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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 2

CHILDHOOD MALTREATMENT AND ITS ROLE IN THE DEVELOPMENT  
OF PAIN AND PSYCHOPATHOLOGY

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# CHILDHOOD MALTREATMENT AND ITS ROLE IN THE DEVELOPMENT OF PAIN AND PSYCHOPATHOLOGY

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## **Abstract**

Childhood maltreatment represents a form of trauma capable of permanently altering fundamental neurobiological properties and negatively impacting neurodevelopmental processes. An outcome of childhood maltreatment is the emergence of psychopathology, which may become evident during childhood or adolescence, but also project into adulthood. Here, we propose a biobehavioral framework, where childhood maltreatment and the associated aberrant neurobiological mechanisms and behavioral processes additionally lead to the onset of altered pain processing and ultimately, the existence of pain syndromes. Considering that sub-populations of maltreated children demonstrate preserved function and minimal psychiatric or pain symptom presentation, compensatory mechanisms perhaps instilled by robust psychosocial support systems are discussed. We present validated tools and experimental methods that may facilitate a better comprehension of the interactions between childhood maltreatment, psychopathology, and pain. Such tools and approaches can in parallel be implemented to monitor abnormal pain-related processes and potentially guide early intervention strategies in cases of childhood maltreatment.

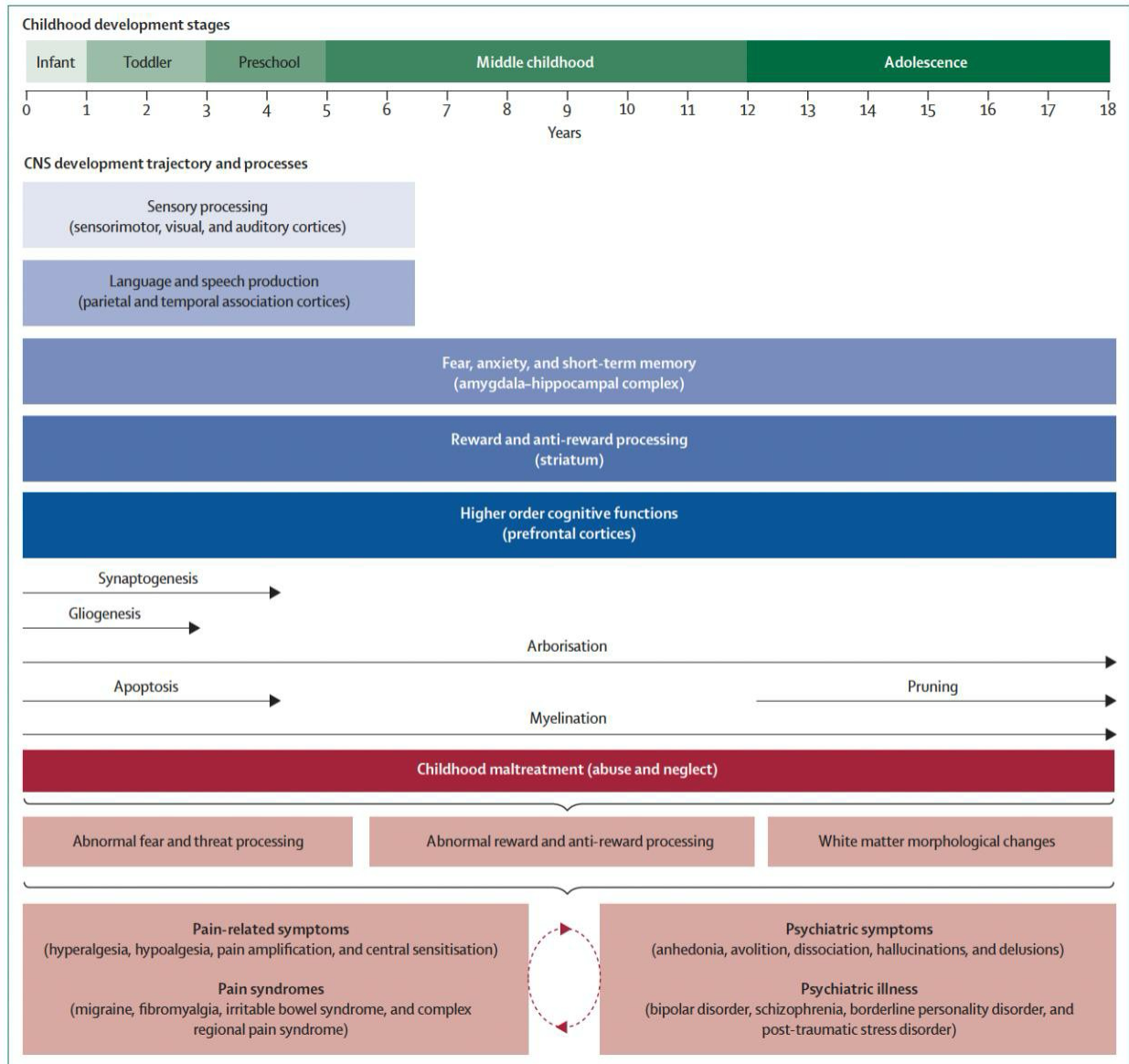
**Key words:** Childhood maltreatment, trauma, threat detection, reward processing, pain, psychiatric symptoms, resilience

## Introduction

Trauma is a ubiquitous human experience. Traumatic events vary greatly and may include physical or sexual assault, natural disaster, death of a loved one, socioeconomic stress, chronic illness, war, or abandonment. Childhood maltreatment is a form of interpersonal trauma, involving physical, sexual, or emotional abuse or neglect of a child. Maltreatment appears to have a critical effect on neurodevelopmental trajectories (**Figure 1**), whereby the morphological, functional, and neurochemical properties of the central nervous system (CNS) are fundamentally altered<sup>1</sup>.

Childhood maltreatment undoubtedly causes neurobiological modifications and increases the risk for developing psychopathology and psychiatric disorders<sup>2</sup>. Arguably, a related and additional outcome of childhood maltreatment is the shift from a normally protective mechanism (i.e., pain), to a maladaptive process, where the body is either not alerted to danger and such safety signals are ultimately suppressed, or the individual is burdened with unnecessary amplification of noxious endogenous or exogenous signals (**Box 1**). An example of a pain-related, loss-of-function symptom is hypoalgesia, which is commonly seen in psychiatric disorders such as schizophrenia<sup>3</sup>, borderline personality disorder (BPD)<sup>4</sup>, and post-traumatic stress disorder (PTSD)<sup>5</sup>. For some psychiatric patients, there may be a gain-of-function profile, where sensory hyper-reactivity or hyperalgesia may develop. Patients with BPD or PTSD may also present with a paradoxical perception of pain in which case hypoalgesia and hyper-reactivity to pain are jointly detected (see also **Supplemental Information**). Furthermore, early signs of pain and sensory abnormalities during or proximal to childhood maltreatment exposure may be predictive factors towards the development of pain syndromes (e.g., migraine, chronic headache, fibromyalgia, and irritable bowel syndrome) or a complex, comorbid state involving chronic pain and psychiatric illnesses including, but not limited to bipolar disorder<sup>6</sup>, BPD<sup>7</sup>, and PTSD<sup>8</sup>. However, the neurobiological, behavioral, and clinical

mechanisms by which pain-related conditions, either as standalone illnesses or components of a comorbid state, arise from childhood maltreatment remain largely unknown.



**Figure 1. Childhood Maltreatment and its Effect on Biobehavioral Systems Implicated in Pain and Psychiatry Disorders.** During the development of the human CNS, distinct neurological systems (i.e., sensorimotor, language, reward, or cognitive circuits) develop at different rates, with some systems continuing to mature well into late adolescence and beyond. Neurodevelopmental mechanisms occurring at the molecular or cellular level (i.e., synaptogenesis, pruning, or myelination) also occur in a variable and age-specific manner. Throughout the neurodevelopmental trajectory, and as a result of ongoing CNS maturation processes, children are arguably more vulnerable to the unfortunate and negative impact of childhood maltreatment. In the developing CNS, maltreatment is hypothesized to especially interfere with systems that regulate threat detection, fear processing, reward/anti-

reward mechanisms, and other fundamental neurological properties (i.e., white matter integrity). Over time, impediment of normal neurodevelopmental process stemming from childhood maltreatment may commonly facilitate abnormal pain and sensory processing, psychiatric symptoms and illnesses, and complex co-morbid states involving pain syndromes and psychiatric disorders. *BPD: Borderline Personality Disorder; CRPS: Complex Regional Pain Syndrome; IBS: Irritable Bowel Syndrome; PTSD: Post-Traumatic Stress Disorder; SZ: Schizophrenia*

Childhood maltreatment has a robust association with a range of mental health and physical symptoms that are often observed during childhood or adolescence, but can also emerge or persist into adulthood<sup>9</sup>.

Considering the amalgam of negative outcomes emanating from childhood abuse that spans mental and physical health, we hypothesize that maltreatment experienced during early and vulnerable stages of life

#### **Panel 1: Pain and psychiatric symptoms**

##### **Somatosensory and pain symptoms**

- Hypoalgesia (lack of response to painful stimuli)
- Hyperalgesia (heightened response to painful stimuli)
- Allodynia (painful response to non-painful stimuli)
- Pain amplification (excessive sensitivity to chronic or acute pain, or both)
- Central sensitisation (heightened response in the CNS to painful or non-painful stimuli)
- Functional somatic syndrome (one or more chronic symptoms with no known bodily cause)
- Nociceptive pain (pain arising from altered nociception without evidence of objective peripheral tissue damage or lesions with the somatosensory system)

##### **Loss of function symptoms**

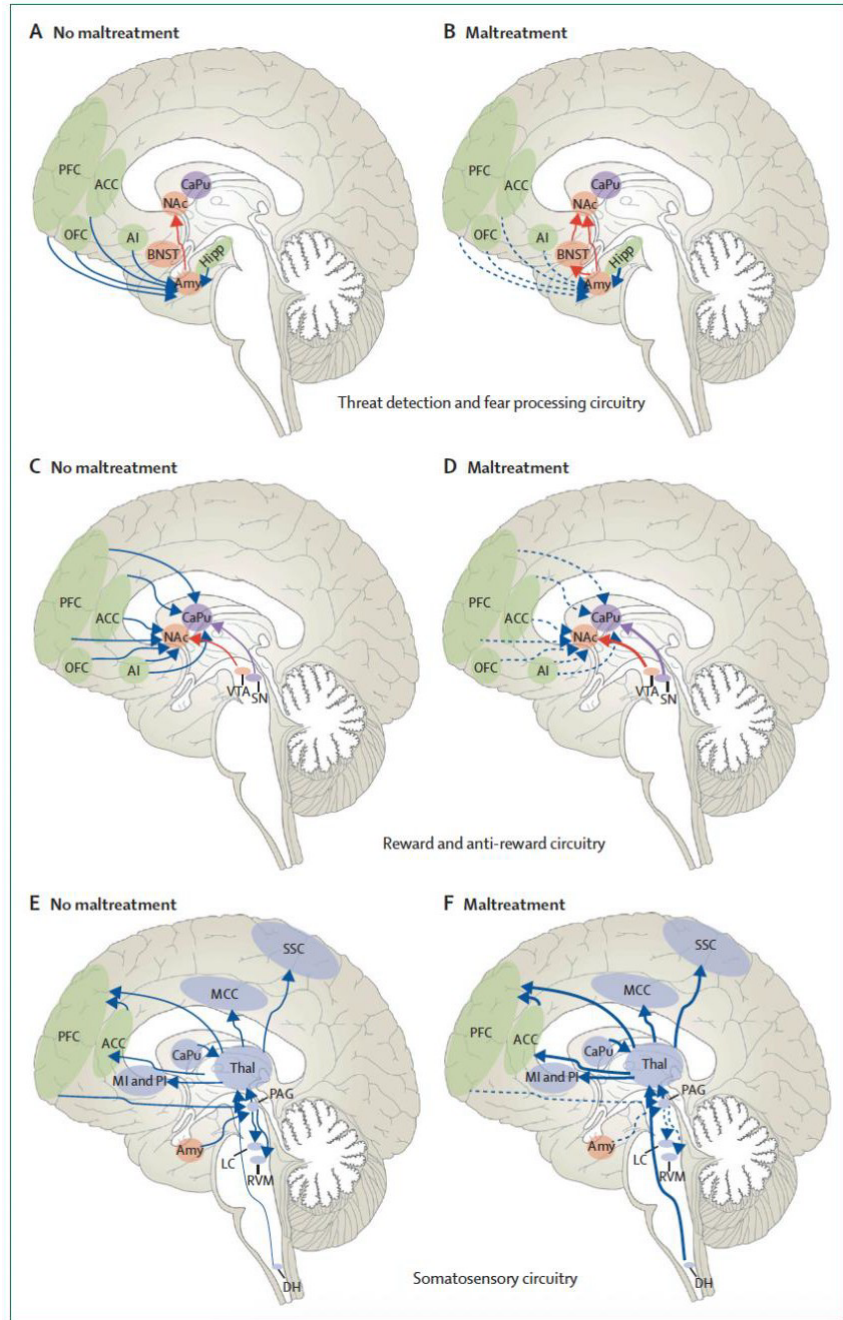
- Anhedonia (lack of pleasure)
- Alexithymia (lack of ability to identify one's emotions)
- Avolition (lack of motivation)
- Apathy (lack of interest)
- Alogia (lack of speech)
- Asociality (lack of interest in social interactions)
- Dissociation (disconnection from one's thoughts, identity, or sensory experiences)
- Numbing (lack of emotions)

is a key contributing factor towards the development of not only psychiatric illness and symptoms, but in parallel, the pain syndromes and sensory abnormalities frequently present in psychiatric patients. Herein, we highlight the importance of childhood maltreatment and its effects on the developing brain when interpreting pain experiences associated with mental illness. To this end, we examine prior work showing morphological and functional alterations stemming from childhood maltreatment embedded in specific neural circuits (i.e., the mesocorticolimbic pathway)

that are implicated in pain and psychiatric symptoms. References were collected through PubMed searches for “childhood maltreatment”, “pain”, “mental illness”, and “psychiatric symptoms” from 2010 to 2021 and included references were based on recency and relevance to this review. Based on our

analyses, we propose a CNS model that encompasses threat detection, fear processing, anticipation and regulation of rewarding and aversive stimuli, and sensory mechanisms, which are collectively hypothesized to facilitate high rates of maltreatment-associated pain and psychiatric symptoms (**Figure 2**), the latter of which are supported by a substantial body of epidemiological observations. Finally, detection of aberrant sensory processing and pain perception early in their presentation, as well as their investigation in the context of childhood maltreatment, is critical towards the goal of mitigating their undesirable and complex impact on childhood and adulthood well-being. Thus, validated clinical instruments and experimental strategies capable of probing pain-related symptoms, behaviors, and mechanisms in children and adults are described.

**Figure 2. Altered CNS Networks Stemming from Childhood Maltreatment.** A model of altered CNS circuitry behavior following exposure to childhood maltreatment is proposed. In individuals without a history of childhood maltreatment, top-down regulation within threat detection and fear processing remains intact as does normal afferent drive from the amygdala-hippocampal complex to striatal regions (**A.**). During or following childhood maltreatment, top-down control is compromised, while engagement of the BNST also occurs (**B.**). Dysregulation of reward/anti-reward circuitry caused by various forms of childhood maltreatment may also occur (**C-D.**). Within the proposed reward/anti-reward circuitry, top-down regulation is also affected by childhood maltreatment alongside more robust signaling within mesocorticolimbic and nigrostriatal pathways. (**E-F.**) Childhood maltreatment is also hypothesized to cause abnormalities within somatosensory or pain pathways, where descending regulation of structures such as the PAG may be disrupted. In parallel, heightened connectivity with ascending sensory and pain pathways is likely and may contribute to amplified pain responses or reactivity. Altered sensitivity or reactivity to other sensory modalities (e.g., visual or auditory) may implicate similar CNS networks. ACC: Anterior Cingulate Cortex; Amy: Amygdala; AI: Anterior Insula; BNST; bed nucleus of the stria terminalis; CaPu: Caudate Putamen; Hipp: Hippocampus; LC: locus coeruleus; ACC: Mid Cingulate Cortex; MI: Middle Insula; NAc: Nucleus Accumbens; OFC: Orbital Frontal Cortex; PAG: Periaqueductal Gray; PFC: Prefrontal Cortex; RVM: Rostral Ventral Medulla; SN: Substantia Nigra; SSC: Somatosensory Cortex; Thal: Thalamus; VTA: Ventral Tegmental Area.



## Impact of Childhood Maltreatment on Neurodevelopmental Trajectories

We propose a neurobehavioral model highlighting maladaptive mechanisms arising from childhood maltreatment that simultaneously increase the development of both pain conditions and psychiatric disorders (**Figure 2**). Childhood maltreatment may have a direct impact on systems that convey

innocuous and noxious sensory information and fundamentally alter morphological properties of sensory processing hubs. For instance, childhood verbal abuse was specifically associated with alterations in gray matter volume (GMV) and white matter integrity along the auditory and language processing streams<sup>10</sup>. Similarly, visual witnessing of domestic violence was associated with reduced GMV in occipital cortex and reduced FA in the inferior longitudinal fasciculus, which interconnects the visual and limbic systems<sup>11</sup>. Childhood sexual abuse has been shown to have a significant association with selective thinning of somatosensory cortex in the area responsible for tactile sensation in the genital area<sup>12</sup>. However, this domain has sparsely been reported on and requires further prospective investigation. As a result, the present review focuses on the effects of childhood maltreatment on threat detection and fear processing, as well as reward and anti-reward processing, but we have incorporated a hypothesized consequence of maltreatment on sensory systems into the proposed neurobehavioral model. We hypothesize that bottom-up and top-down dysregulation of threat, reward, and sensory mechanisms during neurodevelopment may underpin both long-lasting pain and psychopathology.

### ***Threat Detection and Fear Processing Circuitry***

Prospective longitudinal data has suggested that abuse during childhood may relate to increased threat detection in adolescence whereas neglect may correlate with decreased reward perception<sup>13,14</sup>. We postulate that hypervigilance and anxiety arising from childhood maltreatment, especially abuse, may ultimately drive a patient to develop chronic pain and pain hypersensitivity (hyperalgesia and allodynia), while avoidance, dissociative, or deficit symptoms resulting from childhood maltreatment, especially neglect, may be associated with pain hyposensitivity (hypoalgesia). One proposed mechanism is that as opposed to automatic activation of the sympathetic nervous system in the presence of a certain threat, enhanced recruitment of the amygdala-hippocampal complex and striatum to evaluate uncertain threats

may contribute to an allostatic process whereby a progression of fear and acute pain to anxiety and chronic pain, respectively, occurs. An aberrant down-regulation of salience system structures (e.g., anterior insula) may underpin dissociative symptoms in conjunction with pain hyposensitivity.

The frequent perception of threat and ensuing feelings of fear develop as a result of complex, maladaptive mechanisms embedded within subcortical threat and fear networks in addition to corticolimbic systems. Dysregulation of this intricate circuitry can lead to aberrant conscious or subconscious perception of endogenous or exogenous stimuli and one's subjective feelings. In the two-system neurobiological framework for threat detection and fear processing, threat, whether immediately present or *potentially* occurring in the future, elicits sensory afferent signaling to subcortical centers, mainly the amygdala, hippocampus, bed nucleus of the stria terminalis (BNST), and striatum<sup>15</sup>. Here, the subject's survival response entails *defensive reactions* (freezing or flight) or more complex *defensive actions* (escape or avoidance), where threats are processed via a direct (amygdala-hippocampus-striatum) or indirect (amygdala-hippocampus-BNST-striatum) routes. The latter stream being activated in circumstances of potential or 'uncertain' threat. Integrated with these subcortical systems are cortical brain areas (e.g., prefrontal, cingulate, anterior insular, and parietal cortices) that regulate conscious thought, working memory, and self-awareness as well as exert top-down regulation of the hippocampal-amygdala complex via the uncinate fasciculus (UF) white matter tract.

In individuals who have experienced childhood trauma, threat detection is frequently associated with altered amygdala reactivity<sup>16</sup>. Divergent trajectories (i.e., approach vs. avoidance) are perhaps underpinned by differing molecular mechanisms, which in some cases, are related to neurodevelopmental processes. In the context of maltreatment, variable responses in amygdala function have been reported with both increased and decreased activity associated with hyperarousal and

avoidance of threat, respectively<sup>17</sup>. Alterations in the hippocampus have also been linked to childhood maltreatment<sup>18</sup>. Moreover, an upregulation in hippocampal glutamate and glucocorticoid activity, enhanced corticotropin-releasing hormone activity in the amygdala, and reduced glutamate in the medial PFC have been shown to associate with neurodevelopmental vulnerabilities, and also mental illness and chronic pain<sup>19</sup>.

When accounting for various types of maltreatment and the lateralization of the amygdala, abuse may facilitate fear conditioning, which has been shown to lead to avoidance behaviors<sup>20</sup>. Furthermore, maltreated children exposed to family violence demonstrated enhanced right amygdala and bilateral anterior insula activity when shown angry faces<sup>21</sup>; a finding that may extend generally to processing of aversive stimuli in a threatening circumstance, including pain<sup>22</sup>. Such neuroimaging findings also suggest that children exposed to abuse may have heightened anticipation or attention bias towards aversive stimuli in response to specific triggers that may remind them of their own traumatic experiences<sup>22</sup>. Furthermore, fragmentation within prefrontal-hippocampal-amygdala or insular-amygdala circuits is hypothesized to yield a loss of top-down regulation within corticolimbic systems, causing both dysregulation of threat detection and pain. In the hypothalamic-pituitary-adrenal [HPA] axis, stimulus information is first sent to the polymodal prefrontal cortex (PFC), which processes and conceptualizes the stimulus, allowing it to exert top-down control of the basolateral amygdala. Interestingly, healthy subjects at risk for depression show elevated amygdala activity, but only individuals with childhood maltreatment, not those with a genetic risk for depression, displayed impaired top-down regulation of the amygdala via the PFC<sup>23</sup>. For pain, reduced top-down inhibition as a result of childhood trauma can cause an attention bias towards physical rather than emotional pain, potentially contributing to self-injurious behaviors that may relieve affective pain in conditions such as BPD<sup>24</sup>.

In the context of childhood maltreatment, variability in behavioral responses to or neurobiological processing of threatening stimuli or fear may arise from differential, structure-dependent developmental trajectories. HPA axis functionality is dynamic throughout childhood<sup>25</sup>. For example, the PFC displays peak vulnerability between the ages of 14-16<sup>26</sup>. This is in contrast to the amygdala, which is most susceptible to alterations in the first year of life, and then again between the ages of 9 to 11<sup>27</sup>, and the hippocampus, which is most vulnerable between the ages of 3 to 5<sup>28</sup>. Considering the heterogeneity with respect to regional developmental trajectories in the CNS in addition to associated molecular processes, prediction of long-term psychiatric consequences of childhood maltreatment, such as dissociative tendencies<sup>29</sup> and depression<sup>30</sup> is likely multifactorial.

### ***Reward and Anti-Reward Processing Circuitry***

Reward and its limitation, or anti-reward, processes are mediated by the mesocorticolimbic and nigrostriatal dopamine systems, which substantially overlap with the brain's opioid system, but also integrates with neural substrates regulating emotional status (via serotonergic system) and attention (via norepinephrine or noradrenaline circuitry). Assimilation of reward, affect, and top-down control processes incorporates frontostriatal white matter pathways, which have displayed reduced volumes in victims of childhood maltreatment<sup>31</sup>, in particular neglect<sup>13,14</sup>. Moreover, mesocorticolimbic and nigrostriatal dopamine systems are known for controlling affective or motivational aspects of pain processing, but are also crucial for establishing pain-induced mood states and analgesia<sup>32</sup>. Below, we highlight findings demonstrating the impact of childhood maltreatment on reward and anti-reward processing, particularly the anticipation or expectancy phase.

Findings of hypo-responsiveness within the dopaminergic system have been observed in individuals exposed to childhood maltreatment and are suggested to have lasting effects well into adulthood<sup>33</sup>. In a

cohort of adolescents subjected to severe, early-life deprivation in an orphanage setting, suppressed activity was detected in the ventral striatum and caudate nucleus during a monetary incentive delay task<sup>34</sup>, indicating decreased sensitivity to reward. Similarly, children with reactive attachment disorder displayed reduced activity again in both the ventral striatum and the caudate compared to typically developing children. Further, a sensitive period analyses found that these results were associated with maltreatment during the first year of life<sup>35</sup>. Prior reviews have postulated that since subcortical networks and structures (e.g., the basal ganglia) mature early in the neurodevelopmental trajectory, early childhood stressors may be more likely to affect functions regulated by these regions (i.e., approach motivation and reward responsiveness)<sup>36</sup>. In contrast, maltreatment later in childhood and adolescence may have more of an effect on cortical regions, particularly the PFC, and in turn, aspects of reward, such as reward learning are more dysregulated. For example, two key regions in the regulation of reward valuation and anticipation are the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC)<sup>37</sup>, both of which have shown long-term volumetric reductions in relation to childhood maltreatment<sup>2</sup>. In contrast to the early vulnerability seen in bottom-up pathways for reward<sup>36</sup>, reduced ACC volumes in adults were associated with childhood maltreatment after, but not before, the age of 7<sup>38</sup>.

Dysregulation of reward circuitry caused by various forms of childhood maltreatment correlates with the development of depressive symptoms in adolescents<sup>39</sup>. With harsh corporal punishment, Teicher and colleagues have reported a loss of gray matter volume (GMV) in prefrontal cortical regions and increased T2 relaxation time (indicative of reduced rCBV) within dopaminergic system<sup>40</sup>. Childhood social deprivation was associated with decreased ventral striatum behavior during presentation of happy faces<sup>13</sup>. In MDD patients, those with high levels of childhood trauma display increased levels of anhedonia compared to those with little or no childhood trauma<sup>41</sup>. Further, in MDD patients and controls, those with high levels of childhood trauma displayed increased anhedonia and decreased nucleus accumbens-PFC

functional connectivity regardless of diagnosis. Based on differing neural activity patterns in PTSD patients and *trauma-exposed* controls, it is suggested that it is not merely the experience of trauma, but also psychiatric symptoms, that play a role in the bottom-up<sup>42</sup> and top-down<sup>43</sup> perception of reward.

Reward or anti-reward systems have been well-implicated in acute and chronic pain states as well as analgesia<sup>32,44</sup>. Prior neuroimaging evidence indicates suppressed dopaminergic responses during pain states in fibromyalgia patients<sup>45</sup>, which is in accord with subsequent studies revealing diminished activity in the ventral tegmental area during both experienced and anticipated pain, as well as anticipated pain relief<sup>46</sup>. Collectively, alterations in the mesocorticolimbic dopamine system may play a critical role in the development of centralized, chronic pain syndromes and mood disorders<sup>47</sup>. Whether chronic pain or psychiatric conditions (e.g., schizophrenia or MDD) are considered, impairments in the reward-anti-reward system can lead to apathy, avolition, dissociation and anhedonia, the latter of which is often referred to as not only a symptom, but also a mechanism by which psychiatric illnesses and arguably centralized pain states co-develop or worsen in severity<sup>48</sup>.

In conditions such as complex regional pain syndrome, which similarly affects pediatric and adult populations, presence of PTSD symptoms have been reported as a psychological risk factor<sup>49</sup>. Multiple neuroimaging studies have independently identified morphological and functional alterations in CRPS patients, localized to mesocorticolimbic (e.g., nucleus accumbens) or nigrostriatal (putamen) pathways<sup>50</sup>. Additionally, central pain mechanisms have also been interrogated in PTSD patients, where up-regulated evoked pain activity, relative to control cohorts, was quantified in prefrontal cortices, ventral striatum, and dorsal striatum, and also the amygdala and hippocampus<sup>51</sup>. Thus, the amalgam of pain-related neuroimaging signatures elucidated in chronic pain and traumatized patients likely indicate maladaptive mechanisms related to reward or anti-reward mechanisms alongside threat and fear processing.

## **Implications of White Matter Integrity for Resilience and Vulnerability**

Childhood maltreatment, especially when perpetrated by close others, undoubtedly causes neurobiological changes 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>. The presentation of these unfortunate outcomes can occur proximal to maltreatment exposure, but also later during adulthood stages of life. Nevertheless, a sub-population of maltreated individuals appear to demonstrate altered CNS properties, yet show preserved function and a resilience towards harboring psychopathology<sup>53</sup>. Arguably, the relationship between childhood maltreatment and resilience towards development of chronic pain syndromes has been rarely investigated.

Diffusion tensor imaging (DTI), a method of characterization of white matter integrity (i.e., via quantification of fractional anisotropy (FA)) and mapping macroscopic arrangement of axonal pathways, has offered novel insights into the CNS networks impacted by childhood maltreatment. Using DTI, Ohashi and colleagues recently reported a subset of networks and network properties (e.g., nodal efficiency) that differentiate between symptomatic and asymptomatic adults who experienced childhood maltreatment. Interestingly, networks nodes such as the dorsal anterior cingulate cortex, amygdala, supplementary motor area, pre-/post central gyrus, amongst others are not only implicated in psychopathology, but well-known hubs of the central pain processing system. The presence of nodal efficiency at these centers may represent compensatory mechanism at play that enable patients to remain asymptomatic at least at the time of evaluation. Factors such as caregiver social support likely serve as protective mechanisms and potentially key for enabling resilience in traumatized individuals.

An often-implicated pathway in resilience and vulnerability in the context of maltreatment or trauma is the corpus callosum (CC). The CC shows volumetric reductions as a result of maltreatment between the ages

of 9 and 10<sup>26</sup>. In resilient adolescents, higher FA values in the CC have been reported compared to non-resilient and control adolescents; further, the increased FA values corresponded with higher resilience capacity<sup>54</sup>. The involvement of the CC, particularly the genu sub-region, which projects to frontal areas suggests its key role in emotional control. DTI studies have pointed to focal disruptions of integrity and to lower FA values in the CC in patients with schizophrenia as well as bipolar disorder<sup>55</sup>. Reduced CC FA has been reported in children with PTSD following maltreatment<sup>56</sup> and specifically in adolescents with childhood sexual abuse-related PTSD<sup>57</sup>.

White matter abnormalities localized to the CC, but also corticolimbic pathways, have been described in several pain disorders<sup>58</sup>. For instance, lower FA in the splenium of the CC in chronic musculoskeletal pain<sup>59</sup> has been shown. Lower FA in the body of the corpus callosum was also observed in fibromyalgia patients, and FA values were negatively associated with sensory pain and the ratio of sensory pain to affective pain<sup>60</sup>. Furthermore, reduced FA values in both the body and genu of CC in patients with CRPS<sup>61</sup>. The described commonality of altered morphology and integrity in the CC could indicate shared neuropathological mechanisms between psychiatric and pain disorders. Whether childhood maltreatment is a common driver of structural changes within the CC of patients with pain and psychiatric illnesses requires further investigation.

### **Outcomes of Childhood Maltreatment**

Childhood maltreatment, especially when perpetrated by close others, may have a variety of immediate and long-term effects on mental illness and pain perception (**Panel 2**). While trends have been observed according to DSM diagnoses, it is likely that many patients will present with unique phenotypes according to resilience, type and timing of childhood maltreatment, and the comorbidity of various psychiatric and pain-related symptoms.

*Panel 2: Case study of a young woman (aged 17 years) with a history of childhood maltreatment, pain amplification, and psychotic symptoms*

**Background**

Patient A, a young woman aged 17 years, was followed up for 7 years for mood instability, pain amplification syndrome, somatisation, and non-epileptic seizures at Boston Children's Hospital, MA, USA. Patient A had a long history of various gastrointestinal symptoms, most notably constipation, stomach pain, and difficulty eating. She also had a strong family history of psychotic bipolar disorder and had delayed speech development as well as suicidal ideation, severe self-injury, and psychotic symptoms including command auditory hallucinations, paranoia, and ideas of reference and control. Her psychotic symptoms arose in the context of both experiencing and witnessing (towards her parents) repeated physical attacks by a mentally ill sibling from a very young age to age 15 years.

**Pain and somatic symptoms**

Patient A's psychotic symptoms were noticed during a psychological evaluation through the pain service. At age 9 years, she was being treated for chronic pain amplification and reported developing leg pains, which she described as "knives all over" from the hips to toes in an even distribution on both legs. She reported that the pain was constant and nothing alleviated it. Despite the pain and an evaluation at the emergency department due to pain exacerbation after exercise, she was able to play soccer and did not have to miss school. After consultation with a neurology department and reassuring laboratory values, she was discharged home. Over the next 5 years, she presented with various other pain complaints, sometimes with physical findings such as increased warmth and perspiration in the affected area, and she was diagnosed with complex regional pain syndrome due to hyperalgesia as well as vasomotor, sudomotor, and motor changes.

**Psychiatric symptoms**

At age 10 years, she revealed that she had been hearing voices for so long that she did not know if they were real or if her mind was playing tricks on her. She said the voices told her to do things, sometimes with words and sometimes in some other indescribable way. She described times when she would want to

do one thing (eg, reach to her right) but would do something different (eg, reach to her left) in response to the voices.

She had episodes of repeated self-harm so severe that she was brought to the hospital and restrained so as not to continue to hit herself. At other times, she would obey commands from the voices such as wandering into the woods. She felt controlled, annoyed, and distracted by the voices. She also felt the voices could show her the future, such as bumping her head and realising she had already been shown this by the voices. She described often feeling anxious in public because of a strong sensation that someone was going to point at gun at her or harm her in some other way.

**Course of treatment**

Patient A was in on-going psychological therapy for anxiety and depression. She was evaluated by rheumatology for musculoskeletal pain team that was not thought to have an inflammatory component and was not consistent with arthritis. Long-term electroencephalogram monitoring of seizure-like activity showed no epileptiform activity coinciding with the behaviours suspected of having been causing the seizures. She had been on oxcarbazepine in the past, which was stopped due to a negative medical work-up including basic laboratory studies, thyroid function tests, allergy and immunology tests, cerebrospinal fluid studies and culture, electrocardiogram, and polysomnogram. She had trialled a selective serotonin reuptake inhibitor when she developed major depression and suicidal ideation necessitating psychiatric hospitalisation, but this seemed to worsen her anger. The voices, paranoia, and ideas of reference and control ceased with aripiprazole treatment. To a lesser extent, aripiprazole treatment also coincided with cessation of anxiety, depression, and pain symptoms. In later years, when her sibling's aggression was better controlled, she was able to come off the aripiprazole for more than 2 years without the return of psychotic symptoms. Subsequently, she had a relapse of less severe depression; she responded to a selective serotonin reuptake inhibitor and continued that medication.

*Development of Pain Syndromes*

Individuals with a history of childhood trauma are twice as likely to experience chronic pain in adulthood<sup>62</sup>.

Furthermore, when examining childhood maltreatment, specifically, prospective longitudinal data has shown that chronic and widespread pain in adulthood is intricately related to psychological distress during adolescence<sup>9</sup>. In a sample of adults with and without functional abdominal pain, those with pain were 8.2

times more likely to report having experienced some form of child abuse<sup>63</sup>. In adults with non-specific chronic low back pain (nsCLBP), individuals with histories of childhood maltreatment showed lower pressure pain thresholds, indicating hyperalgesia. Furthermore, nsCLBP patients without psychological trauma showed hyperalgesia only in the affected areas of the back, whereas nsCLBP patients with trauma showed generalized areas of pain sensitivity<sup>64</sup>, suggesting that trauma may play a role in the augmentation of central pain processing. For adult migraine patients, retrospective reports of childhood maltreatment were associated with transformation from episodic to chronic migraines, associated pain symptoms, and comorbid chronic pain conditions such as fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, and arthritis<sup>65</sup>.

When including both childhood and adulthood trauma, meta-analyses indicate that the risk for developing a functional somatic syndrome triples, yielding increased odds for fibromyalgia (OR = 2.52), chronic widespread pain (OR = 3.35), chronic fatigue syndrome (OR = 4.06), temporomandibular disorder (OR = 3.33), and irritable bowel syndrome (OR = 2.22)<sup>66</sup>. Research has suggested that the association between trauma exposure and central sensitization in chronic pain patients may be mediated in part by psychiatric symptoms<sup>67</sup>, and further point to the importance of creating a framework to simultaneously examine pain and mental illness in the context of childhood trauma.

#### *Development of Psychiatric Illnesses*

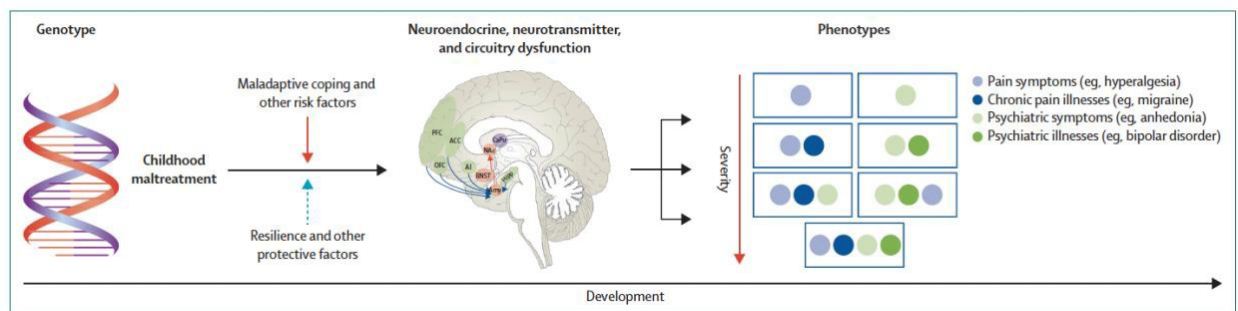
Childhood trauma, especially during critical times of CNS development and maturation, may leave an individual more vulnerable to psychiatric disorders. The pervasive effects of childhood trauma can drastically increase the likelihood for later development of depression, anxiety, PTSD, substance use disorders, personality disorders, bipolar disorder, and schizophrenia<sup>68</sup>. Prospective twin studies have revealed that 16% of children who experience maltreatment by an adult experience at least one psychotic

symptom by the age of 12 compared to 5% of children without maltreatment (OR = 3·16)<sup>69</sup>. Further, the use of identical and fraternal twins to elucidate environmental versus genetic risks showed that even after controlling for genetic vulnerability, children with a history of maltreatment were still twice as likely to experience psychotic symptoms by the age of 12 (OR = 2·16)<sup>69</sup>. Moreover, in clinical high-risk populations, childhood trauma contributes to 33% of the attributable risk for the evolution to a psychotic disorder, even when controlling for intelligence, genetic vulnerabilities, drug use, and other psychiatric comorbidities<sup>70</sup>. Further, in adult patients with major depressive disorder (MDD), those with psychotic features were more likely to report childhood physical (OR = 2·81) or sexual (OR = 2·75) trauma compared to MDD patients without psychosis<sup>71</sup>.

Many patients that experience childhood trauma do not develop a psychotic disorder, suggesting interactions between various risk factors. Understanding the precise mechanisms—which are likely complex and bidirectional—by which trauma magnifies risk could lead to new ways to prevent psychosis. For example, individuals who later develop schizophrenia frequently display early neurodevelopmental differences, and due to the heritability of these traits, often have parents with impaired judgement and impulse control—both factors put individuals at genetic risk for schizophrenia and higher risk for maltreatment, even prior to their first psychotic episode. The interaction between these biological and psychosocial risk factors might be interrupted through early intervention, illustrating the importance of understanding the full complexity of the association between trauma and risk of psychosis.

Exposure to early and recurrent trauma may result in greater deleterious long-term effects, yet research has also pointed to sensitive periods during which exposure to childhood maltreatment may be especially detrimental to the developmental trajectory of certain brain regions<sup>35</sup> (**Figure 1**). The timing of childhood maltreatment may be important in influencing the severity of various psychiatric symptoms (**Panel 1**). For

example, in adults with PTSD, neglect around the age of 4-5 years predicted dissociative symptoms, whereas neglect around age 8-9 heightened symptoms of depression. In schizophrenia spectrum disorders, shutdown dissociation was most influenced by neglect around age 13<sup>29</sup>. Furthermore, among individuals with SZ, maltreatment at 5 and 10 years of age was associated with more severe positive symptoms, such as hallucinations and delusions, while negative symptoms, such as anhedonia and avolition, correlated with maltreatment around the age 12<sup>72</sup>. Interestingly, dissociation has been found to mediate the relationship between childhood trauma psychosis, especially positive symptoms such as hallucinations, delusions, paranoia, and disorganization<sup>73</sup>. These results suggest that perhaps symptoms, rather than diagnoses, might be a more precise avenue for the investigation of relationships between childhood maltreatment, mental illness, and pain.



**Figure 3. Development of Pain and Psychiatric Phenotypes.** A. Subsequent to childhood maltreatment, pain as well as psychiatry symptoms and disorders may emerge at various developmental stages of life. Depending on factors such as maltreatment type, duration, or developmental status of the patient, distinct phenotypes may emerge across individuals. B. Genetic predispositions on their own may yield symptoms and illnesses. C. A combination of genetic variants present and exposure to childhood maltreatment may (i.) accelerate the onset of pain and psychiatry symptoms or disorders, (iii.) increase the propensity for specific phenotypes or (ii.) cause more severe phenotypes.

### Clinical Tools for Assessment of Pain and Their Utility in Cases of Childhood Maltreatment

A number of variables can determine what pain and psychiatric phenotype(s) are expressed following exposure to childhood maltreatment (**Figure 3**). It is important to note that various symptoms, illnesses, and phenotypes often arise in the absence of any childhood maltreatment, yet factors such as the

existence of genetic variants in conjunction with childhood maltreatment may drive individuals towards specific phenotypic trajectories. Moreover, in the context of childhood maltreatment and in adult patients who subsequently develop, for example, psychosis, we postulate that pain and somatic symptoms are perhaps expressed prior to the full manifestation of psychiatric illnesses such as schizophrenia spectrum or bipolar disorders. In fact, early expression of pain and somatic symptoms may represent a nascent maladaptive biological process unfurling within the CNS following exposure to childhood maltreatment. However, to date, neither neurobiological, behavioral, and clinical interactions between pain and psychiatric symptoms in individuals exposed to maltreatment, nor their respective trajectories, have not been thoroughly investigated. By systematically examining sensory processing and pain perception in maltreated individuals, a novel clinical research approach may be implemented, and one that allows for the effects of childhood maltreatment to be investigated from an alternative viewpoint that remains relevant to psychiatric illnesses.

To examine sensory and pain symptoms and the manifestation of pain syndromes, various validated clinical instruments as well as clinical research tools are presented (**Table 1**). The described measures are intended to assess symptoms irrespective of etiology, prognosis, and treatment response. While this list is not exhaustive, it may serve as a guideline for clinicians and researchers alike to monitor pain in instances of emerging psychiatric symptoms and in patients with a history of childhood maltreatment. The proposed clinical toolbox includes multiple pediatric (patient and parent/guardian-based) and adult measures to facilitate investigation of symptoms across developmental stages. For example, the Children's Somatization Inventory has been used to show associations between somatic symptoms and alexithymia<sup>74</sup>, and may be beneficial to examine somatization in relation to other aspects of emotional dysfunction. In patients of all ages, monitoring tools such as the Brief Pain Inventory and McGill Pain Questionnaire can inform clinicians of a patient's overall pain state and symptoms that they may not

otherwise report. In addition to self-report questionnaires, behavioral tasks such as quantitative sensory testing can directly assess sensitivity as measured by subject-specific thresholds and tolerances to acute sensory and pain stimuli spanning thermal and mechanical modalities. Further, the emBODY tool has revealed blunted bodily self-awareness in schizophrenia<sup>75</sup>, which may be related to the hypoalgesic phenotype that has been observed in this population.

## **Conclusion**

Development is a vulnerable time during which the normal imbalance embedded in maturing CNS structures and circuitry can be dramatically offset by childhood maltreatment. This state of vulnerability together with maltreatment may lead to diminished capacity to regulate emotions and higher risk for psychopathology. Across traumatized individuals, there can indeed exist distinct permutations of maltreatment with varying severity, type, and duration, along with diverse genetic predispositions, yet common neural signatures may develop in the CNS yielding overlapping clinical phenotypes. We have proposed that experiencing childhood maltreatment is a root cause of both psychiatric and pain-related symptoms with dysfunctional threat detection, fear processing, and reward/anti-reward mechanisms working in concert to ultimately yield physical and mental health problems ranging from abnormal pain perception to complex comorbid states in adulthood involving chronic pain *and* psychiatric disorders (e.g., bipolar disorder or PTSD). By further probing pain perception and processing in children and adults who experienced maltreatment during development, novel insights regarding mechanisms underpinning pain and somatic symptoms in psychiatric populations may be garnered, while also facilitating investigation of psychopathology from an alternative perspective.

**Table 1.** Overview of clinical tools and research approaches with a focus on measures informing on sensory and pain symptoms in paediatric and adult populations.

	Age group	Information gathered
<b>General measures for pain</b>		
Pediatric Pain Screening Tool	8–18 years	9-item child report of pain experience
Pain Frequency–Severity–Duration Scale	8–18 years	7-item self-report of pain amplification state over 2 weeks
Brief Pain Inventory	≥13 years	32-item self-report of the location, intensity, quality, and relief from chronic or acute pain in the past week
McGill Pain Questionnaire	≥12 years	15-item self-report of sensory and emotional components of pain
<b>Affective and behavioural pain</b>		
Pain Catastrophizing Scale	8–18 years	13-item child and parent report of threat or helplessness in the presence of pain
Fear of Pain Questionnaire	8–17 years	30-item child and parent report of avoidance and fear of pain
PROMIS Pain Quality—Affective	5–17 years	8-item child report to describe affective pain
PROMIS Pain Behavior	5–17 years	8-item child report of behavioural response to pain
<b>Sensory Pain</b>		
PROMIS Pain Quality—Sensory	5–17 years	8-item child report to describe sensory pain
Children’s Somatization Inventory	8–18 years	24-item child and parent report of somatic symptoms over 2 weeks
Central Sensitization Inventory	≥10 years	25-item self-report of multisensory sensitisation
PainDETECT	≥10 years	16-item self-report to detect presence of neuropathic pain
<b>Illness-specific measures</b>		
PedMIDAS	5–18 years	6-item child report of headache severity and frequency
MIDAS	≥18 years	5-item self-report of headache severity and frequency
Headache Impact Test-6	≥6 years	6-item self-report of headache interference with work, school, home, and social functioning
Questionnaire on Pediatric Gastrointestinal Syndromes	4–18 years	83-item parent report and 69-item child report of gastrointestinal symptoms
PROMIS—GI symptom scale	≥18 years	102-item self-report of gastrointestinal symptoms within 8 domains
Modified Fibromyalgia Impact Questionnaire for Children	10–20 years	19-item self-report of fibromyalgia symptoms over 1 week
Fibromyalgia Impact Questionnaire	≥18 years	21-item self-report of fibromyalgia symptoms over 1 week
<b>Research approach</b>		
Cyberball game	≥7 years	Measurement of socioemotional pain
emBODY tool	≥6 years	Measurement of bodily awareness for 14 different emotions
Quantitative Sensory Testing	≥7 years	Behavioural pain testing to measure presence of allodynia, hypoalgesia, and hyperalgesia
pedMIDAS=Pediatric Migraine Disability Assessment. PROMIS=Patient-Reported Outcomes Measurement Information System. GI=gastrointestinal.		
<b>Table: Overview of clinical tools and research approaches with a focus on measures informing on sensory and pain symptoms in paediatric and adult populations</b>		

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