activity. Notably, with chronic primary pain, control group analysis showed convergence in a single cluster involving the MCC and MFG, demonstrating robust activity that survived vFWE correction. This finding aligns with previous assertions regarding the conservative nature of vFWE methods (Eickhoff et al., 2016), and underscores the importance of the MCC and MFG in pain processing among pain-free.

The within-subjects experiments conjunction and single meta-analysis findings of patients using cFWE correction, revealed similar activation patterns. The latter, indicated convergent activity

in the MCC, ACC, dvaIns, Claus, MFG, PreG, and LN. The former identified the daIns, MCC, MFG, and Claus overlaps. The contrasts meta-analysis of patient identified significant differences in two clusters involving the vaIns, Claus, and IFG ($p < 0.007$), daIns and Claus ($p < 0.01$).

Although overlapping activity emerged between patient and control groups in single meta-analyses, these structures were absent in the control contrasts meta-analysis. This suggests stronger spatial convergence among pain-free in the MCC, SFG, and MFG, while patients exhibited stronger activity in the vdaIns, Claus, and IFG. Competing clusters, surpassing the conservative threshold ($p = 0.01$) (Lobo et al., 2023), provide insights into dominant clusters linked to provoked pain and their group-specific associations.

For instance, the Claus appeared in two clusters with patients and one cluster with pain-free. The vaIns and daIns were present in two clusters with patients, and only once for pain-free (i.e., daIns). Conversely, the CG showed convergence in both groups and stronger activity in the contrasts meta-analysis with pain-free, aligning with the "pain matrix" concept. This suggests the Ins and cingulate cortex as critical regions for nociceptive pain (Ingvar, 1999; Peyron et al., 2000; Rainville, 2002; Legrain et al., 2011). It is crucial to clearly understand the distinction between group comparisons and contrast meta-analysis to avoid any misinterpretation of the results, see Table 26.

Moreover, the decreased activity of the ACC, a known pain-processing hub, may contribute to pain symptomatology in patients (Konno and Sekiguchi, 2018; Fuchs et al., 2014). Furthermore, the aIns has previously been implicated in emotional dysregulation in chronic pain (Mandloi et al., 2023). Collectively, these findings suggest the daIns, ACC, and MCC may serve as neural markers for chronic primary pain experiencing provoked pain, reflecting mechanisms such as emotional dysregulation and depression (Nomi et al., 2016; Xiang et al., 2018).

The chronic secondary MSK pain conjunction and contrast analyses revealed no significant differences in convergences between chronic secondary MSK pain patients and pain-free during resting state. This may reflect the variability that exists in chronic secondary MSK pain conditions and factors such as medication, disease stage, symptoms, and studies methodological

Aspects	Meta-analysis Group Comparison	Meta-analysis Contrasts
Objectives	Identify consistent differences between groups	Identify differences in the convergence of activation between groups
Focus	Convergence of differences in brain activation between groups	Differences in convergences of brain activation between groups
Key Results	reflects the **convergence of differences of Group A, compared to Group B**	reflects the **differences in the stability or consistency of activity in one group**
Example interpretation	Group A shows *consistent* convergence in region X, compared to Group B	Group A show *stronger* convergence in region X, than Group B

Figure 26: Differences between meta-analyses of group comparisons and meta-analytic contrast analyses (Müller et al., 2018). Group comparison refers to meta-analysis of between-subjects experiments.

differences (Gerdelat-Mas et al., 2007; Mylius et al., 2009; Brefel-Courbon et al., 2005; Ji et al., 2018a; Tahmasian et al., 2017; Wu et al., 2016; Liu et al., 2015; Tona et al., 2014; Tanasescu et al., 2014). Pain-free showed no convergent activity, this group did not have history of chronic pain which may contribute to the variability, when compared to ongoing pain across chronic secondary MSK pain conditions. The meta-analysis of chronic secondary MSK pain patients revealed a cluster encompassing the IFG, MFG, and subcallosal gyrus. Subgroup analysis of Parkinson's disease studies (k = 17) showed similar trends after excluding multiple sclerosis studies (k = 4). Interestingly, Parkinson's disease subgroup analysis identified an additional cluster in the ACC, absent in the chronic secondary MSK pain primary findings. Similarly, the ACC, IFG, and MFG were identified in chronic primary pain. The subgroup meta-analyses of Parkinson's disease revealed reduced variability and shared neural substrates related to pain perception compared to chronic secondary MSK pain (Xiang et al., 2018). In addition, Parkinson's disease contrast meta-analyses highlighted stronger activity in the subcallosal gyrus, compared to pain-free. Single meta-analysis of pain-free subgroup demonstrated activity in the LN (k = 17), activity that was absent in the primary outcome.

We also examined chronic secondary MSK pain patients with and without symptoms (k = 20). Combined meta-analyses of chronic secondary MSK pain and Parkinson's disease subgroups

identified overlapping structures, including the cerebellum activity, Para and sub-gyral. These findings indicate that the Parkinson's disease population demonstrates consistent differences in convergences. Contrast analyses revealed stronger convergence in the Para among asymptomatic Parkinson's disease patients compared to symptomatic ones ($k = 18$), aligning with chronic secondary MSK pain without symptoms findings (Wu et al., 2016).

Meanwhile, asymptomatic patients showed consistent neural patterns and reduced variability. On the other hand, the reduced convergences when comparing chronic secondary MSK pain to pain-free, may be due to the heterogeneity within this meta-analysis. For the primary findings, chronic secondary MSK pain consisted multiple sclerosis and Parkinson's disease, patients with and without symptoms, and patients on and off medication. These factors within chronic secondary MSK pain increase variability in the brain and may complicate the interpretation of which structure is associated with MSK pain. Previous research has reported that medication reduces brain activity (Blanchet and Brefel-Courbon, 2018). Notably, the studies included that represented patients without symptoms did not report the absence or presence of MSK pain or other symptoms. Likewise, symptoms-related studies did not report the presence or absence of MSK pain. Instead, they reported symptoms such as freezing of gait, excessive daytime sleepiness, akinesia, or depression, all of which exacerbate MSK pain (Buhmann et al., 2020; Perrot et al., 2019). Though, MSK pain was previously linked to rigidity and gait changes commonly in Parkinson's disease and multiple sclerosis (Álvarez-Cubero et al., 2022; Rukavina et al., 2024; O'Connor et al., 2008; Schapira et al., 2017; Perrot et al., 2019). Clear reporting with studies is essential for a better understanding of the onset of MSK pain and related symptoms in chronic secondary MSK pain conditions, which may lead to improved interpretation of the findings.

Based on the biopsychosocial framework, these classifications clarify shared symptoms within groups (Nicholas et al., 2019; Perrot et al., 2019). chronic primary pain revealed consistent convergences compared to chronic secondary MSK pain. This reflects the greater variability and aetiological complexity of chronic secondary MSK pain, where secondary MSK pain arises from underlying diseases (Perrot et al., 2019). These findings highlight distinct but overlapping

neural activity patterns, contributing to our understanding of pain processing in chronic conditions.

4.3. Synthesis and Theoretical Implications

4.3.1. Neuroimaging Findings and Variability in Chronic Pain

Chronic primary pain diagnosis was intended to reduce uncertainty regarding the aetiologies of specific chronic pain conditions and to focus on pain present in one or more anatomical regions (Nicholas et al., 2019). Notably, the nociplastic neurophysiological mechanism has been suggested as applicable to chronic primary pain (Nicholas et al., 2019; Kosek et al., 2016, 2021), although this is not yet fully understood. In contrast, the chronic secondary musculoskeletal pain diagnosis specifies that pain originates from persistent nociception within musculoskeletal structures (Perrot et al., 2019). This includes aetiologies such as local, systemic, or deep somatic lesions, thereby identifying specific causes of musculoskeletal pain (Perrot et al., 2019). Notably, some musculoskeletal pain are not nociceptive, particularly when Parkinson's Disease or multiple sclerosis presents as neuropathic pain (i.e., pain arising from nerve damage causing sensations such as burn or shooting). Therefore, while one taxonomy addresses the aetiology of musculoskeletal pain, neither taxonomy directly addresses the pathophysiological differences. Pain mechanisms include of chronic pain (1) central or peripheral sensitisation, (2) ectopic excitability, and (3) structural reorganisation or phenotypic neuronal changes (Mathew, 2016). The pain mechanisms involved in the reported structures in chronic primary pain are mapped in Table 22.

The mechanism of ectopic neuronal changes suggests that damage to nociceptive neurons and cytokine activity can lead to the generation of ectopic action potentials. Notably, this results in sensory inflow even in the absence of a peripheral stimulus (Crodelle and Maia, 2021). However, a previous study suggested that these changes may be more closely associated with neuropathic pain rather than musculoskeletal pain (Crodelle and Maia, 2021). In particular, lesions in the peripheral fibres may contribute to the generation of ectopic activity in primary afferent fibres, where injury-induced disconnection from the periphery leads to this abnormal

Brain Region	Associated Pain Mechanism	Pain Conditions Likely Involved
Anterior Insula	Central Sensitisation (Amplifies pain perception and emotional distress)	FB (Cagnie et al., 2014), cLBP (Fan et al., 2023), IBS (Bednarska et al., 2019), MI (Coppola et al., 2020)
Anterior Cingulate Cortex	Dysfunctional Descending Modulation	FB (Cagnie et al., 2014) MI (Maizels et al., 2012)
Midcingulate Cortex & Insula*	Central Sensitisation & Glial Activation (Pain processing & inflammation)	FB (Cagnie et al., 2014; Albrecht et al., 2019), cLBP (Özyurt et al., 2024), MI* (Dai et al., 2021)
Medial Frontal Gyrus	Ephapses & Phenotypic Neuronal Changes (Cognitive-affective pain modulation, sensory processing)	FB (Cagnie et al., 2014)
Inferior Frontal Gyrus & Anterior Insula*	Descending Pain Modulation & Emotional Pain Processing (Pain suppression & catastrophising)	FB (Cagnie et al., 2014), CLBP (Fan et al., 2023), IBS* (Bednarska et al., 2019), MI* (Mainero et al., 2011)

Table 22: Mapping Brain Structures Current Findings of Chronic Primary Pain to Pain Mechanisms. *Abbreviations*: FB, Fibromyalgia; cLBP, chronic low back pain; IBS, irritable bowel syndrome; MI, migraine

activity (Crodelle and Maia, 2021; Serra et al., 2012; Kleggetveit et al., 2012; Tesfaye et al., 2013).

Widespread conditions such as fibromyalgia may also exhibit ectopic activity originating from deep somatic tissues (Koroschetz et al., 2011). Continuous ischaemia in muscles has been linked to peripheral sensitisation and ectopic activity in both nociceptive and non-nociceptive afferent neurons (Grassi et al., 1994; Lund et al., 1986; Sandberg et al., 2005; Mense and Stahnke, 1983). Moreover, neuropsychological factors such as severe major depressive disorder may also contribute to pain mechanisms. Previous studies have identified increased activity in the anterior cingulate cortex, suggesting that this activity is predominantly linked to microglial activation during major depressive episodes (Holmes et al., 2018). Thus, while certain mechanisms are more relevant to specific pain types (e.g., nociceptive or neuropathic pain), some pain mechanisms are more strongly associated with specific chronic primary pain conditions compared to others (e.g., central sensitisation and descending pain modulation).

Understanding the mechanisms involved in chronic pain is crucial, as it can facilitate the development of targeted therapeutic interventions (Mathew, 2016).

On the other hand, the mechanisms underlying secondary musculoskeletal pain in Parkinson's disease and multiple sclerosis remain variable or not fully elucidated. Previous studies have linked Parkinson's disease-related pain to motor fluctuations and dyskinesias, resembling both fluctuation-related pain and musculoskeletal pain (Tai and Lin, 2020; Coelho et al., 2008). Moreover, the severity of pain has been shown to correlate significantly with the severity of motor complications (Coelho et al., 2008). One possible explanation is the involvement of dopaminergic pathways in the descending pain inhibitory system (Grashorn et al., 2015). Additionally, another study suggested that small fibre neuropathy may contribute to central sensitisation to peripheral inputs, as it has been associated with an increased perception of pleasantness in response to touch in individuals with Parkinson's disease (Kass-Iliyya et al., 2017). However, this does not necessarily rule out the role of central sensitisation in Parkinson's disease-related pain. While pain and touch are processed through distinct nerve fibres, they may overlap within neural pathways, as seen in allodynia.

For instance, non-specific pain subtypes in Parkinson's disease may be exacerbated by central mechanisms (Marques et al., 2019). In particular, central sensitisation may play a role in various chronic primary pain conditions, including musculoskeletal pain (Arendt-Nielsen et al., 2018). Therefore, this mechanism may be especially relevant to chronic secondary musculoskeletal pain conditions. In line with our findings, previous EEG studies in Parkinson's disease have identified the ACC and Ins as key structures involved in Parkinson's disease-related pain (Lu et al., 2021). Specifically, excitation of cortical synapses—through mechanisms such as increased presynaptic glutamate release, structural synaptic modifications, and enhanced postsynaptic glutamate receptor responses—has been associated with chronic pain and emotional distress, including anxiety (Lu et al., 2021).

Furthermore, long-term potentiation (LTP) plays a crucial role in chronic pain, where heightened synaptic activity leads to amplified and persistent pain perception. In pain-processing structures such as the ACC and Ins, LTP may enhance pain signal transmission,

contributing to chronic pain states (Lu et al., 2021). Animal model studies suggest that inhibiting LTP induction in the ACC and Ins can reduce or block chronic pain (Zhuo, 2016; Li et al., 2019). This indicates that disrupting LTP in these regions could serve as a potential therapeutic target to mitigate long-term pain amplification.

The underlying mechanisms of pain in multiple sclerosis remain unclear (O'Connor et al., 2008). Previously, neuropathic pain type included broader conditions which involve secondary changes in the nervous system (e.g., central sensitisation), suggesting pain may not be directly from nerve damage. This included MSK pain in multiple sclerosis (Truini et al., 2013). Therefore, the updated definition in IASP provides a clearer and more specific distinction between pain types.

Though certain aetiologies/injuries in this disease may result in neuroinflammation, central sensitisation-without peripheral damage (Hains and Waxman, 2006). This suggests that there may be an interaction between peripheral and central sensitisation (Ji et al., 2018b). Previous research was not able to identify the role of central sensitisation in neuropathic pain in multiple sclerosis (Srotova et al., 2021). However, central sensitisation is a key mechanism in MSK pain (Yunus, 2007).

Moreover, research has examined the neuroanatomical and physiological changes associated with painful conditions in multiple sclerosis (O'Connor et al., 2008). A conceptual framework has been proposed to establish an evidence-based approach for identifying pain mechanisms in multiple sclerosis. In particular, this framework includes musculoskeletal pain, such as painful tonic spasms, lower back pain, and muscle spasms (O'Connor et al., 2008).

These symptoms in multiple sclerosis, predispose patients to develop secondary musculoskeletal pain, particularly in the lower back. Moreover, motor neuron lesions can lead to involuntary, intermittent, painful muscle contractions (O'Connor et al., 2008). Although this type of pain is caused by demyelination, it is not classified as neuropathic pain because the nerve damage does not directly affect the somatosensory pathways (Bond et al., 2006; Treede et al., 2008). Additionally, secondary MSK pain in multiple sclerosis has been linked to disease-modifying treatments, such as interferon beta and chronic steroid use (Brola et al.,

2014). This underscores the multifactorial and complex nature of MS-related musculoskeletal dysfunction, highlighting it as a major contributor to pain in these patients, while making it difficult to link specific structures to the pain mechanisms.

Moreover, the difference between central and peripheral pain mechanisms in Parkinson's disease lies in several key distinctions. Central mechanisms, which are linked to musculoskeletal pain (Blanchet and Brefel-Courbon, 2018), involve a lower pain threshold, altered pain processing, and motor/non-motor fluctuations. In contrast, peripheral mechanisms include alterations in inflammatory signals (Tai and Lin, 2020).

Although central pain is a common feature in both neuropathic/peripheral and musculoskeletal pain (O'Connor et al., 2008; cla, 2017), it is heterogeneous in both Parkinson's disease and multiple sclerosis. Pain may be musculoskeletal, affecting muscles or joints; peripheral, originating from nerve damage; or central neuropathic, characterised by burning or tingling sensations. Moreover, diseases considered as non-neurological secondary pain—those without direct damage to the nervous system—are even more heterogeneous, as pain may result from tissue damage, inflammation, or other underlying processes that impact pain processing, thus causing variability in brain function (Jepsen et al., 2021; Bouhassira et al., 2005).

Musculoskeletal pain is often easier to diagnose due to its clear signs and symptoms. In contrast, peripheral and neuropathic pain are more variable, as they lack visible external indicators and often manifest unpredictably with abnormal sensations, such as burning or electric shock-like feelings, which are difficult to pinpoint. However previous studies highlighted the role peripheral mechanisms play in chronic pain, i.e., wide spread pain conditions, highlighting that peripheral nociceptor sensitisation is just as crucial as central sensitisation (Marchand, 2021). However, the mechanism of the peripheral activity is not fully understood and requires further research to better understand the major role peripheral mechanisms play in chronic pain conditions which are often mainly linked to central sensitisation.

Therefore, understanding the mechanisms of peripheral pain in neuropathic pain remains a challenge, as it varies between patients with several sensory abnormalities and only a small percentage of patients with peripheral nerve injury have no sensory deficit is identifiable

(Bannister et al., 2020). As a result, secondary musculoskeletal pain was selected in this work to control and minimise potential functional variability across patients.

Utilising the new taxonomies into neuroimaging has proved partially informative with one classification compared to the other (i.e., CPP vs. CSMP). Firstly, chronic pain as a disease presents complex aetiology and pathophysiologies not fully understood. Interestingly, combining several chronic primary pain conditions into a meta-analysis to identify pain-related activity during provoked pain has informed us of structures recently shown to be associated with pain (Labrakakis, 2023; McBenedict et al., 2024b; Liu et al., 2024; Tso et al., 2015; Nisticò et al., 2022). Particularly, structures that align with the pain matrix and neurological pain signatures, such as the Ins and CG, previously identified in patients and pain-free (Xiang et al., 2018; Wager et al., 2013).

In contrast, we encountered multiple challenges, making it difficult for this work to draw general conclusions regarding the taxonomy when analysing chronic secondary MSK pain studies. Particularly, a substantial number of the studies included represented Parkinson's disease, and a larger number of multiple sclerosis sample population included, this will be discussed in section 4.4.

With this in mind, the implications of the chronic secondary MSK pain and subgroup meta-analyses demonstrated variable activity. The convergence differences observed in the primary results were almost identical to those in the subgroup analyses, which is a good indication that the Parkinson's disease studies were the main contributors to the findings. Nevertheless, the subgroup meta-analysis was able to detect the ACC in Parkinson's disease, which was absent in the primary findings. Similarly, the subgroup meta-analysis revealed contrasts in meta-analyses that were not previously observed. These findings demonstrated spatial convergence in structures possibly related to the symptom (e.g., ACC and pain) in Parkinson's disease, indicating the absence of pain-related convergences in chronic secondary MSK pain. This is possibly due to the complex mechanisms involved in both conditions, where pronounced convergences were detected related to the underlying diseases rather than pain (Perrot et al., 2019), see Tables 19 and 20.

With chronic primary pain, within-subjects experiments conjunction findings predominantly revealed convergent activity in the MCC, MFG, daIns, and Claus. Notably, patients with chronic primary pain exhibited stronger convergence in the vdaIns, Claus, and IFG, while pain-free showed consistent activity in the MCC, MFG, and SFG. These findings are consistent with previous meta-analysis that reported aberrant activity in the Ins with chronic pain patients (Jensen et al., 2016). Specifically, the within-subjects findings in chronic primary pain indicated a wide array of convergences, encompassing the vdaIns, ACC, MCC, MFG, LN, and PreG. This aligns with prior chronic pain meta-analyses (Derbyshire et al., 1997; Ha et al., 2022; Xu et al., 2020; Friebel et al., 2011; Duerden and Albanese, 2013; Tanasescu et al., 2016; Jensen et al., 2016; Lanz et al., 2011; Tillisch et al., 2011; Pujol et al., 2009; Melzack, 2001). Notably, the ACC, MCC, and Ins have been identified as critical components of the pain matrix, as stimulation of these areas elicits pain (Derbyshire et al., 1997; Garcia-Larrea and Bastuji, 2018; Vogt, 2016; Henderson et al., 2007).

Additionally, the Ins has been implicated in various functions, including pain perception and emotional regulation (Fenton et al., 2015). Lesions in the Ins were previously linked to pain asymbolia (McBenedict et al., 2024b) [10]. This may suggest that the Ins is a key structure for processing the affective meaning of pain (Xiang et al., 2018). However, it is not responsible for the awareness of pain. A prior study suggested that body awareness mediates the relationship between central sensitisation symptoms and pain intensity (Colgan et al., 2022). Extending this, high interoceptive sensibility skills in musculoskeletal (MSK) chronic pain have shown that awareness of bodily sensations influences how sensitisation contributes to pain perception and regulation, in comparison to low interoceptive sensibility skills (Oliveira et al., 2024). In contrast, moderate interoceptive sensibility skills (mixed) were associated with higher pain catastrophising, while both high interoceptive sensibility skills and mixed interoceptive sensibility skills demonstrated no difference in pain intensity. These findings suggest that Ins activity observed in chronic primary pain may be due to pain being the primary condition; patients are more aware of the unpleasant direct experience of both provoked pain and ongoing

[10] A form of pain dissociation, where the experience and perception of pain remain intact, without the unpleasantness

chronic pain, which is reflected in high interoceptive sensibility skills. Meanwhile, the absence of Ins activity in chronic secondary MSK pain may be linked to low interoceptive sensibility skills, suggesting reduced awareness of pain perception. This diminished or delayed response to Ins and pain unpleasantness may be related to movement disorders and fluctuating pain symptoms, particularly during fMRI sessions (Perrot et al., 2019; De Andrade et al., 2022). Researchers suggest that aIns and ACC are considered associated with a "secondary cortical pain matrix", which contributes to the affective experience of pain or negative emotions, and that these structures are much less consistently activated during provoked pain (Walter et al., 2016; Derbyshire et al., 1997; Bernhardt and Singer, 2012; Fenton et al., 2015; Vogt, 2005; Xiang et al., 2018). Particularly, abnormal activity was observed in these structures with fibromyalgia (Liu et al., 2024). Moreover, evidence suggests that the aIns and anterior MCC or ACC constitute a "second order" network activated by noxious stimuli (Vogt, 2016; Fenton et al., 2015; Vogt, 2009), and are not exclusive to spinothalamic modalities related to pain and temperature. Consequently, they may also be activated by non-painful sensory stimuli (Garcia-Larrea and Bastuji, 2018). However, the MCC regarded as one of the structures involved in the third cortical pain matrix, associated with cognitive meaning (Xiang et al., 2018). Altogether, these regions have been implicated in the pain matrix, with different functions that are interconnected, including cognitive and affective-motivational components (e.g., distress or unpleasantness). In addition, the pain matrix also encompasses the amygdala as a crucial structure involved in pain processing which was observed in chronic secondary MSK pain; however, this was not observed in chronic primary pain. One possible explanation for this is that the amygdala is a smaller subcortical brain structure, and may have been overlooked in previous research (Simons et al., 2014).

In contrast to our findings, a meta-analysis reported convergences in chronic primary pain during resting state (Wang et al., 2022), indicating increased activity in the striatum and MFG, and decreased activity in the ACC, MCC, and Ins. These results support the pain matrix hypothesis, suggesting involvement of these structures during noxious stimuli relative to resting state conditions (Henderson et al., 2007). Previous studies identified the CG as critical structure

for connecting sensory input with emotional responses, which aligns with our findings with chronic primary pain and chronic secondary MSK pain (i.e., Parkinson's disease) (Bubb et al., 2018; Kobayashi, 2011; Vogt, 2005; Henderson et al., 2006). Interestingly, despite the distinct classifications of chronic primary pain and chronic secondary MSK pain, our resting-state meta-analysis findings of Parkinson's disease subgroup also revealed low contribution of the ACC to the cluster (Wang et al., 2022), while chronic primary pain showed pronounced convergence in the MCC and ACC. Differences in findings across meta-analyses may arise from variations in pain intensity or provoked pain (Henderson et al., 2006). This observation may indicate that the ACC is involved in ongoing and provoked pain across these conditions.

With chronic secondary MSK pain, between-subjects meta-analyses revealed variable spatial convergences in secondary pain, in contrast with our findings from chronic primary pain within-subjects meta-analyses. This variability may stem from the considerable variability in pathophysiology associated with chronic secondary MSK pain conditions, particularly patients with and without symptoms (Perrot et al., 2019). In our analyses, we identified the IFG, subcallosal gyrus, and MFG associated with chronic secondary MSK pain and Parkinson's disease (Gandolfi et al., 2017; Henderson et al., 2006). Notably, we found no spatial convergences when comparing pain-free to chronic secondary MSK pain; however, a pronounced spatial difference was observed in the LN when comparing pain-free to Parkinson's disease.

The findings from the Parkinson's disease subgroup meta-analyses demonstrated trends that echoed those of our primary meta-analyses, thereby reinforcing the robustness of our results and confirming their greater relevance to Parkinson's disease. Nevertheless, it remains uncertain whether an additional meta-analysis focused on multiple sclerosis would yield overlapping or variable findings with those observed in Parkinson's disease, as both conditions encompass shared characteristics of MSK pain. Notably, chronic secondary MSK pain etiology involves potential or actual tissue damage, and a diseases which causes MSK problems (Perrot et al., 2019). Moreover, despite the presence of distinct patterns in both the primary and subgroup meta-analyses, we cannot definitively associate these convergences with MSK pain; we will

elucidate further on this matter in subsequent paragraphs.

Previous research has documented various neural correlates associated with pain conditions, highlighting differences in brain activity in response to symptoms or medication (Oertel et al., 2008; El-Tallawy et al., 2021; Cox, 2010). This aligns with our findings, chronic secondary MSK pain with symptoms demonstrated less spatial convergences, compared to chronic secondary MSK pain without symptoms. However, due to a limited number of experiments of P1 (k =8) and P2 (k =12), we conducted combined meta-analysis. These findings indicated one cluster consisting of the CT, inferior semi-lunar lobule, Tu, and Pyr. The structures identified in the combined meta-analysis were predominantly in the cerebellum which is known to be relevant to motor dysfunction in chronic secondary MSK pain, in line with previous studies (El-Tallawy et al., 2021; Cox, 2010).

In contrast, the second cluster identified included the sub-gyral and the Para. Prior research has shown that low doses of alfentanil reduce pain-related activations in the Para, amygdala, and aIns (Oertel et al., 2008), illustrating the impact of opioids on sensory and affective pain processing in chronic secondary MSK pain. This supports our findings, as combined meta-analyses of chronic secondary MSK pain and Parkinson's disease (i.e., P1 and P2) identified reduced convergent activity in the Para located in amygdala cell type. To add, the Para was observed in the single meta-analyses of chronic secondary MSK pain (P1) and Parkinson's disease patients without symptoms (PD1), and was absent with symptoms. Suggesting, patients with symptoms may have been medicated for pain symptoms; hence pain experience was diminished. Moreover, the convergence in the amygdala identified in chronic secondary MSK pain and Parkinson's disease, supports the pain matrix (Veinante et al., 2013; Xiang et al., 2018). Previously, the amygdala was reported to be involved in emotional memory and affective experience of pain (Pare and Duvarci, 2012; Xiang et al., 2018).

A recent systematic review, which reported decreased Para activity in Parkinson's disease patients without depression (Salehi et al., 2022). This does not support our findings, Parkinson's disease without symptoms demonstrated the highest activity in the Para, however the activity reduced in combined meta-analysis of symptoms (including (n =2) of Parkinson's disease with

depression) and no symptoms were analysed. One explanation of our findings may be related to treatment, previously a study suggested diminished activity in patients receiving treatment for symptoms such as pain or depression (Rosoff et al., 2021). These discrepancies highlight the complexity and variability of Para involvement with symptoms and medication, underscoring the need for further research to elucidate the underlying mechanisms of MSK pain in Parkinson's disease.

4.3.2. Neural and Behavioural implications

We examined distinct pain classifications—chronic primary pain and chronic secondary MSK pain—each representing unique conditions during provoked pain and resting-state (Perrot et al., 2019; Nicholas et al., 2019). Our analyses revealed similar trends across both taxonomies, including notable involvement of the ACC, Claus, MFG, and IFG (Gandolfi et al., 2017; Henderson et al., 2006). Although, the statistical threshold selected in the cluster-level correction was stricter with chronic primary pain (Lobo et al., 2023), compared to chronic secondary MSK pain. This threshold greatly reduces the risk of false positives, ensuring it remains under the threshold $p < 0.01$. However, as a more commonly used threshold $p < 0.05$, it is possible that relevant structures were missed (Eickhoff et al., 2012). Notably, the ACC was only observed in the Parkinson's disease subgroup meta-analysis, suggesting that this activity may be particularly relevant to pain processing (Vogt, 2005; Garcia-Larrea and Bastuji, 2018; Melzack, 2001; Wager et al., 2013). It is essential to note this activity is not only dedicated to pain. Prior research identified the ACC activity during sensory stimuli (Garcia-Larrea and Bastuji, 2018) or basic emotional responses (Vogt et al., 2003).

These investigations revealed shared converging findings. Notably, the ACC was identified in the Parkinson's disease subgroup and within chronic primary pain meta-analysis. This aligns with previous findings implicating the ACC in the affective and emotional dimensions of chronic pain (Fenton et al., 2015). Furthermore, the ACC's role in affective-motivational processes, including the interplay of negative memories related to pain processing, has been highlighted in recent studies (Fenton et al., 2015; Vogt, 2005). Therefore, the relationship between negative emotional memories and pain processing within this structure underscores the

role of emotion in pain processing. Interestingly, one study suggested impaired function in the subgenual ACC can lead to clinical manifestations of depression or mania (Drevets et al., 2008). This observation is particularly relevant to our findings of Parkinson's disease, where depression is a prevalent symptom linked to dysfunction of the limbic network system (Prange et al., 2022). These findings indicate the involvement of the ACC with disease symptoms that are not directly related to pain.

Previous research has established a link between specific brain structures and chronic pain conditions, shedding light on their link to pain processing. Similar convergent activity was observed with chronic secondary MSK pain and Parkinson's disease, with and without symptoms. A comparable activation pattern was identified in the Claus with chronic primary pain and chronic secondary MSK pain (i.e., no symptoms). This observation is consistent with recent cluster-based meta-analysis research, which demonstrated the involvement of the Claus in response to acupuncture treatment in individuals with MSK pain (Ha et al., 2022). Together, these findings highlight the similarities between different classifications of pain concerning MSK disorders, such as fibromyalgia and chronic low back pain. As a result, these findings emphasise the potential involvement of the Claus in MSK pain. Moreover, for more than a decade, the claustrum has been linked to consciousness processing (Crick and Koch, 2005; Liaw and Augustine, 2023).

Interestingly, a recent mega-meta-analysis suggested that the insula has a functionally diverse role, particularly highlighting the involvement of the dorsal anterior insula in processes such as somatic pain, aversion, appetite regulation, and cognitive control (Kwon et al., 2025). Furthermore, the study identified inter-domain convergence within the dorsal anterior insula (extending from the ventral region to the posterior and anterior), linking this activity to goal-directed behaviour and conscious awareness. Moreover, the link between pain and consciousness, where without pain and only consciousness one may not recognise harmful stimuli. On the contrary, pain without consciousness, one may not react meaningfully to avoid pain. This is significant as it highlights the interconnectedness of neighbouring structures such as the Claus and Ins, and their shared function involvement in processing consciousness.

The involvement of the MFG and IFG has emerged as a consistent trend across most meta-analyses in both chronic primary pain and chronic secondary MSK pain, except for chronic secondary MSK pain and Parkinson's disease patients exhibiting symptoms. Our findings align with existing literature indicating the role of the MFG in pain processing within chronic primary pain during resting-state analyses (Wang et al., 2022). Others suggested the IFG and MFG involvement with working memory and attention in patients with multiple sclerosis (Kollndorfer et al., 2013). A decreased activity in the IFG and MFG associated with both depressed and non-depressed Parkinson's disease patients (Salehi et al., 2022). Moreover, other research has indicated that the activity of the ACC and MFG structures may be influenced by depression and anxiety (Otte et al., 2016; Maron and Nutt, 2017). This underscores the role of affective and cognitive processes play in the underlying mechanisms of these taxonomies and the link between both classifications and the neural substrates associated with pain processing. While the hypotheses regarding the involvement of the pIns in pain perception for either taxonomy were not supported (Garcia-Larrea, 2012; Xiang et al., 2018), we observed convergence in the aIns, MCC, and ACC with chronic primary pain. Moreover, with chronic secondary MSK pain, no activity was identified in the Ins; instead, we observed reduced activity in the ACC and Para located in the amygdala. Previous chronic primary pain resting-state meta-analyses reported decreased gray matter in the Ins, ACC, and MCC (Wang et al., 2022). Though we cannot link BOLD signals to grey matter findings, structural reduced grey matter does not necessarily mean functional inactivity (Wang et al., 2022). In the context of chronic pain, it may suggest hyperactivity due to increased pain processing demands or neuroplastic changes (Rodriguez-Raecke et al., 2009).

Similarly, in line with our functional findings, voxel-based morphometric analysis of structural changes in Parkinson's disease with dementia identified reduced grey matter in the parahippocampus, thalamus, ACC, and STG (Summerfield et al., 2005). This may suggest heightened activity in these structures are associated with Parkinson's disease or its symptoms. However, it remains unclear whether they are relevant to pain processing in Parkinson's disease. A systematic review compared structural changes in multiple sclerosis with and without fatigue

(Barbi et al., 2022). They found that increased structural changes in the SFG and ACC, along with decreased activity in the SFG, fusiform gyrus, and cerebellum in multiple sclerosis with fatigue. However, in patients without fatigue, changes were observed in the SFG and parahippocampus (Barbi et al., 2022). Therefore, it is clear that these structures are involved with structural and functional analysis which may be viewed as pain processing hub for chronic primary pain and secondary musculoskeletal pain during provoked and ongoing pain, potentially serving as a neural marker.

As mentioned earlier, in both meta-analyses (chronic primary pain and chronic secondary MSK pain), clinical populations were either exposed to provoked or ongoing pain. The choice of pain paradigm, or the absence of a pain paradigm, for each classification depended on data availability (e.g., neural coordinates and clear reporting) and whether studies met our inclusion criteria (e.g., whole-brain analyses). For chronic primary pain, we identified a substantial number of studies investigating provoked pain, which prompted us to focus our meta-analysis on this pain type.

Earlier findings regarding brain regions involved in the three levels cortical pain matrix (Xiang et al., 2018). Suggesting the involvement of the aIns, ACC, hippocampus and amygdala in the affective experience of pain, while the MCC is involved in mediating the cognitive meaning of pain (Xiang et al., 2018). Hence, these findings suggest in both chronic primary pain and chronic secondary MSK pain, the primary cortical activity of the pain matrix, which is involved in pain perception and location, did not contribute to the neural substrates of these taxonomies, see 4. Although, it would be expected to observe this activity with chronic primary pain during provoked pain. Instead, chronic primary pain showed activity in structures associated with affective and cognitive meaning. While the activity observed in chronic secondary MSK pain and Parkinson's disease during resting state may be responsible for the affective and cognitive meaning of pain, which supports previous research (Fenton et al., 2015; Xiang et al., 2018). Furthermore, specific types of pain (i.e., deep vs superficial) with similar intensities recruits different neural structures in pain-free (Henderson et al., 2006). Previous research suggested that superficial and deep pain broadly recruit structures in the pain neuromatrix, with the most

significant difference identified in the pregenual cingulate (PC); a decrease in the PC and an increase in the aIns during deep pain, and no change during superficial pain. This findings suggest a distinct activity linked to pain originating from different tissues of the body associated with pain intensity and perception to noxious stimuli (Henderson et al., 2006). This partially supports our within-subjects findings, pain-free participants exposed to different types of painful stimuli showed convergent activity in the aIns. Therefore, this activity may be related to the pain-free individuals pain perception and affective process. However, other researchers suggested the aIns involvement in affective experience, while the pIns is associated with pain perception (Xiang et al., 2018).

Notably, the CG is associated with many functions with chronic pain conditions (Bubb et al., 2018). For instance, the involvement of: 1) the dorsal ACC with emotions, 2) the ACC and the MCC with pain, and 3) the MCC with a motor function (Bubb et al., 2018). Aligning with the neuromatrix concept, suggesting an intricate relationship between structures resulting from sensory, emotional, and cognitive components involved in chronic pain processing (Iannetti and Mouraux, 2010). Moreover, chronic pain is generally accompanied with symptoms such as depression and/or anxiety, as discussed earlier. Hence, psychological distress may influence pain experience, thus impacting the neurosignatures within the neuromatrix (Genoese et al., 2022; Oliveira et al., 2024). This may explain the variability and the lack of consistency observed in both taxonomies.

These insights may inform future diagnostic frameworks, particularly those targeting the psychological and pharmacological interventions for chronic primary pain and chronic secondary MSK pain. They highlight a shared pattern associated with affective and cognitive processes, which may serve as a neural marker and provide a neurobiological framework for these these conditions/classifications. By integrating the biopsychosocial framework with neuroimaging, this work contributes to a growing body of evidence aimed at improving our understanding of the complex aetiology of chronic pain and enhancing clinical approaches.

4.4. Limitations and Future Direction

Despite the theoretical contributions of this research, several limitations must be acknowledged. First, the chronic primary pain classification did not fully encompass all relevant conditions. One condition was selected from each parent code of the classification (Nicholas et al., 2019), and complex regional pain conditions were excluded due to insufficient studies that follow the inclusion criteria. The predominance of IBS and migraine studies introduced a potential bias favouring these conditions in the results. While there were enough studies for primary findings, subgroup meta-analyses could not be conducted due to a lack of experiments. Moreover, the significant findings identified represented within-subjects experiments consistently activated structures, as between-subjects experiments presented high variability (Xu et al., 2021).

The chronic secondary MSK pain classification was similarly limited by the under-representation of multiple sclerosis studies, restricting definitive conclusions for this classification. This work focused primarily on between-subjects experiments, as within-subjects neural coordinates were rarely reported. In several cases, these coordinates were either omitted, presented in aggregated formats (e.g., "Patients vs. Pain-free"), or excluded because within-subjects designs were not employed. The coexistence of MSK pain with other neuropathic pain conditions in multiple sclerosis further complicates its identification and characterisation (Zella et al., 2019; Perrot et al., 2019; Tueth and Duncan, 2021). Variability in Parkinson's disease findings also suggests that disease stage may contribute to observed heterogeneity (Krüger et al., 2017). Additionally, many multiple sclerosis and Parkinson's disease studies were excluded because they used FC methods (e.g., seed-to-voxel or independent component analysis) (Albano et al., 2022; Tahedl et al., 2018). While FC approaches provide valuable insights into connectivity, they lack the spatial resolution necessary for CBMA and often exclude whole-brain analyses (Tahedl et al., 2018).

A key limitation of cFWE inference in CBMA is the influence of sample size. Studies with smaller sample sizes (e.g., Parkinson's disease) produce broader Gaussians, leading to larger clusters and potentially inflating statistical significance. Conversely, larger sample sizes (e.g., MS) result in narrower Gaussians, which may produce smaller clusters and underestimate their

contribution (Eickhoff et al., 2012). This introduces the risk of misinterpreting results, as greater activity may be overestimated in small sample sizes and underestimated in large ones. Another caveat is the lack of effect size reporting with cFWE correction. Effect size in this context would indicate the proportion of experiments surviving a given threshold at a specific location within a cluster (Eickhoff et al., 2016). Effect size reporting could enhance comparisons between clusters and clarify whether observed effects are genuine. However, in ALE meta-analyses, this is particularly challenging due to the limited number of clusters identified (e.g., no more than three clusters across per analyses, with fewer than 21 experiments per meta-analysis) (Eickhoff et al., 2016, 2009). This limitation restricted our ability to compare within- or between-group effects effectively.

This research also focused on identifying neural substrates associated with chronic primary pain and chronic secondary MSK pain using ALE rather than exploring neural networks (Bilek et al., 2019; Xu et al., 2021; Tanasescu et al., 2016; Xu et al., 2020; Friebel et al., 2011; Jensen et al., 2016; Müller et al., 2018). While vFWE correction is known for its high spatial specificity, its conservative nature likely limited the findings. For example, significant activity was identified exclusively in pain-free (k = 18), with no significant activity in patients or combined groups, highlighting greater variability in patients, particularly in the between-subjects experiments. This variability may explain the lack of convergences across the all meta-analyses, where vFWE was applied.

Finally, although chronic pain is intertwined with biopsychosocial components, few chronic secondary MSK pain studies reported data on anxiety (k = 2) or depression (k = 7), and nearly all failed to specify the type of pain experienced by patients, such as MSK pain. Notably, all authors were contacted for clarification, however only one confirmed that this data was not collected (Bonavita et al., 2011). This highlights the urgent need for more detailed data collection in these cohorts to improve understanding of the biopsychosocial contributions to these classifications.

4.4.1. Recommendations for Future Research

To advance this area of research, future studies should include a broader range of chronic primary pain and chronic secondary MSK pain conditions to fully represent the taxonomies. This ensuring a more well-distributed meta-analysis, particularly with conditions such as chronic low back pain, fibromyalgia, and MS. Expanding the scope to these conditions will provide deeper insights into the variability and shared patterns associated with pain processing within each classification. Of note, researchers should adopt standardised methodologies to reduce study variability, particularly regarding sample size, pain paradigms, correction methods, and statistical thresholds (Müller et al., 2018). Additionally, future studies should analyse both within-subjects and between-subjects experiments separately to explore differences within and between groups effects. Altogether, these efforts would ensure these studies are included in whole-brain CBMA and improve the interpretability of the findings.

Another promising avenue is to investigate the differences between Chronic primary MSK pain (CPM) conditions (Fitzcharles et al., 2022), compared with chronic primary pain during rest-state (e.g., (Wang et al., 2022)) and provoked pain presented in this work. The CPM, characterised by nociplastic pain mechanisms, includes both neuropathic and nociceptive pain (Fitzcharles et al., 2022). Subgroup meta-analyses of both types of pain could offer valuable insights into the mechanistic processes underlying pain and potential shared neural activity - as pain is the primary source. Also, identifying shared or distinct neural convergences in chronic primary pain and chronic secondary MSK pain to CPM may shed light on potential biomarkers because of the overlapping characteristics within each classification. Notably, chronic secondary MSK pain represents a nervous system disease (e.g., Parkinson's disease) that causes MSK pain rather than being a MSK condition itself (Perrot et al., 2019). This distinction may explain the different neural activity observed in chronic secondary MSK pain compared to chronic primary pain, reflecting the influence of the primary disease (e.g., Parkinson's disease). Additionally, it may shed light on CPM classification as the converging point that may connect both chronic primary pain and chronic secondary MSK pain see Figure 27.

Additionally, longitudinal studies can identify early neural markers and risk factors, such as

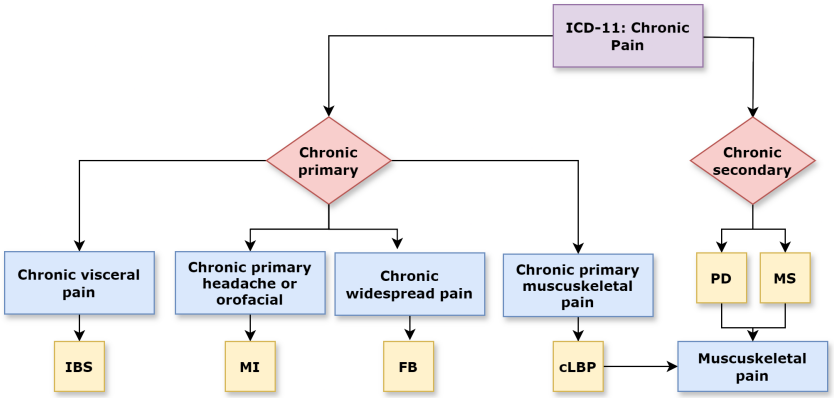

Figure 27: Flowchart of the link between between chronic primary pain, CPM, and chronic secondary MSK pain

acute pain, sleeplessness, or stressful life events, while offering a clearer understanding of identifying the mechanisms of chronic pain development and disease progression over time (Chapman and Vierck, 2017; Martinez-Martin et al., 2019). This deeper insight into disease progression, stage-specific neural mechanisms, and early detection enables the development of timely interventions, ultimately improving patient outcomes.

4.5. General conclusion

The quest to identify pain biomarkers in chronic pain patients, with the aim of advancing research and treatment approaches, has been a long-standing objective. However, the pathophysiology of the recently defined classifications of chronic primary pain and chronic secondary MSK pain remains poorly understood. The traditional perspective of chronic pain as merely a symptom, or as pain associated with known or unknown pathological conditions, was overly simplistic. This necessitated a shift in perspective, prompting researchers to recognise pain as a distinct issue with a multifactorial nature, in order to better understand the mechanisms underlying chronic pain.

The development of refined classifications through improved definitions and diagnostic categorisation of chronic pain conditions—based on symptom descriptions and underlying aetiology—provides an opportunity to tackle the long-standing issue of heterogeneity in the literature. Dissecting these differences within clinical populations can reduce heterogeneity and

improve the reliability of research outcomes. Hence, standardised classifications, such as those provided by International Classification of Disease 11th edition, prompts researchers to explore specific neural correlates associated with different pain types, such as neuropathic or nociceptive pain.

Coordinate-based meta-analyses of pain fMRI studies, using rigorous statistical inferences, have revealed consistent patterns associated with pain processing. These findings support the *neuromatrix* concept, which suggests that pain is a diverse and complex phenomenon influenced by a neural network integrating sensory, affective, and cognitive inputs (Melzack, 2001). A potential association with central nervous sensitisation increases network activity and disrupts pain processing (Gracely and Ambrose, 2011; Duschek et al., 2013; Reyes del Paso et al., 2012). Additionally, evidence aligns with the notion that the *pain matrix* is only partially pain-specific (Iannetti et al., 2013). Convergent activity in regions such as the aIns, amygdala, Para, and ACC highlights their involvement in modulating the unpleasantness of pain (Rainville et al., 1997, 1999). The limbic system appears predominantly involved in the emotional and psychological aspects of pain (Hofbauer et al., 2001), while the MCC has been postulated to contribute to the cognitive meaning of pain (Xiang et al., 2018). In addition, aberrant shared activity was revealed with both classification in the IFG, MFG, and Claus (Gandolfi et al., 2017; Henderson et al., 2006) suggesting their involvement in pain processing (Wang et al., 2022; Ellis et al., 2023; Ha et al., 2022). While chronic primary pain and Parkinson's disease showed shared activity in the ACC. This suggests that pain in patients is mediated by fluid systems interacting with networks involved in affective and cognitive pain processes, whether in the presence of nociceptive or non-nociceptive inputs (Fenton et al., 2015; Xiang et al., 2018). Nevertheless, variability within pain fMRI studies continues to hinder advancements in understanding the neural mechanisms of chronic pain. Addressing this variability requires careful consideration of experimental designs (within-subject and between-subject), reporting neural coordinates across the whole brain, and adhering to standardised methods commonly used in pain research (Baliki et al., 2006; Müller et al., 2018; Eickhoff et al., 2016). Methodological differences across studies act as a catalyst for variability, amplifying

discrepancies in findings and consequently obscuring the identification of consistent patterns in chronic pain meta-analyses. This thesis emphasises the importance of utilising International Classification of Disease 11th edition diagnoses alongside neuroimaging empirical studies to bridge the gap between chronic pain research and its relevance to clinical practice. By improving efficiency in clinical categorisation, promoting greater methodological harmonisation in neuroimaging studies spanning from pain-free individuals to patients, and fostering collaboration between clinicians and neuroscientists, a virtuous circle can be created. This, in turn, would enhance both clinical categorisation and methodological coherence. Only through such integration can researchers produce more robust and generalisable insights into the neural mechanisms of chronic pain, ensuring that research findings align with and inform current clinical practice.

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