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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 10

GENERAL DISCUSSION

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This thesis weaves together the threads of inflammation, pain, and cognitive and emotional process to provide a rich tapestry that showcases neurobiological and psychopathological factors impacting brain development and present across various disorders. Coursing through the thesis chapters, conditions such as early-onset psychosis, Juvenile Idiopathic Arthritis (JIA), Systemic Lupus Erythematosus (SLE), and Fibrous Dysplasia/McCune-Albright Syndrome (FD/MAS) are explored. This thesis places together the puzzle pieces that clarify the neurobiological underpinnings of pain and emotional dysregulation by connecting inflammation, cognitive dysfunction, and pain perception across developmental stages and disease conditions. The chief aim of this work is to explore the neural substrates and psychological aspects of pain, psychopathology and cognitive dysfunction. Examining the inflammatory processes, structural changes, and functional disruptions contribute to the development of complex symptom profiles across both child and adult patient populations enhances our current understanding of how pathological changes in the CNS influence cognitive, emotional, and psychological health.

**Chapter 1** lays the foundational overview of the key topics and conditions that are explored in the subsequent chapters. Neurobiological pathways of pain, neuroinflammation and neurodevelopment are discussed including main clinical presentations, pathology and etiology of childhood systemic lupus erythematosus (cSLE), Early-Onset Psychosis (EOP), Schizophrenia (SZ) and Bipolar Disorder (BD), Juvenile Idiopathic Arthritis (JIA) and Fibrous Dysplasia/ McCune- Albright Syndrome (FD/MAS).

The developing brain is highly susceptible to environmental influences during childhood, a period marked by pronounced neuroplasticity. Early adversities, including childhood maltreatment and trauma, disrupt the formation of neural circuits involved in stress regulation, emotional processing, and cognition. Alterations in key brain regions such as the hippocampus, amygdala, and prefrontal cortex lead to long-

lasting consequences, which may manifest as psychopathology and pain in later life. As discussed in **Chapter 2**, childhood maltreatment not only affects emotional development but also plays a significant role in shaping the experience of pain and psychopathology. This relationship is particularly pronounced in individuals who have experienced early adversity, in which disrupted pain processing mechanisms may serve as early markers of vulnerability to mental health disorders.

While inflammation is an essential protective response, chronic inflammation can interfere with neurodevelopmental processes, which can contribute to cognitive and behavioral impairments. This is evident in patient with cSLE, wherein immune and inflammatory processes impact both the central nervous system and in which neuropsychiatric symptoms are frequently present. **Chapter 3** sets the forum for understanding the role of inflammation in pediatric autoimmune diseases, which offers valuable insights into the complex interplay between systemic inflammation, brain function, and subsequent psychopathology. Chronic inflammation, particularly in childhood, may also heighten the risk of neuropsychiatric conditions, amplifying both pain and emotional dysregulation across the lifespan.

Pain and psychopathology are often tightly linked, with dysfunctional networks within the central nervous system playing a pivotal role. Dysregulation in these systems can intensify emotional responses such as anxiety and depression, consequently amplifying pain perception. As examined in **Chapter 4**, conditions such as depression, anxiety, and PTSD frequently occur in tandem with chronic pain, which suggests a shared neurobiological foundation. In the case of EOP, pain may act as both a symptom and a modulator of emotional disturbances. The interactions between emotional dysregulation, pain and psychopathological symptoms underscore the need for holistic treatment approaches that address both the emotional and physical dimensions of mental health.

Aside from psychotic symptoms, EOP patients consistently portray neurocognitive dysfunction, wherein cognitive impairments in areas such as memory, attention, and executive functioning are observed. **Chapter 5** describes abnormalities of neural circuits involved in cognition and psychosis, thereby suggestive of shared neurobiological pathways underlying both phenomena. By evaluating cerebellar and frontal brain morphology, this research highlights the importance of the fronto-cerebellar networks in regulating both cognition and emotion, which lends a potential for new intervention strategies for cognitive decline in childhood psychosis.

The investigation presented in **Chapter 6** examines brain-behavior relationships underlying negative symptoms in individuals with SZ and BD. Negative symptoms, which impair functioning in psychosis, may stem from disruptions in reward-motivation circuits involving cortical, subcortical, and cerebellar regions.

**Chapter 7** sheds light on the complex relationship between physical pain and emotional regulation in JIA. Children with JIA experience pain as a result of joint inflammation, yet the degree of pain often extends beyond what is detectable in joint pathology. This disconnect suggests that neurobiological mechanisms underlying pain and pain-related emotional processing may be altered. The psychosocial burden of JIA is significant, with pain contributing to heightened risks of anxiety and depression. This underscores the need for integrative approaches to treatment that address both the physical and emotional dimensions of pain, particularly in pediatric populations wherein the long-term impact on mental health is profound.

**Chapter 8** details the roles of serum proteins in the context of biomarkers of pain and disease pathology and describes their inflammatory and non-inflammatory pain mechanism. For example, cytokines can penetrate the blood-brain barrier and influence neurobiological processes such as

neurotransmitter release. In the context of JIA and other inflammatory conditions, the identified serum proteins reflect systemic inflammation and modulate central nervous system activity, contributing to both pain perception and the development of neuropsychiatric symptoms. The interaction between peripheral inflammation and central nervous system disorders highlights the importance of understanding these dynamics when considering therapeutic interventions for chronic pain syndromes.

**Chapter 9** expands the understanding of pain beyond inflammatory diseases by investigating FD/MAS, a genetic bone disease wherein patient-reported pain is not directly reflective of skeletal disease burden. To that end, this chapter emphasizes the neuropsychological and neurobiological aspects contributing to pain severity in FD/MAS. Indeed, these contributions to the pain severity suggests that maladaptive pain processing mechanisms outside the skeletal system may be at play. As discussed in this chapter, the findings in FD/MAS patients further reinforce the notion that pain is a multifaceted experience that is shaped by both biological and psychological features.

## Integration of Findings

### *Vulnerability of the Developing Brain to Environmental and Disease-Related Insults in Childhood*

The developing brain is highly susceptible to environmental influences during childhood, a period marked by neuroplasticity. Early adversities and disease related insults can critically impact neurodevelopmental trajectories, thereby affecting the morphological and functional neurobiology of the central nervous system. **Chapter 2** outlines the current body of evidence on the impact of childhood maltreatment on neurobiological structures and mechanisms, while the work in **Chapter 3** focuses on the impact of the childhood autoimmune disease cSLE. Moreover, the susceptibility of neurobiological systems in childhood is hypothesized throughout **Chapter 4** and **Chapter 5**, in the context of EOP, as well as in **Chapter 7** and **Chapter 8** in the arthritic condition JIA. A common feature across the childhood conditions—cSLE, EOP, and JIA—is that symptom presentation and health-related outcomes are more severe compared to their adult counterparts. Taken together, these chapters point to the high susceptibility of the developing brain during childhood, which is essential for inform clinical practice in childhood populations. On the other hand, mechanisms underlying the disruption of neurobiological circuitry by childhood adversities remain topics of further investigation. The impact of inflammatory factors on neurobiological systems is first hypothesized in **Chapter 3** based on the current research on cSLE. Inflammatory factors are further explored in **Chapter 8** by proteomic analysis of blood serum in JIA, wherein various immune related proteins are found to be upregulated in the patient group.

### *Neurobiological Underpinnings of Neuropsychiatric Symptoms*

Whether it is due to inflammatory insult or other pathological processes, disrupted neurobiological networks or abnormalities within neural structures are well-known to underpin various neuropsychiatric presentations. In **Chapter 2**, neurobiological changes within the mesocorticolimbic and nigrostriatal

pathways are discussed that may very well underpin a host of devastating effects ranging from the development of chronic pain or somatization to psychosis, psychopathology, and suicidal ideation<sup>52</sup>. Moreover, subcortical structures and cortical regions may be key modulators of neuropsychiatric symptoms such as cognitive dysfunctions. This distinguishing feature is highlighted in **Chapter 5**, which establishes the association between cognitive impairments and reduced cerebellar and frontal cortical volumes in children with EOP. Similarly, cerebellar aberrancies that linked to poorer cognitive functioning in adults with psychosis, and abnormalities within mesocorticolimbic circuitry - e.g. the nucleus accumbens and fornix - that appear to contribute to negative symptoms are described in **Chapter 6**. In parallel, volume of the caudate nuclei corresponded negatively with clinical pain severity in children with JIA, while decreased functional connectivity among prefrontal regions and the anterior insula corresponded with increased pain severity, as shown in **Chapter 7**. Evoked pain responses in the left anterior insular are also greater in JIA patients with pain than those without. Functional activation correlated more strongly with affective pain than sensory pain quality, which further implicates the role of insular cortex in emotional processing of pain. Furthermore, as discussed in Chapter 8, insular thickness correlates with depression scores in FD/MASS patients, while thickness of sensorimotor regions (e.g., precentral and paracentral gyrus) correlates negatively with clinical pain severity. In these patients, evoked functional activation of sensorimotor, frontal and temporal regions corresponds with greater pain measures, pain catastrophizing and depression.

#### *Interactions between Pain and Emotional Processing*

The described findings make apparent the complex interactions between pain and emotional constructs relating to pain, modulated by specific processing centers of brain circuitry. **Chapter 4** demonstrates pervasive pain in children with EOP and captures the multidimensional nature of the pain and sensory

symptoms through constructs such as pain catastrophizing, central sensitization and somatization. Moreover, **Chapters 7 and 9** detail the disconnect between objective disease activity and clinical pain severity in both JIA and FD/MAS patient populations. Taken together, the findings in these two chapters Similar to what is observed in EOP patients, the magnitude of pain catastrophizing and depressive symptoms correlates with pain severity in FD/MAS patients. Similar to what is observed in EOP patients, the magnitude of pain catastrophizing and depressive symptoms correlated with pain severity in FD/MAS patients, and reports of higher pain rating linked to more difficulty with cognitive functioning in JIA patients.

#### *Intersections between Pain and Psychosis*

Given the close connection between pain and cognitive as well as emotional processes, the interaction between pain and psychosis is readily apparent. **Chapter 2** sets the stage for the link between pain and psychiatric symptoms aberrancies in the context of childhood maltreatment, based on the current body of literature. While **Chapter 3** did not explicitly delve into the occurrence of pain in cSLE, the most prevalent neuropsychiatric symptoms in these patients include headache, cognitive dysfunction, mood disorder and psychosis, again suggestive of the coexistence of pain and psychopathology. To that effect, children with EOP reported high levels of pain, which corresponded with a higher degree of psychopathology in **Chapter 4**.

#### *Cerebellar Abnormalities as Key Contributors to Cognitive and Neuropsychiatric Symptoms Across Disorders*

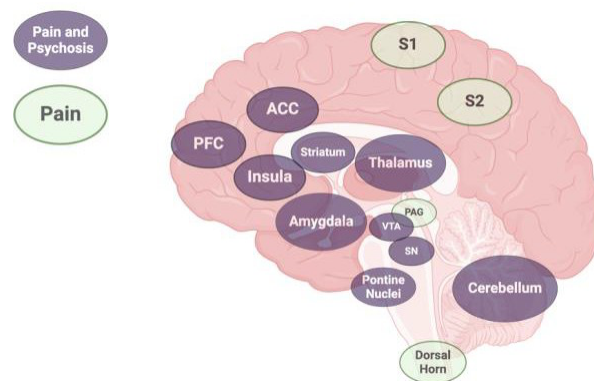
Abnormalities within subregions of the cerebellum are also implicated in several of the discussed conditions. In **Chapter 3**, the role of the cerebellum in neuropsychiatric symptoms in cSLE is suggested based on existing literature, although the evidence is sparse. The aberrancies within cerebellar regions, specifically Crus I and II and lobules V, VI, VIIIa, VIIIb and IX, in children with EOP, are central to the

investigation that is presented in **Chapter 5**. Adult patients with SZ similarly show decreased volumes in Crus I and II and lobules V and VI, as described in **Chapter 6**. Reductions in cerebellar volumes corresponded with P300 attenuation as measure of cognitive functioning in children with EOP, as well as with poorer performance on cognitive tasks in adults with psychosis. Moreover, functional connectivity analysis in JIA patients in **Chapter 7** demonstrate both decreased (lobules IV, V and VII) and increased (Crus II and lobule VIII) cerebellar connectivity to various cortical structures. The repeated observation of aberrancies within cerebellar regions and cortico-cerebellar functional connectivity across different patient populations indicate that cerebellum is an important hub in the pathological processes that underpin cognitive and neuropsychiatric symptoms.

#### *Neural Circuitry underlying Pain and Psychopathology*

A model of altered CNS circuitry giving rise to pain and psychotic symptoms is first proposed in **Chapter 2** in the context of childhood maltreatment, implicating regions within mesocorticolimbic and nigrostriatal pathways including but not limited to the prefrontal Cortex (PFC), thalamus, cingulate cortex, insula and nucleus accumbens. For example, regional alterations in the PFC, thalamus, caudate nucleus, brainstem nuclei, and cerebellar lobules contributing to neuropsychiatric symptoms in cSLE are also hypothesized based on current literature in **Chapter 3**. Subsequently, experimental evidence for cerebellar and prefrontal cortex aberrancies linked to cognitive functioning in children with psychosis is presented in **Chapter 4**. Dysfunction within mesocorticolimbic circuitry is once again suggested in adults with psychosis in **Chapter 5**, as volumetric and functional alterations of the nucleus accumbens and cerebellar lobules are demonstrated. Moreover, a neuroimaging evaluation of abnormal pain processing in JIA patients implicated the insula, cingulate cortex, caudate, thalamus, amygdala, striatum and cerebellar subregions, as described in **Chapter 6**. Finally, **Chapter 7** reveals morphological and functional

abnormalities in the insula, cingulate cortex, pre- and paracentral gyri, as well as white matter sensorimotor tracts that associate to pain and emotional aspects of pain in FD patients. Altogether, based on presented experimental findings as well as current literature, the overlap between pain processing circuitry and brain regions implicated in psychosis becomes apparent (**Fig. 1**). It can be hypothesized that the neural mechanisms and circuitry underlying psychotic symptoms also give rise to diminished bodily awareness and reduced salience of painful stimuli.



**Figure 1.** Schematic illustration of brain regions involved in pain and psychosis, highlighting areas of overlap in neural circuitry. The brain regions shown here are associated with both pain processing and psychosis-related functions. Areas in dark purple indicate structures implicated in both pain and psychosis, while green labels show regions primarily linked to pain. PFC (Prefrontal Cortex), ACC (Anterior Cingulate Cortex), S1 (Primary) and S2 (Secondary Somatosensory cortex), VTA (Ventral Tegmental Area), PAG (Periaqueductal Gray), SN (Substantia Nigra).

## Future Directions

This dissertation underscores the pressing need for a deeper understanding of the neurobiological systems that interact to drive chronic pain and contribute to psychopathology in pediatric populations. The findings presented in this work reveal key mechanisms involving inflammation, and abnormal structural and functional neurobiological circuitry, highlighting the role of these processes in pain perception,

emotional processing, and cognitive development. These insights have the potential to inform more comprehensive diagnostic and therapeutic approaches that address the complex interplay between physical and psychological health in children with chronic conditions.

#### *Neurobiological Mechanisms: Inflammation and Neurotransmitters*

While current research identifies inflammation as a key factor in neurodevelopmental and psychiatric disorders, there is a lack of long-term studies following children with chronic inflammation (e.g., due to autoimmune conditions such as JIA or SLE) to track the development of psychopathology over time. Longitudinal studies that focus on pain and neuropsychiatric symptoms are specifically required to ascertain how persistent inflammation during childhood impacts cognitive development, emotional regulation, and susceptibility to mental health disorders in adulthood.

As observed across conditions including FD/MAS and JIA, subjective pain experience is often not attributable to objective disease related cause. Neurobiological and psychological factors that drive this pain are still underexplored. Accordingly, future studies that tease apart maladaptive pain processing mechanisms in inflammatory and non-inflammatory conditions will be valuable in uncovering the psychological and neurobiological contributors to pain severity, independent of physical disease burden.

Though cytokines and serum proteins have been shown to cross the blood brain barrier and other brain barriers and consequently disrupting neurobiological processes. However, many questions remain about which specific conditions (e.g., inflammation, stress) may trigger these maladaptive processes, and how it contributes to psychiatric symptoms. For instance, the precise mechanisms of cytokine transport across the brain barriers and their impact on brain structures involved in pain and emotional processing should be explored. Moreover, careful mapping of cytokine profiles that relate to psychiatric presentation in chronic pain patients is warranted.

Neurotransmitters such as glutamate, substance P, serotonin, norepinephrine, and dopamine play critical roles in nociceptive pathways, which relay pain signals from the peripheral nervous system to the brain. The relevance of glutamatergic dysfunction and dopamine dysregulation is particularly significant given their roles in both chronic pain states and psychosis, with altered levels affecting pain and mood symptoms. These neurotransmitters are involved in pain pathways, which also include brain regions responsible for cognitive and emotional processing. This connection suggests that chronic pain may worsen cognitive dysfunction and psychotic symptoms by affecting shared neural circuits and vice versa. Further research should examine how early-life neurotransmitter imbalances might shape long-term mental health and pain perception.

#### *Brain Structures and Neuropsychiatric Pathways: Cerebellum and Shared Circuits*

Emerging evidence points to the cerebellum as an important contributor to cognitive and emotional regulation, with its involvement increasingly recognized in conditions beyond traditional motor functions. However, in the context of pain and psychopathology, particularly in pediatric populations, the cerebellum's role remains underexplored. This dissertation's findings on cerebellar dysfunction in pediatric conditions (e.g., EOP, JIA) underscore its likely role in the intersection of pain processing, emotional dysregulation, and cognitive function. However, further functional and structural imaging studies will clarify how cerebellar abnormalities and cortico-cerebellar connectivity influence both pain perception and neuropsychiatric symptoms, especially in childhood conditions such as EOP.

#### *Longitudinal and Developmental Impacts*

The studies discussed in this dissertation reveal that children with chronic inflammation or neurodevelopmental challenges (e.g., cSLE, JIA, childhood trauma) often experience complex

neuropsychiatric symptoms, yet longitudinal data are scarce. Longitudinal research could address how persistent inflammation or stressors during childhood may influence cognitive development, emotional regulation, and risk for mental health disorders. Studies that leverage neuroimaging with biochemical and neuropsychiatric assessments over time would provide a more comprehensive understanding of these developmental trajectories, allowing for the identification of early markers that might inform preventive or early intervention strategies.

#### *Treatment Considerations: Biopsychosocial and Pharmacological Approaches*

Although a biopsychosocial approach is increasingly implemented in various treatment strategies, there is a shortage of comprehensive, integrative treatment models that address the dual nature of chronic pain and psychopathology in children with conditions such as JIA or FD/MAS. Many current treatments focus on either the physical or emotional dimensions, while these treatments rarely address both simultaneously. The efficacy of multidisciplinary interventions that combine psychological therapies (e.g., cognitive behavioral therapy) with pharmacological treatments (e.g., anti-inflammatories) should be assessed, particularly in pediatric patients.

Furthermore, understanding the differential effects of first- and second-generation antipsychotics in pediatric populations with neuropsychiatric and chronic pain conditions is crucial. Current second-generation antipsychotics (SGAs) are preferred for their lower incidence of motor side effects and broader impact on both dopamine and serotonin systems. However, their short and long-term effects on cognitive and emotional symptoms in pediatric populations should be further explored. Future research on pediatric antipsychotic treatment that prioritize personalized approaches are valuable because these approaches enable clinicians to target specific neurotransmitter systems. Such approaches hold promises for maximizing therapeutic benefits while minimizing adverse effects.

By addressing these knowledge gaps in the field through longitudinal studies, neuroimaging, and clinical trials of integrative treatment models, future research can advance our understanding of neurobiological systems and psychological processes that underpin pain and psychopathology in pediatric and adult populations. These insights could lead to early diagnostic tools and interventions that more holistically address both physical and emotional dimensions of chronic illness.

### **Conclusion: A Unified Perspective on Pain and Psychopathology**

This dissertation demonstrates the profound interconnectivity between pain and psychopathology across pediatric and adult disease populations. Neurobiological systems, when compromised by childhood adversities such as trauma or illness, lay a foundation for lasting disruptions in emotional regulation, cognitive function, and pain perception. Neural mechanisms and circuitry underlying neuropsychiatric and psychotic symptoms may also give rise to aberrant salience of painful stimuli. In pediatric autoimmune diseases (e.g., cSLE and JIA), as well as non-inflammatory (e.g., FD/MAS) diseases and psychotic disorders (e.g., EOP, BD and SZ), shared pathways linking pain, emotional dysregulation, and cognitive dysfunction underscore the need for comprehensive, multidisciplinary approaches. Understanding these complex interactions creates opportunities for early intervention and targeted therapies to enhance both mental and physical health outcomes.