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Wired for pain, shaped by the mind

Interactions between pain and psychopathology in pediatric and adult patient populations

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CHAPTER 1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

This chapter will provide foundational background on the key topics and conditions explored throughout this thesis. Setting the stage for a detailed investigation of the biobehavioral mechanisms underlying pain and neuropsychiatric symptoms across different ages and disease contexts, the key clinical presentations, pathophysiology and etiology of each condition will be introduced; childhood-onset Systemic Lupus Erythematosus (cSLE), early-onset psychosis (EOP), schizophrenia (SZ), bipolar disorder (BP), juvenile idiopathic arthritis (JIA), and fibrous dysplasia/McCune-Albright syndrome (FD/MAS). Subsequently, a comprehensive basis will be provided on the neurobiological underpinnings of acute and chronic pain, as well as on neuroinflammation and neurodevelopment, thereby establishing the groundwork for understanding the complex interactions between these processes. Lastly, this chapter will provide the aim and outline of the thesis.

Overview of Relevant Conditions

In the following section, relevant background about the various diseases and conditions that are central to this dissertation will be discussed. While each condition has unique pathological features, the conditions share commonalities related to pain or neuropsychiatric manifestations. Such symptoms, either attributable to direct inflammatory mechanisms or secondary effects, significantly impact quality of life of the patients. The pathophysiology, clinical presentations, and broader relevance of each condition will be outlined, highlighting the links between disease-related inflammation, pain, and neuropsychiatric outcomes.

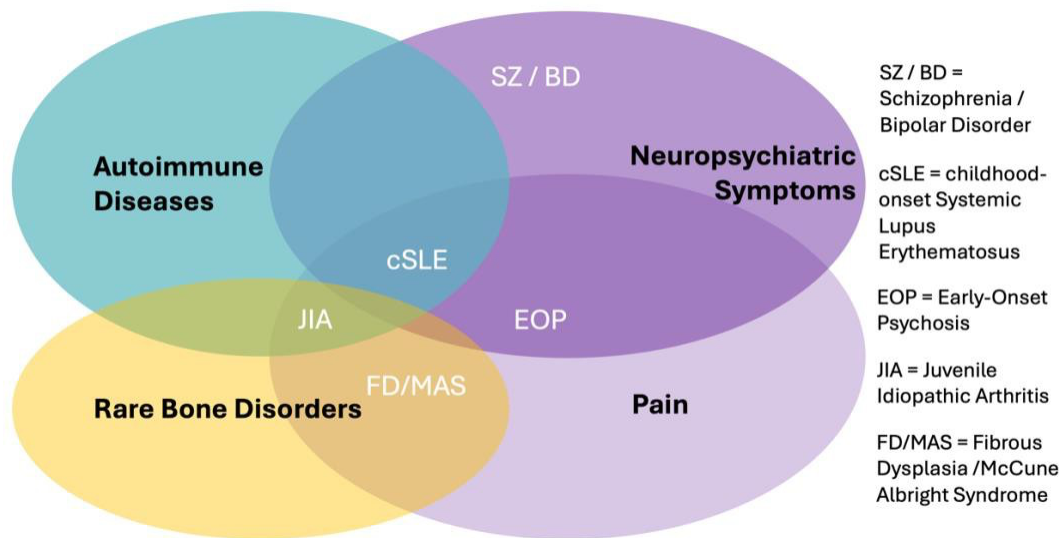


Figure 1. Venn diagram illustrating the overlap between the relevant diseases and conditions: Autoimmune diseases include cSLE (childhood-onset Systemic Lupus Erythematosus) and JIA (Juvenile Idiopathic Arthritis), and cSLE patients may present with cooccurring neuropsychiatric symptoms. Neuropsychiatric conditions include Schizophrenia/Bipolar Disorder (SZ/BD) and Early-Onset Psychosis (EOP). FD/MAS (Fibrous Dysplasia/McCune Albright Syndrome) is primarily classified as a rare bone disorder, while JIA also affects the bone. Pain is observed across JIA, cSLE, EOP and FD/MAS patient populations.

Childhood Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic, autoimmune disorder^{1, 2}. SLE is more commonly diagnosed in adults compared to children, with an estimated prevalence of childhood SLE (cSLE) of 1.89 to 25.7 per 100,000 children³. However, the disease tends to follow a more aggressive course in children compared to adults, with earlier involvement of major organs such as the kidneys, heart, and CNS^{4, 5}.

The pathophysiology of cSLE is complex and not yet fully understood, but genetic, hormonal, and environmental factors that trigger immune dysregulation are implicated^{6, 7}. This immune dysfunction leads to the production of autoantibodies, including antinuclear antibodies (ANAs) and anti-double-stranded DNA (anti-dsDNA) antibodies, which form immune complexes that deposit in tissues, causing inflammation and damage. In addition to its physical effects, cSLE can have profound psychological and developmental consequences due to its early onset during critical stages of growth and maturation.

Management of cSLE requires a multidisciplinary approach, combining immunosuppressive therapies to control disease activity with supportive treatments to manage symptoms and prevent long-term disease related organ damage. Early diagnosis and aggressive treatment are crucial in reducing morbidity and improving quality of life in affected children. However, the unpredictable course and heterogeneity in symptom presentation in cSLE poses significant diagnostic and therapeutic challenges.

cSLE can affect multiple organs simultaneously, leading to diverse clinical presentations, ranging from mild symptoms such as fatigue and joint pain to severe complications like nephritis, neurological impairments, and cardiovascular issues⁸. Moreover, a subset of patients experiences neuropsychiatric symptoms, such as cognitive dysfunction, depression or psychosis, with a large heterogeneity in severity and type of neuropsychiatric presentations.

Early-Onset Psychosis

Early-Onset Psychosis (EOP) refers to the onset of the first psychotic symptoms such as hallucinations, delusions, and disorganized thinking occurring before the age of 18^{9, 10}. While psychotic disorders are more commonly diagnosed in late adolescence or early adulthood, the early onset of these symptoms presents unique challenges and typically signals a more severe and complex form of illness¹¹. EOP can manifest as various psychiatric conditions, including early-onset schizophrenia, bipolar disorder with psychotic features, or schizoaffective disorder. Individuals with EOP tend to experience greater cognitive impairments, more negative symptoms (such as social withdrawal and lack of motivation), and a higher risk of chronic disability compared to adults with psychosis^{12, 13}.

The etiology of EOP is multifactorial, involving a combination of genetic, neurodevelopmental, and environmental factors¹⁴. Neurobiological studies suggest that abnormal brain development, including structural alterations in regions such as the prefrontal cortex, hippocampus, and cerebellum, may contribute to the emergence of psychotic symptoms^{15, 16}. Moreover, disruptions in neurotransmitter systems, e.g., dopamine, glutamate, and GABA, play a key role in the onset and progression of psychosis¹⁷. Environmental stressors such as trauma, substance abuse, and social adversity such as poverty or family conflict are thought to increase the risk of EOP, particularly in individuals with a genetic predisposition^{18, 19}.

Early identification and intervention are critical in the management of EOP, as untreated psychosis may lead to worse long-term neurocognitive deficits and functional decline. Treatment typically involves a combination of antipsychotic medication and psychosocial interventions aimed at stabilizing symptoms and supporting the developmental and social needs of the adolescent^{20, 21}. However, the early onset of psychosis presents unique diagnostic challenges, since symptoms that are common in youth, such as

mood and anxiety disorders, may overlap with psychotic presentations^{9, 22, 23}. Despite these challenges, early and sustained intervention can improve long-term outcomes, thereby emphasizing the need for early detection through biomarkers, such as behavioral, neurobiological or blood serum measures.

Schizophrenia and Bipolar Disorder

Individuals suffering from psychotic illnesses (i.e., schizophrenia spectrum disorder (SZ) or bipolar I disorder with psychotic symptoms (BD) often experience a range of complex clinical symptoms. While there are distinct presentations of disease in SZ and BD patients, significantly overlapping symptoms, risk factors, genetic biomarkers and outcomes are also observed^{24, 25}. Despite recent debate, the fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) has retained the distinction between SZ and BP, and also includes the controversial diagnosis of schizoaffective disorder^{26, 27}. SZ patients demonstrate psychotic symptoms of delusions and/or hallucinations, as well as diminished affect and motivation or negative symptoms. BD is characterized by severe but periodic mania and depression, where manic episodes may include minimal sleep, heightened energy, impulsivity and extreme changes in mood. Somewhere on the spectrum of BD and SZ, schizoaffective disorder has predominantly psychotic symptoms whilst also demonstrating mood symptoms, where periods of psychosis without mood disturbance must have occurred. The diagnosis for schizoaffective disorder has received much criticism, as it may be a midline on the spectrum of SZ and BD rather than a distinct diagnosis. Moreover, it highlights the limitations of the DSM-5 categorical approach, which may oversimplify the clinical spectrum of symptom presentation in SZ and BD, failing to fully capture the overlapping nature of psychotic and mood symptoms that often exist between these two conditions. For example, negative symptoms are present in both SZ and BD, which are broadly described as impairments in either motivation or pleasure and

emotional expression²⁸⁻³⁰. Disruption in the reward-motivation processing circuits are suggested to contribute to negative symptoms as well as to cognitive impairment in these populations³¹. The questions raised regarding overlap between SZ and BD have fueled growing research into their shared and unique neurobiological pathways, with the goal of uncovering novel insights into their etiology, course, and treatment³².

Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disease in children and adolescents, characterized by persistent joint inflammation that begins before the age of 16 and lasts for at least six weeks^{33, 34}. As a heterogeneous group of autoimmune conditions, JIA encompasses several subtypes, each distinguished by the number of joints affected, the presence of systemic symptoms, and the involvement of other organs. These subtypes include oligoarticular, polyarticular, and systemic JIA, among others, all of which vary in severity and prognosis. The hallmark of JIA is inflammation of the synovium, the tissue lining the joints, leading to swelling, pain, stiffness, and, over time, potential joint damage and disability.

The exact cause of JIA is unknown, but it is believed to result from a complex interplay of genetic susceptibility and environmental triggers, which lead to immune system dysregulation³⁵⁻³⁷. This abnormal immune response causes the body to attack its own tissues, particularly the joints, resulting in chronic inflammation. In the case of systemic JIA, other organs, including eyes, skin, liver, lymph nodes or spleen can also be affected.

Early diagnosis and treatment are essential in preventing long-term complications, including joint deformities and impaired physical development^{38, 39}. Treatment strategies for JIA typically involve a

combination of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and biologic agents that target specific components of the immune system^{40, 41}. Physical therapy and regular monitoring are also important in managing the disease and maintaining joint function⁴².⁴³ Although some children achieve remission, others may continue to experience disease activity into adulthood, making JIA a lifelong challenge for many affected individuals⁴⁴.

Fibrous Dysplasia/McCune-Albright Syndrome

Fibrous dysplasia (FD) is a rare, non-hereditary bone disorder characterized by the replacement of normal bone tissue with fibrous tissue, leading to weak, misshapen bones, fractures, and bone pain^{45, 46}. FD can affect one bone (monostotic) or multiple bones (polyostotic), with the most commonly involved sites being the skull, femur, tibia, and ribs. The condition arises due to a post-zygotic mutation in the *GNAS* gene, which leads to abnormal regulation of bone-forming cells and the overproduction of fibrous tissue in place of normal bone⁴⁷.

McCune-Albright Syndrome (MAS) is a more severe, multisystem form of FD, characterized by the presence of polyostotic fibrous dysplasia, café-au-lait skin spots, and endocrine abnormalities, particularly precocious puberty⁴⁸. MAS results from the same activating mutation in the *GNAS* gene but involves broader systemic effects due to the mutation's impact on various tissues. In MAS, the overactive *GNAS* mutation leads to the excessive production of hormones, causing endocrine dysfunctions such as hyperthyroidism, Cushing syndrome, and growth hormone excess, in addition to bone deformities.

The clinical presentation of FD and MAS varies widely depending on the extent of bone involvement and associated endocrine abnormalities⁴⁹. In severe cases, patients with MAS may experience significant

skeletal deformities, hormonal imbalances, and complications related to endocrine hyperactivity. Treatment primarily focuses on managing symptoms and complications, including surgical interventions for bone deformities, medications to regulate endocrine function, and bisphosphonates to reduce bone pain and fractures⁵⁰. Pain treatment in FD/MAS remains challenging, further complicated by the heterogenous presentation of the disease as well as the fluctuations in disease activity across the lifespan

^{51, 52}.

Neurodevelopment Across The Lifespan

The childhood onset of diseases often leads to a worse long-term prognosis due to the prolonged duration of illness and early disruption of normal growth and development. Early exposure to disease-related inflammation or treatments can increase the risk of long-term complications, including organ damage and reduced quality of life, as well as impact psychological and social development.

Brain development follows distinct trajectories during childhood and adulthood, characterized by dynamic changes in structure and function⁵³ (**Fig. 2**). In childhood, the brain undergoes rapid growth and reorganization, involving substantial increases in synaptogenesis, neuroplasticity, and cortical maturation⁵⁴. The brain experiences a surge in the formation of synaptic connections that peak in early childhood^{55, 56}. This overproduction of synapses is followed by a period of synaptic pruning, in which weaker connections are eliminated to promote more efficient neural networks⁵⁷. These processes are particularly pronounced in regions such as the prefrontal cortex, which is responsible for executive functions, decision-making, and social cognition⁵⁸. Myelination, the process by which neurons are insulated to enhance signal transmission, also rapidly increases during childhood, particularly in areas involved in sensory and motor functions⁵⁹.

In contrast, adult brain development is directed to refinement and maintenance rather than growth. By early adulthood, synaptic pruning has largely stabilized, while myelination continues, particularly in higher-order association areas such as the prefrontal cortex, which support complex functions such as abstract thinking, planning, and emotional regulation^{60,61}.

The marked brain plasticity in childhood may render this developmental stage a critical period for learning and adaptation, while the reduced plasticity in adulthood exhibits experience-dependent plasticity to facilitate learning and adaptation⁶⁰. This difference in plasticity may be one reason childhood brain injury recovery can often be more successful than in adults^{62,63}. On the other hand, neurobiological structures and systems are neurodevelopmentally immature in childhood and are more likely vulnerable to inflammatory stressors and other external impact. Owing to these factors, this developmental stage has been interpreted as "sensitive periods"⁶⁴. The neurodevelopmental trajectories across the lifespan highlight the importance of early developmental experiences by either formative or disruptive impact on neurocircuitry.

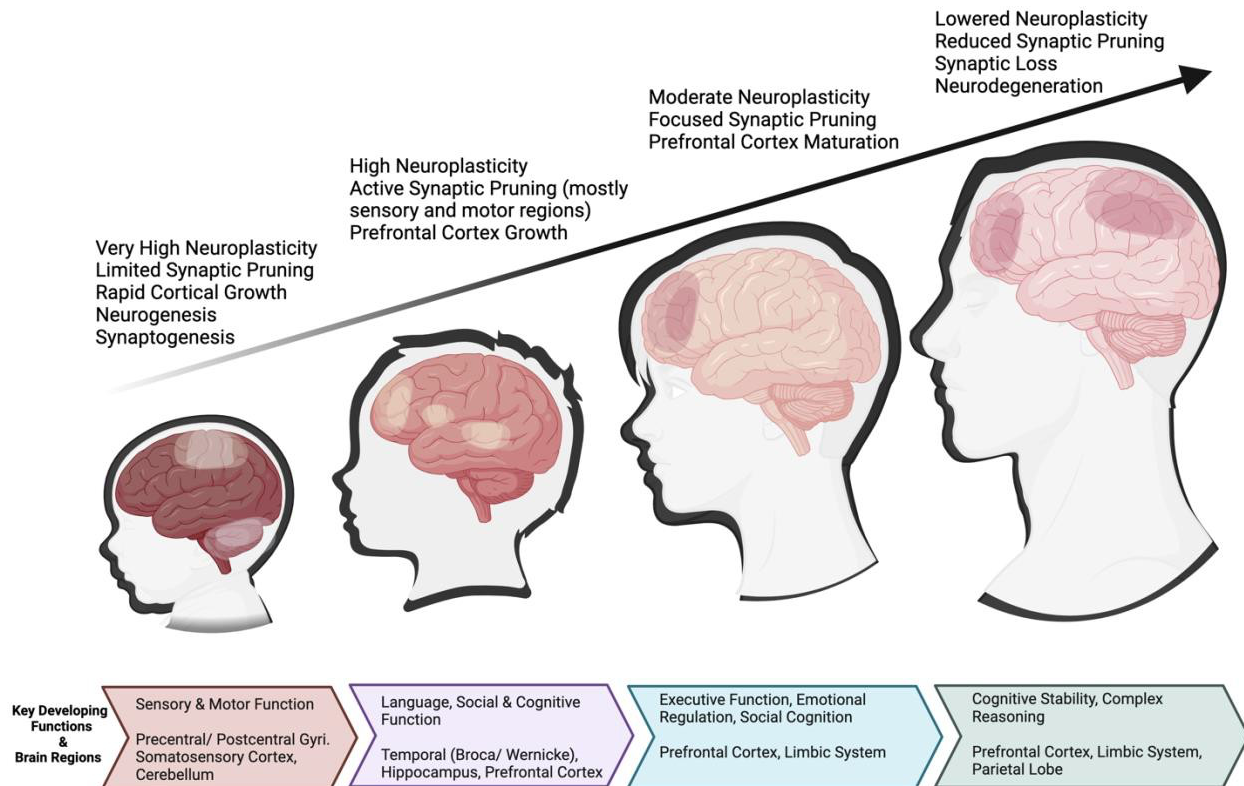


Figure 2. Neurodevelopmental trajectories across the lifespan. Simplified overview of changes in neuroplasticity, synaptic pruning, and regional maturation from infancy to adulthood are illustrated. Early stages show rapid cortical growth and limited pruning, supporting sensory and motor functions. Childhood and adolescence involve active pruning and prefrontal cortex development, enabling enhanced social and cognitive functions. In adulthood, reduced neuroplasticity and pruning support cognitive stability and complex reasoning, primarily in the prefrontal cortex, limbic system, and parietal lobe.

Acute and Chronic Pain Pathways

Acute and chronic pain constitute two distinct mechanisms by which the nervous system processes and regulates pain⁶⁵. Acute pain arises from immediate tissue damage or injury, serving as a protective response to prevent further harm. Acute pain is mediated primarily by nociceptors, which transmit sensory signals through fast, myelinated A-delta fibers and slower, unmyelinated C-fibers to the spinal cord and brain, resulting in the perception of pain⁶⁶. In contrast, chronic pain is not attributable to immediate injury

and may result from sensitization, where the nervous system becomes hyper-responsive to stimuli, arising from maladaptive processing within the central and peripheral nervous systems (**Fig. 3**). In the periphery, damaged or inflamed tissues can cause prolonged activation of nociceptors, while in the CNS, repeated pain signals can lead to central sensitization⁶⁷. Prolonged activation can result in changes within the dorsal horn of the spinal cord, where pain signals are amplified, and the normal inhibitory controls become disrupted. In chronic pain, key salience network regions such as thalamus, amygdala, insula and prefrontal cortex also show structural and functional changes, which contribute to the persistence of pain and the emotional and cognitive impact of pain⁶⁸⁻⁷². Consequently, chronic pain does not arise solely from tissue damage but is regulated by dysfunctional neural circuits even after the initial nociceptive signal has subsided. Such processes suggest that pain chronification should be considered as a continuous and dynamic process that evolves over time, that is influenced by biological, psychological, and social factors⁷³. Understanding the shifts from acute to chronic pain mechanisms is crucial for developing effective treatments tailored to the nature of the pain being experienced.

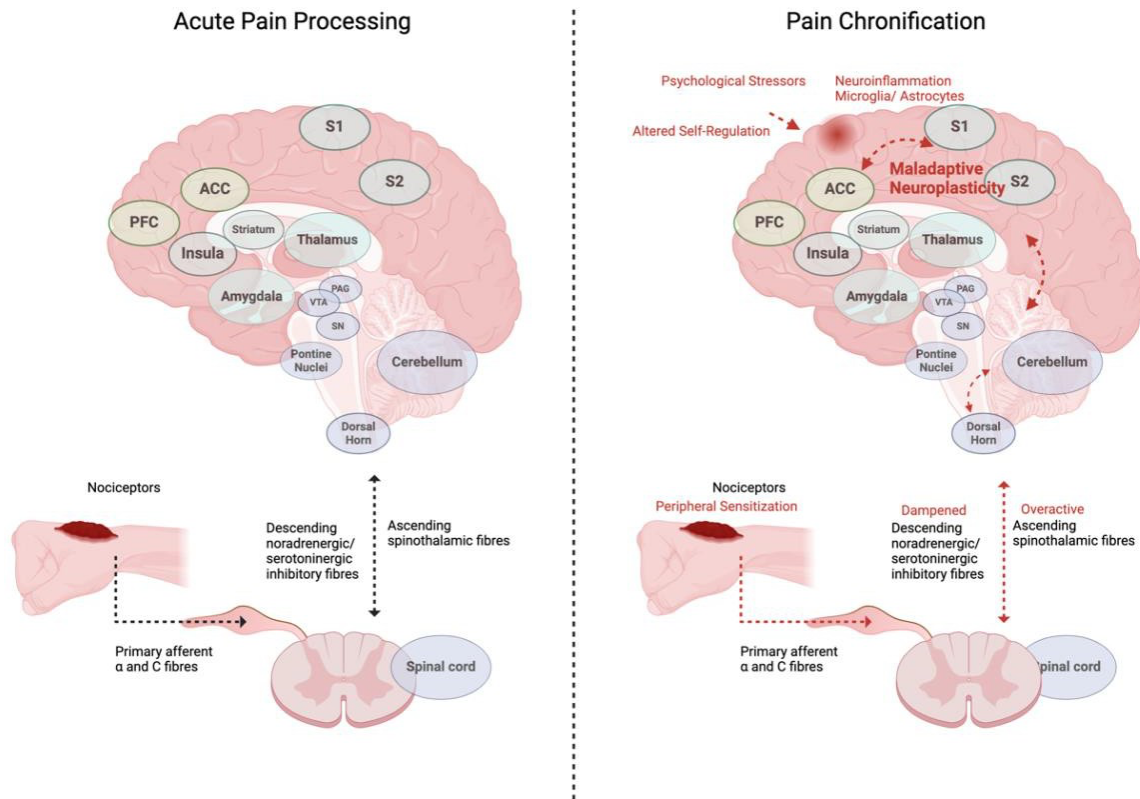


Figure 3. Simplified illustration of normal pain processing vs. pain chronification. Acute Pain Processing (left): Nociceptive signals from peripheral nociceptors travel via primary afferent α and C fibers to the spinal cord, where they ascend through spinothalamic fibers to various brain regions. Pain Chronification (right): The persistence of pain leads to maladaptive neuroplasticity and changes in central and peripheral pain pathways, characterized by: Peripheral Sensitization: Increased sensitivity at the site of injury, enhancing nociceptive input. Central Sensitization: Hyperactivity of ascending spinothalamic fibers and dampening of descending noradrenergic/serotonergic inhibitory fibers from brainstem structures, contributing to prolonged pain. Neuroinflammation: Activation of microglia and astrocytes promotes ongoing pain through inflammatory pathways. Psychological factors, such as stress and altered self-regulation, can further exacerbate pain chronification. Prefrontal Cortex (PFC), Anterior Cingulate Cortex (ACC), S1 (Primary Somatosensory Cortex), S2 (Secondary Somatosensory Cortex), Ventral Tegmental Area (VTA), Substantia Nigra (SN), Periaqueductal Gray (PAG).

Neuroinflammation

Neuroinflammation is a complex and tightly regulated immune response occurring within the CNS, primarily mediated by the activation of resident immune cells such as microglia and astrocytes, along with peripheral immune cells that infiltrate the brain under certain conditions⁷⁴ (Fig. 4). While acute

neuroinflammation can be protective, through clearing pathogens or repairing tissue after injury, chronic or dysregulated neuroinflammation can lead to lasting damage within the CNS⁷⁵. In fact, persistent activation of glial cells leads to a cascade release of pro-inflammatory cytokines, chemokines, and reactive oxygen species, which collectively can disrupt neuronal function, damage synapses, and compromise the blood-brain barrier⁷⁶. The occurrence of a sustained inflammatory state is increasingly recognized as a key player in the pathogenesis of various neurodegenerative diseases, such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (ALS), wherein neuroinflammation accelerates neuronal death and disease progression⁷⁷⁻⁷⁹. Aside from neurodegenerative diseases, chronic neuroinflammation is also implicated in psychiatric conditions including depression, BD and SZ, in which inflammatory markers are often elevated and linked to alterations in mood and cognition⁸⁰⁻⁸². Moreover, significant crosstalk between the immune system and the CNS contribute to neuroinflammation in autoimmune diseases such as JIA and cSLE.

Understanding the dual role of neuroinflammation—both as a protective and a harmful force—is critical for developing targeted interventions. For instance, anti-inflammatory therapies aimed at modulating the immune response hold promise for mitigating the harmful effects of chronic neuroinflammation while preserving its beneficial aspects, which offer new therapeutic avenues for a wide range of CNS disorders⁸³.

⁸⁴.

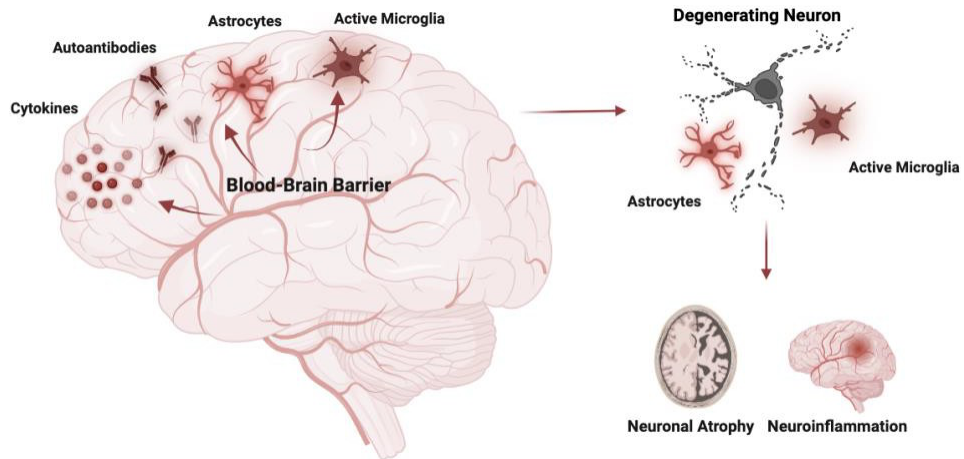


Figure 4: Schematic representation of neuroinflammation and its role in neuronal degeneration. Cytokines and autoantibodies breach the blood-brain barrier, leading to activation of astrocytes and microglia. This immune response contributes to neurodegenerative processes, as evidenced by the degeneration of neurons. The figure highlights key cellular and molecular players involved in the pathogenesis of neuroinflammatory conditions.

Aim and Outline of the Thesis

The primary objective of this work is to explore neural circuitry and mechanisms that link disease processes to neuropsychiatric presentations, focusing particularly on the interaction between pain and psychopathology. By examining these dynamics across childhood and adult patient populations, this research enhances the current understanding of how pathological changes in the CNS shape cognitive, emotional, and psychological well-being. To further guide the reader through this dissertation, the following paragraphs describe how each of the chapters contribute to the overarching aim.

Vulnerability of the Developing Brain

Neurobiological systems are particularly vulnerable during childhood, a critical period of brain development marked by rapid growth and heightened plasticity. During this time, the brain is more sensitive to both positive and negative environmental influences. This may render it especially susceptible to various types of impact, including childhood maltreatment, trauma, and inflammatory processes. Childhood maltreatment and trauma can disrupt the normal development of neural circuits, particularly those involved in stress regulation, emotional processing, and cognition, leading to long-term consequences for mental health and cognitive function. The brain's response to early adversity often involves changes in key regions like the hippocampus, amygdala, and prefrontal cortex, which are associated with memory, emotional regulation, and decision-making. Additionally, chronic inflammation during childhood, whether due to infections, autoimmune conditions, or other factors, can further impair neurodevelopmental processes, exacerbating the risk of cognitive and behavioral problems. **Chapter 2** will delve into the impact of childhood maltreatment and its role in the development of pain and psychopathology. Understanding how pain perception and processing in children and adults who

experienced maltreatment during development are disrupted may aid to identify early markers of vulnerability and facilitate investigation of psychopathology from an alternative perspective.

Inflammatory Impact on the Developing Brain

Inflammation plays a critical role in both childhood and adult diseases, affecting a wide range of bodily systems and functions. As an essential component of the immune response, inflammation is involved in defending the body against infections and injuries. However, when dysregulated or chronic, it can lead to significant pathophysiological consequences. In both early developmental stages and later life, inflammatory processes have been implicated in various diseases, from autoimmune and metabolic disorders to cardiovascular and neurodegenerative conditions. Importantly the impact of inflammation extends beyond physical health, influencing neurocognitive processes. In childhood, neuroinflammatory conditions can affect brain development, potentially leading to long-term cognitive deficits. In **Chapter 3**, the inflammatory interplay between the brain and other systems in childhood Systemic Lupus Erythematosus is explored through review of current literature. Understanding the complex role of inflammation across different stages of life and its effects on the brain and body can provide valuable insights into disease mechanisms and potential therapeutic interventions.

Interconnections of Psychopathology, Emotional Processes and Pain

CNS networks such as the limbic system, the hypothalamic-pituitary-adrenal (HPA) axis and dopaminergic and serotonergic pathways plays a crucial role in linking emotional processes, psychopathology, and pain. Dysregulation in one or more of these systems may contribute to heightened

emotional responses, such as anxiety, depression, and fear, which in turn amplify the perception and experience of pain. Pain can further exacerbate emotional disturbances, creating a feedback loop that fuels both pain and psychopathology. Conditions like depression, anxiety, and post-traumatic stress disorder (PTSD) are commonly associated with chronic pain, suggesting that shared neurobiological pathways underlie both emotional and physical symptoms. The high prevalence of pain in early onset psychosis is first described in **Chapter 4**, and the associations between pain and psychopathology in these children is further explored. This complex relationship highlights the importance of treating both the emotional and physical dimensions of psychopathology, as addressing emotional dysregulation can improve pain management and enhance overall well-being.

Neurobiological Aberrancies Underlying Cognition and Psychopathology

The complex nature of neuropsychiatric conditions is further shown when looking at the presence of cognitive dysfunction in psychosis, where deficits in memory, attention, and executive function often appear alongside psychotic symptoms. There is significant overlap among CNS circuits implicated in pain and also core positive and negative symptoms of psychosis. Neurocognitive impairments suggest that shared neurobiological networks, including disruptions in prefrontal-limbic circuits and dopamine pathways, may underlie both cognitive deficits and psychotic phenomena. The work presented in **Chapter 5** highlights the link between cerebellar and frontal brain morphology in regulating cognition in early onset psychosis and discusses the involvement of the cerebellar networks in the context of psychotic symptoms.

Moreover, alterations within corticolimbic and cerebellar circuitry in adult SZ and BD are explored in **Chapter 6**. Individuals suffering from psychotic illnesses often experience a range of complex clinical

symptoms, where negative symptoms are transdiagnostic phenomena that substantially impair functioning in patients with psychosis. Disruptions in reward-motivation circuits that span (sub-)cortical and cerebellar subdivisions are hypothesized to underpin negative symptoms, and other symptom domains of psychosis such as cognitive impairment. The objective of this investigation was to identify biobehavioral markers of negative symptoms in patients with BD and SZ.

Pain Mechanisms and Affective Qualities of Pain

Children suffering from rheumatic conditions that involve joint inflammation unsurprisingly often experience pain, as is the case for Juvenile Idiopathic Arthritis. However, there appears to be a disconnect between detectable joint pathology and the degree of pain that is experienced. Pain in children with JIA can interfere with their ability to regulate emotions, contributing to increased risks of anxiety and depression. The investigation described in **Chapter 7** suggests that in this condition neural pathways associated with both emotional and cognitive processing may be altered, intensifying the psychosocial burden of the disease.

Pain-associated Proteins and Inflammatory Processes

In the context of disease, serum proteins can serve as biomarkers for various conditions and contribute to disease pathology. Serum proteins are diverse biomolecules present in the blood plasma, encompassing a wide range of functions including immune response, nutrient transport, and clotting. Key serum proteins such as albumin, globulins, and various cytokines play vital roles in maintaining homeostasis and responding to physiological challenges. Such proteins reflect the systemic inflammatory state and can

exacerbate disease symptoms by influencing local inflammation and joint degradation. Moreover, serum proteins circulate through the bloodstream and can penetrate various tissues, including the brain. The blood-brain barrier, though selective, allows certain proteins to cross, thereby impacting neuronal function and synaptic plasticity. This circulation and subsequent access of serum proteins to the brain can profoundly affect neurobiological processes, such as neurotransmitter release, neuroinflammation, and pain signaling pathways. As demonstrated in **Chapter 8**, serum proteins that associate with pain in JIA are identified, and their role in inflammatory and non-inflammatory processes is discussed. Consequently, the interaction between circulating proteins and the CNS may not only contribute to the regulation of pain but also links peripheral inflammation to CNS disorders, highlighting the importance of understanding these dynamics in the context of neuroinflammation and chronic pain syndromes.

Pain in a Primary Bone Disease

To gain a broader understanding of pain mechanisms beyond just inflammatory diseases, it is helpful to examine conditions with different causes and underlying processes. To that end, a rare non-inherited bone disease caused by a genetic mutation in the GNAS gene, FD/MAS, is described. The absence of an association between skeletal abnormalities and patient-reported pain suggests that maladaptive or pathological mechanisms beyond the skeletal system may contribute to pain. Therefore, **Chapter 9** explores neuropsychological and neurobiological factors associated with pain severity and phenotypes in patients with FD/MAS.

Integration of Findings Across Diseases and Discussion

Considering the broad range of topics that are discussed in this dissertation, **Chapter 10** will provide a brief overview of findings with regards to pain, psychopathology and cognition from the presented investigations. Moreover, this chapter will dive deeper into the shared neurobiological signatures across conditions, raise several questions that remain to be elucidated and suggest future directions to further unravel the complex interplay of pain and psychopathology.

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