


# Developmental mechanisms of CPSP: Clinical observations and translational laboratory evaluations

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## ABSTRACT

Understanding mechanisms that underly the transition from acute to chronic pain and identifying potential targets for preventing or minimizing this progression have specific relevance for chronic postsurgical pain (CPSP). Though it is clear that multiple psychosocial, family, and environmental factors may influence CPSP, this review will focus on parallels between clinical observations and translational laboratory studies investigating the acute and long-term effects of surgical injury on nociceptive pathways. This includes data related to alterations in sensitivity at different points along nociceptive pathways from the periphery to the brain; age- and sex-dependent mechanisms underlying the transition from acute to persistent pain; potential targets for preventive interventions; and the impact of prior surgical injury. Ongoing preclinical studies evaluating age- and sex-dependent mechanisms will also inform comparative efficacy and preclinical safety assessments of potential preventive pharmacological interventions aimed at reducing the risk of CPSP. In future clinical studies, more detailed and longitudinal peri-operative phenotyping with patient- and parent-reported chronic pain core outcomes, alongside more specialized evaluations of somatosensory function, modulation, and circuitry, may enhance understanding of individual variability in postsurgical pain trajectories and improve recognition and management of CPSP.

## RÉSUMÉ

La compréhension des mécanismes qui sous-tendent la transition de la douleur aiguë à la douleur chronique et la détermination de cibles potentielles pour prévenir ou minimiser cette progression ont une pertinence particulière pour la douleur chronique. La détermination de cibles potentielles pour prévenir ou minimiser cette progression sont particulièrement pertinentes pour la douleur postopératoire chronique (DPOC). Bien qu'il soit clair que de multiples facteurs psychosociaux, familiaux et environnementaux peuvent influencer la DPOC, cette revue se concentrera sur les parallèles entre les observations cliniques et les études translationnelles en laboratoire qui étudient les effets aigus et à long terme d'une blessure chirurgicale sur les voies nociceptives. Cela inclut les données relatives aux altérations de la sensibilité à différents points le long des nociceptives, de la périphérie au cerveau; les mécanismes dépendant de l'âge et du sexe qui sous-tendent la transition de la douleur aiguë à la douleur persistante; les cibles potentielles des interventions préventives et l'impact d'une blessure chirurgicale antérieure. Les études précliniques en cours, qui évaluent les mécanismes dépendant de l'âge et du sexe, permettront également d'évaluer l'efficacité comparative et la sécurité préclinique d'éventuelles interventions pharmacologiques préventives potentielles visant à réduire le risque de DPOC. Dans les futures études cliniques, un phénotypage péri-opératoire plus détaillé et longitudinal avec des résultats rapportés par les patients - et les parents - ainsi que des évaluations plus spécialisées de la fonction de la modulation et des circuits somatosensoriels, pourrait améliorer la compréhension de la variabilité individuelle des trajectoires de la douleur postopératoire et améliorer la reconnaissance et la gestion de la DPOC.

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## Introduction

Understanding mechanisms that underly the transition from acute to chronic pain and identifying potential targets for preventing or minimizing this progression are high priorities for pain research<sup>1,2</sup> and have specific relevance for persistent postsurgical pain.<sup>3</sup> Though enhanced

sensitivity of nociceptive mechanisms provides a warning of acute injury and is adaptive, pain that persists beyond the expected period of recovery can be associated with significant pain-related disability and mediated at multiple points along nociceptive pathways. Chronic pain may reflect ongoing excitation, decreased inhibition or inability to

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recruit endogenous inhibition, failure of active resolution mechanisms (e.g., resolvins and interleukin 10), or unmasking of hyperalgesia related to prior exposures or injuries.<sup>2,4-6</sup>

Nociceptive mechanisms and responses to injury and analgesia vary throughout postnatal development.<sup>7</sup> Laboratory studies can evaluate mechanisms underlying clinical observations in children with chronic postsurgical pain (CPSP) by (1) quantifying alterations in sensitivity at different points along nociceptive pathways from the periphery to brain, (2) evaluating age- and sex-dependent mechanisms underlying the transition from acute to persistent pain, (3) identifying potential therapeutic targets and comparing the safety and efficacy of interventions instituted before surgery (i.e., preventive) and/or after injury (i.e., during maintenance phase when hypersensitivity is established), and (4) determining the impact of prior exposures, such as different forms of stress and injury. This review will focus on parallels between clinical observations and related evaluations in translational laboratory studies to investigate the mechanisms and pathophysiology of CPSP.

### Laboratory Models of Surgical Injury

Because pain following surgery may be related to skin incision, muscle injury, inflammation, and/or nerve injury,<sup>8</sup> specific models have been developed to investigate acute and persistent alterations in nociceptive processing following surgical injury.<sup>9</sup> Specific contributions of additional factors that can contribute to, or exacerbate, pain following surgery (e.g., peripheral inflammation, full-thickness skin wound, visceral injury, immune challenge, traumatic nerve injury, stress) can also be evaluated at different postnatal ages. Studies performed in rodents allow comparison of age- and sex-dependent injury effects across different stages of mammalian development.<sup>10</sup> Many evaluations have focused on initial injury in the neonatal period and early infancy (first one to two weeks of postnatal life in rodents) because responses in the developing nervous system may differ from those at older ages, but associated persistent changes in somatosensory function can have an impact on the response to subsequent injury into adulthood.<sup>11</sup>

Plantar hind paw incision incorporates incision of the skin and underlying plantaris muscle and produces cellular and molecular alterations specific to this type of injury.<sup>6,12,13</sup> Acute behavioral hyperalgesia (reduced hindlimb reflex thresholds) is evoked, with the degree and duration of sensitivity influenced by postnatal age<sup>14,15</sup> but not sex.<sup>16</sup> In younger animals, incision-induced electrophysiological changes in large dorsal

root ganglion neurons persist beyond the period of behavioral hyperalgesia, afferent-evoked activity in second-order dorsal horn neurons is more marked and rapid,<sup>17,18</sup> and noxious-evoked potentials in the somatosensory cortex are enhanced and more resistant to increasing isoflurane anesthesia.<sup>19</sup> In addition, incision produces developmentally regulated long-term changes in nociceptive processing and response to re-incision<sup>20,21</sup> that differ from other injury models (see reviews for inflammatory, nerve injury, arthritis, stress, and immune challenge models<sup>7,11,22-28</sup>).

Laparotomy in newborn mice<sup>29</sup> and skin/muscle incision on the thigh (modified from the adult skin/muscle incision and retraction model<sup>30</sup>) at postnatal day (P)3 are associated with persistent alterations in sensory thresholds and in the latter with an enhanced degree and duration of hyperalgesia following re-incision of the ipsilateral hind paw.<sup>16</sup> Rodent models of inguinal hernia repair<sup>31,32</sup> and thoracotomy<sup>33</sup> have not been assessed in juvenile animals.

### Developmental Mechanisms of Acute and Chronic Surgical Pain

Pain and hyperalgesia following surgical injury involve alterations in peripheral and central nociceptive pathways.<sup>6,9</sup> In clinical studies, this can be evaluated with a range of techniques during or after surgery that include, but are not limited to, measurement of reflex thresholds,<sup>34</sup> somatosensory testing,<sup>35-37</sup> physiological reactivity and evoked responses (e.g., stress hormones,<sup>38</sup> inflammatory markers, monitors of autonomic tone<sup>39</sup>), and brain responses with electroencephalography and neuroimaging.<sup>40-42</sup> Though these measures may identify children and adolescents with enhanced sensitivity in the perioperative period or delayed recovery, further longitudinal studies are required to assess feasibility and utility at different ages and evaluate associations with the degree and/or risk of CPSP.

Nociceptive mechanisms contributing to persistent pain can include cellular plasticity with changes in molecular profile and translation regulation that shift the nociceptor toward hyperexcitability, alterations in neuronal circuitry and activity, systems-level changes such as immune cell recruitment or cell proliferation, and organism-level effects related to comorbidities and affective, behavioral, and motivational changes.<sup>2</sup>

### Peripheral and Spinal Mechanisms

Acute peripheral hyperalgesia following surgery has been quantified by changes in sensory withdrawal thresholds in human infants.<sup>34</sup> At older ages, quantitative sensory

testing (QST) has identified altered sensitivity and dynamic allodynia adjacent to neonatal surgical scars in extremely preterm-born children and young adults<sup>43,44</sup> and punctate hyperalgesia many years following childhood surgery.<sup>45–47</sup> Associations between persistent alterations in scar-related sensitivity and the degree or duration of pain if subsequent surgery is required in the same region require further evaluation.

Peripheral nociceptors respond to noxious stimuli following birth, and primary hyperalgesia in the region of plantar hind paw incision has been demonstrated across a range of postnatal ages in rodents.<sup>14,15</sup> Surgical injury will also evoke a peripheral inflammatory response that can contribute to acute hyperalgesia at all postnatal ages, with longer-term alterations in sensitivity varying with the type and degree of insult.<sup>48,49</sup>

Growth hormone signaling influences activity and development of peripheral nociceptive neurons in neonatal rodents, and a detailed series of experiments following dorsal hind paw and muscle incision identified sequestration of growth hormone by infiltrating macrophages and upregulation of transcription factors related to excitatory receptors and channels that lead to nociceptor sensitization.<sup>50</sup> Hyperinnervation following full-thickness skin wounding may contribute to persistent sensitivity and is more pronounced at younger ages due to differences in trophic and nerve guidance factors (nerve growth factor,<sup>51</sup> neurotrophin 3,<sup>52</sup> ephrin signaling<sup>53</sup>) and is also seen following plantar incision.<sup>11</sup>

Afferent input induces central sensitization in the spinal cord, with increased excitation and/or impaired inhibition.<sup>6,54</sup> Mechanisms can include changes in synaptic function, reduced local and/or descending inhibitory effects, and potential maladaptive and long-term changes due to translational effects on gene expression.<sup>54</sup> Developmental changes in spinal cord structure and function, including larger and overlapping cutaneous receptive fields and a relative excess of excitatory and delayed maturation of inhibitory synaptic signaling, contribute to low reflex thresholds.<sup>20,55</sup> Hind paw incision in neonatal rodents induces a range of age-dependent acute and persistent alterations in spinal cord synaptic function, including increased excitatory signaling and reduced inhibitory transmission, alterations in receptor expression, ion channel function, and differential gene expression<sup>56</sup> (see Brewer and Baccell's<sup>20</sup> review for details).

Clinically, preventive interventions for postsurgical pain focus on reducing afferent input (e.g., local anesthetic blockade), reducing excitation (e.g., N-methyl-D-aspartate antagonist), or enhancing inhibition (e.g., gabapentinoids).<sup>57–59</sup> In rodents, neonatal peri-incision sciatic blockade has preventive analgesic effects (lack of hyperalgesia at 24 h),<sup>15,60</sup> whereas opioids block

hyperalgesia only during the duration of action of the drug and sensitivity at later time points does not differ from saline controls.<sup>61</sup> More specific targeting of mechanisms that underlie the transition from acute to persistent pain or that enhance endogenous pain resolution mechanisms may more specifically reduce the risk of CPSP,<sup>1</sup> but efficacy and safety require evaluation in preclinical models at different stages of postnatal development.

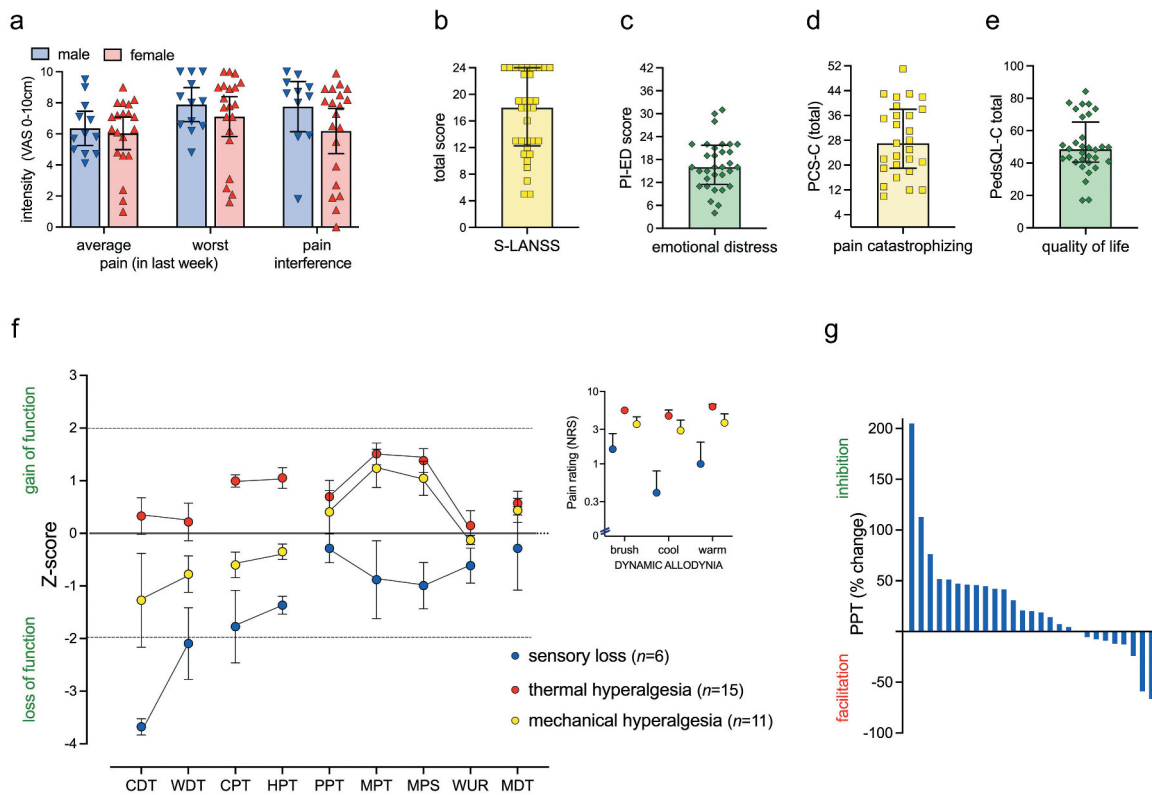
### Descending Modulation

The balance between descending inhibition and facilitation can be assessed in clinical populations with conditioned pain modulation (CPM).<sup>62</sup> In adults, inhibition is the usual baseline response, and reduced inhibitory CPM before surgery predicted CPSP.<sup>59,63</sup> In adolescents with idiopathic scoliosis, reduced inhibitory modulation or a shift to facilitation was seen in 21% and 28% respectively,<sup>64</sup> but potential links with risk of CPSP require evaluation in longitudinal perioperative studies. In adolescents with established neuropathic CPSP, robust inhibition was identified in only 44%, and 30% demonstrated a facilitatory response (Figure 1).<sup>35</sup> Though identifying impaired CPM preoperatively may inform risk and individualized therapy,<sup>36,63</sup> age-dependent effects also need to be considered because the degree of inhibitory CPM is reduced at younger ages (8–11 vs. 12–17 years).<sup>65</sup>

Descending modulation is mediated by brainstem centers (e.g., periaqueductal gray, rostroventral medulla, locus coeruleus) that receive input from higher centers (e.g., amygdala and limbic system) and have descending projections that can inhibit or facilitate spinal excitability.<sup>66</sup> In adult rodents, nociceptive C-fiber input is tonically inhibited (although this shifts to facilitation following injury), whereas at younger ages there is a relative excess of facilitation.<sup>67,68</sup> The delayed maturation of inhibitory mechanisms is influenced by endogenous opioid and endocannabinoid signaling,<sup>69</sup> and surgical injury in neonatal rodents produces long-term changes in the balance of inhibitory/facilitatory modulation.<sup>70</sup>

### Brain Structure and Circuits

Clinical neuroimaging studies have evaluated changes in structure, connectivity, or blood flow in brain regions associated with attention, sensory/discriminative, and affective/motivational aspects of pain experience<sup>71–74</sup> and also identified predictors of the transition from acute to persistent pain.<sup>75</sup> In adolescents with complex regional pain syndrome, alterations in brain structure and connectivity have been linked with self-reported outcomes (e.g., amygdala circuits and fear of pain) that improved following interdisciplinary treatment.<sup>76,77</sup>



**Figure 1.** Characteristics and impact of neuropathic CPSP. (a) Neuropathic CPSP is graded as moderate–severe intensity in both male ( $n = 12$ ) and female ( $n = 20$ ) adolescents (median [interquartile range] age: 15 [12.9, 16.5] years) and interferes with normal activity. (b) Total scores on the Self-report Leeds Assessment of Neuropathic Symptoms and Signs screening tool in the majority of adolescents above the cutoff for identification of neuropathic pain in adults (score of 12 or above in 25/32, 78%). (c) Increased anxiety and depression is reflected by Pediatric Index of Emotional Distress scores (16–20, mild; 22–28, moderate). (d) Pain Catastrophizing Scale for Children scores are increased (15–25, moderate; 26 and above, severe). (e) Impaired quality of life in school, physical, emotional, and social domains (Pediatric Quality of Life Inventory–Child Scale) is reflected by low total scores (<78, mild; <70 severe). (g) Quantitative sensory testing with a range of modalities identified distinct sensory profiles. Individual patient pain site thresholds were converted into z-scores calculated with reference to within-cohort body region–specific control data. The z-score plot for each individual patient was grouped according to the closest matching mechanism-related sensory profiles identified in adults: sensory loss ( $n = 6$ ), thermal hyperalgesia ( $n = 15$ ), or mechanical hyperalgesia ( $n = 11$ ). Dynamic allodynia to brush, cool (25°C) and warm (40°C) rollers in the region of pain was rated on a 0 to 10 numerical rating scale. (h) Conditioned pain modulation was assessed with a cold conditioning stimulus (immersion of hand in 5°C water bath) and variable test stimulus (change in contralateral knee pressure pain threshold). CPM effect (% change from baseline pressure pain threshold at 15 s) shows a spectrum of individual responses, with a shift to facilitation in 8/27 adolescents. CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; PPT, pressure pain threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; WUR, wind-up ratio; MDT, mechanical detection threshold. Data for CPSP subgroup extracted from Verriotis et al.<sup>35</sup>; see full manuscript<sup>28</sup> for further details of project registration (clinicaltrials.gov NCT03312881), methodology, parental consent and participant consent/assent was obtained and ethics approval was gained from National Health Service West Midlands-Black Country Research Ethics Committee (Ref: 17/WM/0306; Approval Date: 23-8-2017).

Magnetic resonance imaging is feasible in children with moderate–severe persistent postsurgical pain,<sup>78</sup> but pre- and postsurgery studies are yet to identify risk factors for CPSP in children, and effects on brain structure associated with prior neonatal surgery and intensive care also require consideration.<sup>43,79,80</sup>

Nociceptive circuits in the brain and central responses to noxious and innocuous stimuli undergo significant changes in the postnatal period, and activity-dependent maturation of circuits may be altered by injury.<sup>20</sup> In infant

rodents, evoked electroencephalograph responses in the somatosensory cortex were rapidly sensitized by hindpaw incision.<sup>19</sup> Following hind paw surgical injury in adult rodents, functional magnetic resonance imaging identified evoked responses in brain regions involved in sensory/discriminative, affective/attentional, and descending modulation,<sup>81</sup> and incision-induced reductions in the volume of different brain regions (anterior cingulate cortex, amygdala, thalamus, corpus callosum) were also influenced by early life stress and maternal separation.<sup>82</sup>

## Nerve Injury and Neuropathic CPSP

CPSP is often associated with characteristics of neuropathic pain in adults.<sup>83,84</sup> Although multiple mechanisms including inflammation and pain arising from muscles, joints, and viscera may also contribute to CPSP,<sup>85</sup> this section will focus on neuropathic pain, because this can be difficult to recognize in children and has specific implications for management.<sup>86</sup> In pediatric studies, there is significant variability in the diagnostic criteria and reported prevalence of neuropathic CPSP (e.g., 10%–89% with CPSP following scoliosis surgery<sup>87–89</sup>). Outcomes used to support possible or probable neuropathic pain have included history and clinical descriptors, neuropathic screening tool questionnaires, somatosensory testing, conditioned pain modulation, and response to treatment (e.g., topical lidocaine patch)<sup>35,87,88–91</sup>. In our tertiary pediatric pain clinic cohort of adolescents with peripheral neuropathic pain (based on clinical features, sensory descriptors, screening tool, and somatosensory testing), CPSP accounted for 32/52 (62%) cases and was associated with moderate–severe pain intensity (Figure 1a) and significant pain-related disability (Figures 1b–1e).<sup>35</sup> QST identified dynamic allodynia and distinct sensory profiles in the region of pain and prior surgical scars (Figure 1f) that have parallels with QST findings in adults.<sup>92</sup> Rather than being specific to the etiology of neuropathic pain, underlying mechanisms and relative efficacy of neuropathic medications may be more closely related to the different sensory profiles: sensory loss (denervation and spontaneous pain due to ectopic action potentials proximal to injured nociceptors; response to antidepressants), thermal hyperalgesia (peripheral sensitization with low threshold and spontaneous activity in “irritable nociceptors”; predicted efficacy with a sodium channel blocker, such as lidocaine patch and moderate response to antidepressant or gabapentinoid), and mechanical hyperalgesia (sensitization and spontaneous activity in peripheral and/or central nervous system and predicted efficacy with gabapentinoids).<sup>92,93</sup>

In rodents, responses to traumatic nerve injury vary throughout postnatal development, with a delayed onset of allodynia following nerve injury at younger ages that has been associated with a switch from an anti-inflammatory to pro-inflammatory response in the spinal cord.<sup>23</sup> Delayed emergence of neuropathic pain has also been reported following traumatic or surgical nerve injury in children.<sup>35,86,94</sup> The potential for preclinical studies to also link specific sensory modalities and mechanisms to efficacy of pharmacological interventions has been highlighted<sup>95</sup> and warrants further assessment at different developmental stages. In addition, more complex behavioral tasks in adult rodents have

evaluated alterations in motivational–affective response (e.g., conditioned place preference, social interaction, anxiety) and cognitive function (e.g., memory and attention)<sup>95–98</sup> and have identified long-term effects following surgical injury in early life (increased anxiety, impaired attentional performance and learning<sup>99</sup>).

## Impact of Prior Injury

Prior surgery is a risk factor for CPSP in adults,<sup>59</sup> and repeated surgery is not uncommon during childhood. Surgery may be required in early life for congenital anomalies and complications of prematurity, and 20% of 5609 neonates recruited from 31 European countries required repeat surgery prior to 60 weeks postmenstrual age.<sup>100</sup> In infants, repeat surgery in the same dermatome as prior neonatal surgery was associated with increased perioperative pain and stress.<sup>38</sup> A study recruiting 8- to 18-year-olds for evaluation of CPSP noted that 148/237 (61%) had undergone previous surgery and 148 (62%) had an ongoing pain problem prior to surgery.<sup>101</sup> In our cohort of 32 adolescents with neuropathic CPSP, 40% had required multiple surgeries throughout childhood, and pain had only become persistent after the most recent surgery in 20%.<sup>35</sup> Multiple psychosocial, environmental, and genetic factors can influence pain experience and the transition from acute to chronic pain,<sup>1,2,102</sup> and prior hospitalization may influence psychosocial factors such as anxiety and catastrophizing that are associated with increased risk of CPSP.<sup>101,103</sup> Because the response to surgery and nerve injury varies with age and surgery during childhood has been associated with persistent alterations in sensory processing, a past history of prior surgery and pain exposures is relevant for the clinical assessment of CPSP and evaluation of underlying mechanisms. Despite undergoing the same surgery, only a proportion of patients develop CPSP, and not all children and adults with persistent sensory changes related to surgical scars have associated pain. Therefore, in addition to identifying factors that increase the risk of CPSP, factors associated with improved recovery and resilience need to be evaluated.<sup>104,105</sup>

Epidural, regional, and systemic local anesthetic administration reduces the risk of chronic postsurgical pain in adults,<sup>59</sup> particularly following thoracotomy, breast cancer surgery, and cesarean section.<sup>106</sup> One pediatric study met the inclusion criteria (single study following pectus excavatum surgery<sup>107</sup> not included in meta-analysis), and the authors<sup>106</sup> highlighted the need for larger, high-quality studies assessing the impact of regional anesthesia on CPSP in children. An increasing range of local anesthetic techniques are utilized to

reduce perioperative pain in children,<sup>59,108</sup> and laboratory studies demonstrate both acute perioperative and long-term benefit on the response to repeat surgery. Use of peripheral, regional, and potential long-acting preparations and catheter techniques may have additional benefit in children to both reduce the risk of CPSP and also minimize the impact of early life surgery on subsequent injury response.

Prior surgery may have triggered biological changes that contribute to CPSP, because nociceptive pathways can be “primed” by noxious input/injury. Early life injury has been associated with a range of developmentally regulated peripheral and spinal cord mechanisms that contribute to an enhanced degree and duration of hyperalgesia following subsequent re-incision in adulthood.<sup>11,20</sup> In rodents, reducing primary afferent input by sciatic nerve blockade at the time of neonatal hind paw incision prevents persistent changes in synaptic signaling.<sup>109</sup> In addition, pre- and postincision neonatal sciatic block prevents the enhanced response to re-incision in adulthood (incision-induced hyperalgesia does not differ from animals without a prior injury),<sup>61</sup> whereas neonatal opioids do not have this long-term effect (enhanced re-incision hyperalgesia does not differ from control animals receiving saline at the time of neonatal incision).<sup>61</sup> As noted above, peripheral growth hormone signaling is altered by neonatal incision, and injection of growth hormone into hind paw muscles at the time of neonatal incision prevented the enhanced re-incision response in adulthood.<sup>50</sup>

Hyperalgesic priming is a form of plasticity in primary afferent nociceptive fibers.<sup>110</sup> Prior exposure to an inflammatory stimulus (e.g., hind paw injection of carrageenan or interleukin 6) or hind paw incision results in more prolonged hyperalgesia following a subsequent challenge several weeks later with a different or previously subthreshold mediator.<sup>111</sup> Targeting this form of plasticity may reduce the transition to persistent pain,<sup>111,112</sup> but sex-dependent effects need to be considered because mechanisms and response to preventive interventions differ in adult male and female rodents.<sup>113–115</sup>

Tissue injuries, including surgical incision, activate endogenous inhibitory mechanisms in the spinal cord and brain that contribute to the resolution of pain but may also mask ongoing hypersensitivity (i.e., latent sensitization).<sup>116,117</sup> Pathways include endogenous opioid signaling, with subsequent opioid antagonist administration unmasking the hypersensitivity, and long-term alterations in the constitutive activity of the mu opioid receptor increasing excitatory actions via altered N-methyl-D-aspartate receptor function.<sup>118</sup> Activity at mu opioid receptors and kappa opioid receptors, but not delta opioid receptors, modulates latent sensitization

following hind paw incision, and kappa opioid receptor-mediated inhibition of latent sensitization was greater in females.<sup>119</sup> Similarly, in human adult volunteers, high-dose naloxone unmasks hyperalgesia following an experimental thermal injury.<sup>120,121</sup> Mechanism-based preventive interventions are effective in adults,<sup>2</sup> but because the acute and long-term effects of opioid exposure vary with postnatal age and sex,<sup>122,123</sup> and when opioid is administered in the presence or absence of surgical injury,<sup>61</sup> evaluation at younger ages is also required.<sup>122,123</sup>

Neuroimmune interactions involving neurons, microglia, astrocytes, and T cells contribute to injury-induced changes in sensitivity and persistent pain.<sup>124,125</sup> However, neuroimmune signaling is sexually dimorphic.<sup>56,126,127</sup> Microglial inhibitors in male, but not female, adult rodents reduce pain behaviors following peripheral nerve injury,<sup>128,129</sup> hind paw inflammation,<sup>130</sup> and hyperalgesic priming,<sup>131</sup> whereas T cells may play key modulatory roles in females.<sup>132</sup> Microglia can be primed by early life exposures, resulting in intrinsic phenotypic changes and an exaggerated response to subsequent challenges.<sup>133,134</sup> Neonatal surgical incision primes spinal microglia, resulting in an enhanced degree and duration of microglial reactivity following re-incision in later life, and the associated enhanced hyperalgesia is reduced by microglial inhibitors in adult males.<sup>135,136</sup> Preventive, but sex-dependent, effects are also evident from early development, because microglial inhibitors at the time of neonatal incision prevented the enhanced response to adult re-incision in males but not females.<sup>16</sup> Microglia also have important roles in developing neural circuits (e.g., neurogenesis, synaptic pruning, and synaptic plasticity),<sup>137,138</sup> and perinatal insults can alter the normal sex-dependent trajectory of microglial development.<sup>139</sup> Therefore, alongside the well-documented persistent alterations in excitatory and inhibitory signaling induced by neonatal incision,<sup>20</sup> microglia may also influence developing spinal circuits.

## Summary

The prevalence and impact of CPSP in children and adolescents is increasingly recognized. Detailed perioperative phenotyping and longitudinal follow-up will improve prediction of CPSP and identify targets for intervention. Alongside patient- and parent-reported measures that encompass recommended domains of core outcomes for pediatric chronic pain,<sup>140</sup> specialized evaluations of somatosensory function and pain modulation, and assessments of connectivity and activity in central pain circuits, will contribute to understanding variability in postoperative pain trajectories. Ongoing translational preclinical studies evaluating age- and sex-dependent mechanisms will also inform comparative

efficacy and preclinical safety assessments of potential preventive pharmacological interventions.

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## References

- Price TJ, Basbaum AI, Bresnahan J, Chambers JF, De Koninck Y, Edwards RR, Ji RR, Katz J, Kavelaars A, Levine JD, et al. Transition to chronic pain: opportunities for novel therapeutics. *Nat Rev Neurosci*. 2018;19(7):383–84. doi:10.1038/s41583-018-0012-5.
- Price TJ, Ray PR. Recent advances towards understanding the mysteries of the acute to chronic pain transition. *Curr Opin Physiol*. 2019;11:42–50. doi:10.1016/j.cophys.2019.05.015.
- Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. *Expert Rev Neurother*. 2009;9(5):723–44. doi:10.1586/ern.09.20.
- Serhan CN. Pro-resolving lipid mediators are leads for resolution physiology. *Nature*. 2014;510(7503):92–101. doi:10.1038/nature13479.
- Ji RR, Xu ZZ, Strichartz G, Serhan CN. Emerging roles of resolvins in the resolution of inflammation and pain. *Trends Neurosci*. 2011;34(11):599–609. doi:10.1016/j.tins.2011.08.005.
- Richebe P, Capdevila X, Rivat C. Persistent postsurgical pain: pathophysiology and preventative pharmacologic considerations. *Anesthesiology*. 2018;129(3):590–607. doi:10.1097/ALN.0000000000002238.
- Fitzgerald M, Walker SM. Infant pain management: a developmental neurobiological approach. *Nat Clin Pract Neurol*. 2009;5(1):35–50. doi:10.1038/ncpneuro0984.
- Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet*. 2006;367(9522):1618–25. doi:10.1016/S0140-6736(06)68700-X.
- Segelcke D, Pradier B, Pogatzki-Zahn E. Advances in assessment of pain behaviors and mechanisms of post-operative pain models. *Curr Opin Physiol*. 2019;11:85–92. doi:10.1016/j.cophys.2019.07.002.
- McCutcheon JE, Marinelli M. Age matters. *Eur J Neurosci*. 2009;29(5):997–1014. doi:10.1111/j.1460-9568.2009.06648.x.
- Walker SM. Early life pain—effects in the adult. *Curr Opin Physiol*. 2019;11:16–24. doi:10.1016/j.cophys.2019.04.011.
- Brennan TJ. Incisional sensitivity and pain measurements: dissecting mechanisms for postoperative pain. *Anesthesiology*. 2005;103(1):3–4. doi:10.1097/0000542-200507000-00003.
- Xu J, Brennan TJ. Comparison of skin incision vs. skin plus deep tissue incision on ongoing pain and spontaneous activity in dorsal horn neurons. *Pain*. 2009;144(3):329–39. doi:10.1016/j.pain.2009.05.019.
- Ririe DG, Vernon TL, Tobin JR, Eisenach JC. Age-dependent responses to thermal hyperalgesia and mechanical allodynia in a rat model of acute postoperative pain. *Anesthesiology*. 2003;99(2):443–48. doi:10.1097/0000542-200308000-00027.
- Walker SM, Tochiki KK, Fitzgerald M. Hindpaw incision in early life increases the hyperalgesic response to repeat surgical injury: critical period and dependence on initial afferent activity. *Pain*. 2009;147(1–3):99–106.
- Moriarty O, Tu Y, Sengar AS, Salter MW, Beggs S, Walker SM. Priming of adult incision response by early-life injury: neonatal microglial inhibition has persistent but sexually dimorphic effects in adult rats. *J Neurosci*. 2019;39(16):3081–93. doi:10.1523/JNEUROSCI.1786-18.2019.
- Ririe DG, Bremner LR, Fitzgerald M. Comparison of the immediate effects of surgical incision on dorsal horn neuronal receptive field size and responses during postnatal development. *Anesthesiology*. 2008;109(4):698–706. doi:10.1097/ALN.0b013e3181870a32.
- Ririe DG, Liu B, Clayton B, Tong C, Eisenach JC. Electrophysiologic characteristics of large neurons in dorsal root ganglia during development and after hind paw incision in the rat. *Anesthesiology*. 2008;109(1):111–17. doi:10.1097/ALN.0b013e31817c1ab9.
- Chang PS, Walker SM, Fitzgerald M. Differential suppression of spontaneous and noxious-evoked somatosensory cortical activity by Isoflurane in the Neonatal rat. *Anesthesiology*. 2016;124(4):885–98. doi:10.1097/ALN.0000000000001017.
- Brewer CL, Baccei ML. The development of pain circuits and unique effects of neonatal injury. *J Neur Transm*. 2020;127(4):467–79. doi:10.1007/s00702-019-02059-z.
- Walker SM, Beggs S, Baccei ML. Persistent changes in peripheral and spinal nociceptive processing after early tissue injury. *Exp Neurol*. 2016;275(Pt 2):253–60. doi:10.1016/j.expneurol.2015.06.020.
- Melchior M, Kuhn P, Poisbeau P. The burden of early life stress on the nociceptive system development and pain responses. *Eur J Neurosci*. 2021; Online ahead of print Feb 22. doi:10.1111/ejn.15153.
- Fitzgerald M, McKelvey R. Nerve injury and neuropathic pain - A question of age. *Exp Neurol*. 2016;275(Pt 2):296–302. doi:10.1016/j.expneurol.2015.07.013.
- La Hausse de Lalouviere L, Ioannou Y, Fitzgerald M. Neural mechanisms underlying the pain of juvenile idiopathic arthritis. *Nat Rev Rheumatol*. 2014;10(4):205–11. doi:10.1038/nrrheum.2014.4.
- Walker SM. Translational studies identify long-term impact of prior neonatal pain experience. *Pain*. 2017;158(Suppl 1):S29–S42. doi:10.1097/j.pain.0000000000000784.
- Burke NN, Finn DP, McGuire BE, Roche M. Psychological stress in early life as a predisposing

- factor for the development of chronic pain: clinical and preclinical evidence and neurobiological mechanisms. *J Neurosci Res.* 2017;95(6):1257–70. doi:10.1002/jnr.23802.
27. Zouikr I, Bartholomeusz MD, Hodgson DM. Early life programming of pain: focus on neuroimmune to endocrine communication. *J Transl Med.* 2016;14(1):123. doi:10.1186/s12967-016-0879-8.
  28. Victoria NC, Murphy AZ. The long-term impact of early life pain on adult responses to anxiety and stress: historical perspectives and empirical evidence. *Exp Neurol.* 2016;275(Pt 2):261–73. doi:10.1016/j.expneurol.2015.07.017.
  29. Sternberg WF, Scorr L, Smith LD, Ridgway CG, Stout M. Long-term effects of neonatal surgery on adulthood pain behavior. *Pain.* 2005;113(3):347–53. doi:10.1016/j.pain.2004.11.013.
  30. Flatters SJ. Characterization of a model of persistent postoperative pain evoked by skin/muscle incision and retraction (SMIR). *Pain.* 2008;135(1–2):119–30. doi:10.1016/j.pain.2007.05.013.
  31. Bree D, Moriarty O, Broom DC, Kelly JP, Roche M, Finn DP. Characterization of the affective component of acute postoperative pain associated with a Novel Rat model of Inguinal Hernia repair pain. *CNS Neurosci Ther.* 2016;22(2):146–53. doi:10.1111/cns.12483.
  32. Bree D, Moriarty O, O'Mahony CM, Morris B, Bannerton K, Broom DC, Kelly JP, Roche M, Finn DP. Development and characterization of a novel, anatomically relevant rat model of acute postoperative pain. *J Pain.* 2015;16(5):421–35.e1–6. doi:10.1016/j.jpain.2015.01.010.
  33. Khasabov SG, Wang JC, Simone DA, Strichartz GR. A role for neurokinin-1 receptor neurons in the rostral ventromedial medulla in the development of chronic postthoracotomy pain. *Pain.* 2017;158(7):1332–41. doi:10.1097/j.pain.0000000000000919.
  34. Andrews K, Fitzgerald M. Wound sensitivity as a measure of analgesic effects following surgery in human neonates and infants. *Pain.* 2002;99(1–2):185–95. doi:10.1016/S0304-3959(02)00100-8.
  35. Verriotis M, Peters J, Sorger C, Walker SM. Phenotyping peripheral neuropathic pain in male and female adolescents: pain descriptors, somatosensory profiles, conditioned pain modulation, and child-parent reported disability. *Pain.* 2021;162(6):1732–48. doi:10.1097/j.pain.0000000000002172.
  36. Treede RD. The role of quantitative sensory testing in the prediction of chronic pain. *Pain.* 2019;160(Suppl 1):S66–S9. doi:10.1097/j.pain.0000000000001544.
  37. Petersen KK, Graven-Nielsen T, Simonsen O, Laursen MB, Arendt-Nielsen L. Preoperative pain mechanisms assessed by cuff algometry are associated with chronic postoperative pain relief after total knee replacement. *Pain.* 2016;157(7):1400–06. doi:10.1097/j.pain.0000000000000531.
  38. Peters JW, Schouw R, Anand KJ, van Dijk M, Duivenvoorden HJ, Tibboel D. Does neonatal surgery lead to increased pain sensitivity in later childhood? *Pain.* 2005;114(3):444–54. doi:10.1016/j.pain.2005.01.014.
  39. Ledowski T. Objective monitoring of nociception: a review of current commercial solutions. *Br J Anaesth.* 2019;123(2):e312–e21. doi:10.1016/j.bja.2019.03.024.
  40. Gursul D, Hartley C, Slater R. Nociception and the neonatal brain. *Semin Fetal Neonatal Med.* 2019;24(4):101016. doi:10.1016/j.siny.2019.05.008.
  41. Verriotis M, Chang P, Fitzgerald M, Fabrizi L. The development of the nociceptive brain. *Neuroscience.* 2016;338:207–19. doi:10.1016/j.neuroscience.2016.07.026.
  42. Borsook D, Youssef AM, Simons L, Elman I, Eccleston C. When pain gets stuck: the evolution of pain chronification and treatment resistance. *Pain.* 2018;159(12):2421–36. doi:10.1097/j.pain.0000000000001401.
  43. Walker SM, Melbourne A, O'Reilly H, Beckmann J, Eaton-Rosen Z, Ourselin S, Marlow N. Somatosensory function and pain in extremely preterm young adults from the UK EPICure cohort: sex-dependent differences and impact of neonatal surgery. *Br J Anaesth.* 2018;121(3):623–35. doi:10.1016/j.bja.2018.03.035.
  44. Walker SM, Franck LS, Fitzgerald M, Myles J, Stocks J, Marlow N. Long-term impact of neonatal intensive care and surgery on somatosensory perception in children born extremely preterm. *Pain.* 2009;141(1–2):79–87. doi:10.1016/j.pain.2008.10.012.
  45. Kristensen AD, Ahlburg P, Lauridsen MC, Jensen TS, Nikolajsen L. Chronic pain after inguinal hernia repair in children. *Br J Anaesth.* 2012;109(4):603–08. doi:10.1093/bja/aes250.
  46. Lauridsen MH, Kristensen AD, Hjortdal VE, Jensen TS, Nikolajsen L. Chronic pain in children after cardiac surgery via sternotomy. *Cardiol Young.* 2014;24(5):893–99. doi:10.1017/S104795111300139X.
  47. Kristensen AD, Pedersen TA, Hjortdal VE, Jensen TS, Nikolajsen L. Chronic pain in adults after thoracotomy in childhood or youth. *Br J Anaesth.* 2010;104(1):75–79. doi:10.1093/bja/aep317.
  48. Walker SM, Meredith-Middleton J, Cooke-Yarborough C, Fitzgerald M. Neonatal inflammation and primary afferent terminal plasticity in the rat dorsal horn. *Pain.* 2003;105(1–2):185–95. doi:10.1016/S0304-3959(03)00201-X.
  49. Ren K, Anseloni V, Zou SP, Wade EB, Novikova SI, Ennis M, Traub RJ, Gold MS, Dubner R, Lidow MS. Characterization of basal and re-inflammation-associated long-term alteration in pain responsiveness following short-lasting neonatal local inflammatory insult. *Pain.* 2004;110(3):588–96. doi:10.1016/j.pain.2004.04.006.
  50. Dourson AJ, Ford ZK, Green KJ, McCrossan CE, Hofmann MC, Hudgins RC, Jankowski MP. Early life nociception is influenced by peripheral growth hormone signaling. *J Neurosci.* 2021;41(20):4410–27. doi:10.1523/JNEUROSCI.3081-20.2021.
  51. Reynolds M, Alvares D, Middleton J, Fitzgerald M. Neonatally wounded skin induces NGF-independent sensory neurite outgrowth in vitro. *Brain Res Dev Brain Res.* 1997;102(2):275–83. doi:10.1016/S0165-3806(97)00105-3.
  52. Beggs S, Alvares D, Moss A, Currie G, Middleton J, Salter MW, Fitzgerald M. A role for NT-3 in the hyperinnervation of neonatally wounded skin. *Pain.* 2012;153(10):2133–39. doi:10.1016/j.pain.2012.07.012.
  53. Moss A, Alvares D, Meredith-Middleton J, Robinson M, Slater R, Hunt SP, Fitzgerald M. Ephrin-A4 inhibits sensory neurite outgrowth and is regulated by neonatal skin wounding. *Eur J Neurosci.* 2005;22(10):2413–21. doi:10.1111/j.1460-9568.2005.04452.x.



54. Tansley SN, Wong C, Uttam S, Mogil JS, Khoutorsky A. Translation regulation in the spinal dorsal horn - A key mechanism for development of chronic pain. *Neurobiol Pain*. 2018;4:20–26. doi:10.1016/j.ynpai.2018.03.003.
55. Fitzgerald M. The development of nociceptive circuits. *Nat Rev Neurosci*. 2005;6(7):507–20. doi:10.1038/nrn1701.
56. Serafin EK, Paranjpe A, Brewer CL, Baccei ML. Single-nucleus characterization of adult mouse spinal dynorphin-lineage cells and identification of persistent transcriptional effects of neonatal hindpaw incision. *Pain*. 2021;162(1):203–18. doi:10.1097/j.pain.0000000000002007.
57. Steyaert A, Lavand'homme P. Prevention and treatment of chronic postsurgical pain: a narrative review. *Drugs*. 2018;78(3):339–54. doi:10.1007/s40265-018-0866-x.
58. Clarke H, Poon M, Weinrib A, Katznelson R, Wentlandt K, Katz J. Preventive analgesia and novel strategies for the prevention of chronic post-surgical pain. *Drugs*. 2015;75(4):339–51. doi:10.1007/s40265-015-0365-2.
59. Schug SA, Palmer GM, Scott DA, Alcock M, Halliwell R, Mott JF. APM:SE working group of the Australian and New Zealand college of anaesthetists and faculty of pain medicine. In: *Acute pain management: scientific evidence*. 5th ed. Melbourne, Victoria, Australia: ANZCA & FPM ; 2020; p. 1-1215.
60. Ririe DG, Barclay D, Prout H, Tong C, Tobin JR, Eisenach JC. Preoperative sciatic nerve block decreases mechanical allodynia more in young rats: is preemptive analgesia developmentally modulated? *Anesth Analg*. 2004;99(1):140–45. doi:10.1213/01.ANE.0000114181.69204.72.
61. Moriarty O, Harrington L, Beggs S, Walker SM. Opioid analgesia and the somatosensory memory of neonatal surgical injury in the adult rat. *Br J Anaesth*. 2018;121(1):314–24. doi:10.1016/j.bja.2017.11.111.
62. Yarnitsky D, Dahan A. Endogenous pain modulation: from humans to animals and back. *Anesthesiology*. 2015;122(4):734–35. doi:10.1097/ALN.0000000000000594.
63. Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, Best LA, Granot M. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. *Pain*. 2008;138(1):22–28. doi:10.1016/j.pain.2007.10.033.
64. Teles AR, Ocay DD, Bin Shebreen A, Tice A, Saran N, Ouellet JA, Ferland CE. Evidence of impaired pain modulation in adolescents with idiopathic scoliosis and chronic back pain. *Spine J*. 2019;19(4):677–86. doi:10.1016/j.spinee.2018.10.009.
65. Tsao JC, Seidman LC, Evans S, Lung KC, Zeltzer LK, Naliboff BD. Conditioned pain modulation in children and adolescents: effects of sex and age. *J Pain*. 2013;14(6):558–67. doi:10.1016/j.jpain.2013.01.010.
66. Donaldson LF, Lumb BM. Top-down control of pain. *J Physiol*. 2017;595(13):4139–40. doi:10.1113/JP273361.
67. Koch SC, Fitzgerald M. The selectivity of rostroventral medulla descending control of spinal sensory inputs shifts postnatally from A fibre to C fibre evoked activity. *J Physiol*. 2014;592(Pt 7):1535–44. doi:10.1113/jphysiol.2013.267518.
68. Schwaller F, Kwok C, Fitzgerald M. Postnatal maturation of the spinal-bulbo-spinal loop: brainstem control of spinal nociception is independent of sensory input in neonatal rats. *Pain*. 2016;157(3):677–86. doi:10.1097/j.pain.0000000000000420.
69. Battell EE, Lilywhite A, Hathway GJ. The changing role of descending control of spinal nociception over post-natal development. *Curr Opin Physiol*. 2019;11:93–96. doi:10.1016/j.cophys.2019.08.003.
70. Walker SM, Fitzgerald M, Hathway GJ. Surgical injury in the neonatal rat alters the adult pattern of descending modulation from the rostroventral medulla. *Anesthesiology*. 2015;122(6):1391–400. doi:10.1097/ALN.0000000000000658.
71. Horiuchi Y, Tsuji O, Komaki Y, Fujiyoshi K, Hikishima K, Konomi T, Nagoshi N, Watanabe K, Matsumoto M, Horiuchi K, et al. Characteristic cerebral structural changes identified using voxel-based morphometry in patients with post-surgical chronic myelopathic pain. *Spinal Cord*. 2020;58(4):467–75. doi:10.1038/s41393-019-0391-0.
72. Howard MA, Krause K, Khawaja N, Massat N, Zelaya F, Schumann G, Huggins JP, Vennart W, Williams SC, Renton TF. Beyond patient reported pain: perfusion magnetic resonance imaging demonstrates reproducible cerebral representation of ongoing post-surgical pain. *PLoS One*. 2011;6(2):e17096. doi:10.1371/journal.pone.0017096.
73. Loggia ML, Segerdahl AR, Howard MA, Tracey I. Imaging clinically relevant pain states using arterial spin labeling. *Pain Rep*. 2019;4(4). doi:10.1097/PR9.0000000000000750.
74. Davis KD, Flor H, Greely HT, Iannetti GD, Mackey S, Ploner M, Pustilnik A, Tracey I, Treede RD, Wager TD. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. *Nat Rev Neurol*. 2017;13(10):624–38. doi:10.1038/nrneuro.2017.122.
75. Vachon-Preseau E, Tetreault P, Petre B, Huang L, Berger SE, Torbey S, Baria AT, Mansour AR, Hashmi JA, Griffith JW, et al. Corticolimbic anatomical characteristics predetermine risk for chronic pain. *Brain*. 2016;139(Pt 7):1958–70. doi:10.1093/brain/aww100.
76. Simons LE. Fear of pain in children and adolescents with neuropathic pain and complex regional pain syndrome. *Pain*. 2016;157(Suppl 1):S90–7. doi:10.1097/j.pain.0000000000000377.
77. Erpelding N, Simons L, Lebel A, Serrano P, Pielech M, Prabhu S, Becerra L, Borsook D. Rapid treatment-induced brain changes in pediatric CRPS. *Brain Struct Funct*. 2016;221(2):1095–111. doi:10.1007/s00429-014-0957-8.
78. Verriotis M, Moayedi M, Sorger C, Peters J, Seunarine K, Clark CA, Walker SM. The feasibility and acceptability of research magnetic resonance imaging in adolescents with moderate-severe neuropathic pain. *Pain Rep*. 2020;5(1):e807. doi:10.1097/PR9.0000000000000807.
79. Chau CM, Ranger M, Bichin M, Park M, Amaral R, Chakravarty M, Poskitt K, Synnes A, Miller SP, Grunau RE. Hippocampus, Amygdala, and Thalamus volumes in very preterm children at 8 years: neonatal pain and genetic variation. *Front Behav Neurosci*. 2019;13:51. doi:10.3389/fnbeh.2019.00051.

80. Mongerson CRL, Jaimes C, Zurakowski D, Jennings RW, Bajic D. Infant Corpus Callosum size after surgery and critical care for long-gap Esophageal Atresia: qualitative and quantitative MRI. *Sci Rep*. 2020;10(1):6408. doi:10.1038/s41598-020-63212-3.
81. Amirmohseni S, Segelcke D, Reichl S, Wachsmuth L, Gorlich D, Faber C, Pogatzki-Zahn E. Characterization of incisional and inflammatory pain in rats using functional tools of MRI. *Neuroimage*. 2016;127:110–22. doi:10.1016/j.neuroimage.2015.11.052.
82. Salberg S, Yamakawa GR, Griep Y, Bain J, Beveridge JK, Sun M, McDonald SJ, Shultz SR, Brady RD, Wright DK, et al. Pain in the developing brain: early life factors alter nociception and neurobiological function in adolescent rats. *Cereb Cortex Commun*. 2021;2(2):tgab014. doi:10.1093/texcom/tgab014.
83. Steyaert A, Lavand'homme P. Acute and chronic neuropathic pain after surgery: still a lot to learn. *Eur J Anaesthesiol*. 2017;34(10):650–51. doi:10.1097/EJA.0000000000000682.
84. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. *Pain*. 2013;154(1):95–102. doi:10.1016/j.pain.2012.09.010.
85. Sikandar S, Aasvang EK, Dickenson AH. Scratching the surface: the processing of pain from deep tissues. *Pain Manag*. 2016;6(2):95–102. doi:10.2217/pmt.15.50.
86. Walker SM. Neuropathic pain in children: steps towards improved recognition and management. *EBioMedicine*. 2020;62:103124. doi:10.1016/j.ebiom.2020.103124.
87. Hasan MS, Goh KJ, Yip HW, Mohamad SM, Chan TS, Chong KI, Haseeb A, Chiu CK, Wei CCY, Kwan MK. Neuropathic pain after adolescent Idiopathic Scoliosis correction surgery. *Asian Spine J*. 2020;15(5):628–35. Online ahead of print Oct 29. doi:10.31616/asj.2020.0006.
88. Julien-Marsollier F, David R, Hilly J, Brasher C, Michelet D, Dahmani S. Predictors of chronic neuropathic pain after scoliosis surgery in children. *Scand J Pain*. 2017;17(1):339–44. doi:10.1016/j.sjpain.2017.09.002.
89. Perello M, Artes D, Pascuets C, Esteban E, Ey Batlle AM. Prolonged perioperative low-dose Ketamine does not improve short and long-term outcomes after pediatric Idiopathic Scoliosis surgery. *Spine*. 2017;42(5):E304–e12. doi:10.1097/BRS.0000000000001772.
90. Goddard JM, Reaney RL. Lidocaine 5%-medicated plaster (Versatis) for localised neuropathic pain: results of a multicentre evaluation of use in children and adolescents. *Br J Pain*. 2018;12(3):189–93. doi:10.1177/2049463718756431.
91. Batoz H, Semjen F, Bordes-Demolis M, Benard A, Nouette-Gaulain K. Chronic postsurgical pain in children: prevalence and risk factors. A prospective observational study. *Br J Anaesth*. 2016;117(4):489–96. doi:10.1093/bja/aew260.
92. Baron R, Maier C, Attal N, Binder A, Bouhassira D, Cruccu G, Finnerup NB, Haanpaa M, Hansson P, Hulleman P, et al. Peripheral neuropathic pain: a mechanism-related organizing principle based on sensory profiles. *Pain*. 2017;158(2):261–72. doi:10.1097/j.pain.0000000000000753.
93. Forstenpointner J, Otto J, Baron R. Individualized neuropathic pain therapy based on phenotyping: are we there yet? *Pain*. 2018;159(3):569–75. doi:10.1097/j.pain.0000000000001088.
94. Corkum JP, Kuta V, Tang DT, Bezuhly M. Sensory outcomes following brachial plexus birth palsy: a systematic review. *J Plast Reconstr Aesthet Surg*. 2017;70(8):987–95. doi:10.1016/j.bjps.2017.05.007.
95. Dickenson AH, Patel R. Translational issues in precision medicine in neuropathic pain. *Can J Pain*. 2020;4(1):30–38. doi:10.1080/24740527.2020.1720502.
96. Keay KA, Argueta MA, Zafir DN, Wyllie PM, Michael GJ, Boorman DC. Evidence that increased cholecystokinin (CCK) in the periaqueductal gray (PAG) facilitates changes in resident-intruder social interactions triggered by peripheral nerve injury. *J Neurochem*. 2021;158(5):1151–71. doi:10.1111/jnc.15476.
97. Boada MD, Ririe DG, Martin CW, Martin SJ, Kim SA, Eisenach JC, Martin TJ. Nociceptive input after peripheral nerve injury results in cognitive impairment and alterations in primary afferent physiology in rats. *Pain*. 2020;161(5):960–69. doi:10.1097/j.pain.0000000000001782.
98. Navratilova E, Nation K, Remeniuk B, Neugebauer V, Bannister K, Dickenson AH, Porreca F. Selective modulation of tonic aversive qualities of neuropathic pain by morphine in the central nucleus of the amygdala requires endogenous opioid signaling in the anterior cingulate cortex. *Pain*. 2020;161(3):609–18. doi:10.1097/j.pain.0000000000001748.
99. Ririe DG, Eisenach JC, Martin TJ. A painful beginning: early life surgery produces long-term behavioral disruption in the rat. *Front Behav Neurosci*. 2021;15:630889. doi:10.3389/fnbeh.2021.630889.
100. Disma N, Veyckemans F, Virag K, Hansen TG, Becke K, Harlet P, Vutskits L, Walker SM, de Graaff JC, Zielinska M, et al. Morbidity and mortality after anaesthesia in early life: results of the European prospective multicentre observational study, neonate and children audit of anaesthesia practice in Europe (NECTARINE). *Br J Anaesth*. 2021;126(6):1157–72. doi:10.1016/j.bja.2021.02.016.
101. Noel M, Rosenbloom B, Pavlova M, Campbell F, Isaac L, Page MG, Stinson J, Katz J. Remembering the pain of surgery 1 year later: a longitudinal examination of anxiety in children's pain memory development. *Pain*. 2019;160(8):1729–39. doi:10.1097/j.pain.0000000000001582.
102. Perry M, Sieberg CB, Young EE, Baumbauer K, Singh V, Wong C, Starkweather A. The potential role of preoperative pain, Catastrophizing, and differential gene expression on pain outcomes after pediatric spinal fusion. *Pain Manag Nurs*. 2021;22(1):44–49. doi:10.1016/j.pmn.2020.05.007.
103. Rabbitts JA, Fisher E, Rosenbloom BN, Palermo TM. Prevalence and predictors of chronic postsurgical pain in children: a systematic review and meta-analysis. *J Pain*. 2017;18(6):605–14. doi:10.1016/j.jpain.2017.03.007.

104. Rabbitts JA, Palermo TM, Lang EA. A conceptual model of biopsychosocial mechanisms of transition from acute to chronic postsurgical pain in children and adolescents. *J Pain Res.* 2020;13:3071–80. doi:10.2147/JPR.S239320.
105. Hemington KS, Rogachov A, Cheng JC, Bosma RL, Kim JA, Osborne NR, Inman RD, Davis KD. Patients with chronic pain exhibit a complex relationship triad between pain, resilience, and within- and cross-network functional connectivity of the default mode network. *Pain.* 2018;159(8):1621–30. doi:10.1097/j.pain.0000000000001252.
106. Weinstein EJ, Levene JL, Cohen MS, Andreae DA, Chao JY, Johnson M, Hall CB, Andreae MH. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. *Cochrane Database Syst Rev.* 2018;6:Cd007105. doi:10.1002/14651858.CD007105.pub4.
107. Weber T, Matzl J, Rokitansky A, Klimscha W, Neumann K, Deusch E, Medical Research S. Superior postoperative pain relief with thoracic epidural analgesia versus intravenous patient-controlled analgesia after minimally invasive pectus excavatum repair. *J Thorac Cardiovasc Surg.* 2007;134(4):865–70. doi:10.1016/j.jtcvs.2007.05.050.
108. Pinto N, Sawardekar A, Suresh S. Regional anesthesia: options for the pediatric patient. *Anesthesiol Clin.* 2020;38(3):559–75. doi:10.1016/j.anclin.2020.05.005.
109. Li J, Walker SM, Fitzgerald M, Baccei ML. Activity-dependent modulation of glutamatergic signaling in the developing rat dorsal horn by early tissue injury. *J Neurophysiol.* 2009;102(4):2208–19. doi:10.1152/jn.00520.2009.
110. Reichling DB, Levine JD. Critical role of nociceptor plasticity in chronic pain. *Trends Neurosci.* 2009;32(12):611–18. doi:10.1016/j.tins.2009.07.007.
111. Burton MD, Tillu DV, Mazhar K, Mejia GL, Asiedu MN, Inyang K, Hughes T, Lian B, Dussor G, Price TJ. Pharmacological activation of AMPK inhibits incision-evoked mechanical hypersensitivity and the development of hyperalgesic priming in mice. *Neuroscience.* 2017;359:119–29. doi:10.1016/j.neuroscience.2017.07.020.
112. Kandasamy R, Price TJ. The pharmacology of nociceptor priming. *Handb Exp Pharmacol.* 2015;227:15–37.
113. Khomula EV, Ferrari LF, Araldi D, Levine JD. Sexual Dimorphism in a reciprocal interaction of ryanodine and IP3 receptors in the induction of hyperalgesic priming. *J Neurosci.* 2017;37(8):2032–44. doi:10.1523/JNEUROSCI.2911-16.2017.
114. Moy JK, Szabo-Pardi T, Tillu DV, Megat S, Pradhan G, Kume M, Asiedu MN, Burton MD, Dussor G, Price TJ. Temporal and sex differences in the role of BDNF/TrkB signaling in hyperalgesic priming in mice and rats. *Neurobiol Pain.* 2019;5:100024. doi:10.1016/j.ynpai.2018.10.001.
115. Baptista-de-souza D, Tavares-Ferreira D, Megat S, Sankaranarayanan I, Shiers S, Flores CM, Ghosh S, Luiz Nunes-de-souza R, Canto-de-souza A, Price TJ. Sex differences in the role of atypical PKC within the basolateral nucleus of the amygdala in a mouse hyperalgesic priming model. *Neurobiol Pain.* 2020;8:100049. doi:10.1016/j.ynpai.2020.100049.
116. Cooper AH, Hedden NS, Corder G, Lamerand SR, Donahue RR, Morales-Medina JC, Selan L, Prasoon P, Taylor BK. Endogenous micro-opioid receptor activity in the lateral and capsular subdivisions of the right central nucleus of the amygdala prevents chronic postoperative pain. *J Neurosci Res.* 2021; Online ahead of print May 6. doi:10.1002/jnr.24846.
117. Nelson TS, Taylor BK. Targeting spinal neuropeptide Y1 receptor-expressing interneurons to alleviate chronic pain and itch. *Prog Neurobiol.* 2021;196:101894. doi:10.1016/j.pneurobio.2020.101894.
118. Taylor BK, Corder G. Endogenous analgesia, dependence, and latent pain sensitization. *Curr Top Behav Neurosci.* 2014;20:283–325.
119. Custodio-Patsey L, Donahue RR, Fu W, Lambert J, Smith BN, Taylor BK. Sex differences in kappa opioid receptor inhibition of latent postoperative pain sensitization in dorsal horn. *Neuropharmacology.* 2020;163:107726. doi:10.1016/j.neuropharm.2019.107726.
120. Pereira MP, Donahue RR, Dahl JB, Werner M, Taylor BK, Werner MU. Endogenous opioid-masked latent pain sensitization: studies from mouse to human. *PLoS One.* 2015;10(8):e0134441. doi:10.1371/journal.pone.0134441.
121. Springborg AD, Jensen EK, Taylor BK, Werner MU. Effects of target-controlled infusion of high-dose naloxone on pain and hyperalgesia in a human thermal injury model: a study protocol: a randomized, double-blind, placebo-controlled, crossover trial with an enriched design. *Medicine.* 2016;95(46):e5336. doi:10.1097/MD.0000000000005336.
122. Fullerton EF, Doyle HH, Murphy AZ. Impact of sex on pain and opioid analgesia: a review. *Curr Opin Behav Sci.* 2018;23:183–90. doi:10.1016/j.cobeha.2018.08.001.
123. Harder HJ, Murphy AZ. Early life opioid exposure and potential long-term effects. *Neurobiol Stress.* 2019;10:100156. doi:10.1016/j.yjnstr.2019.100156.
124. Mapplebeck JC, Beggs S, Salter MW. Molecules in pain and sex: a developing story. *Mol Brain.* 2017;10(1):9. doi:10.1186/s13041-017-0289-8.
125. Ji RR, Donnelly CR, Nedergaard M. Astrocytes in chronic pain and itch. *Nat Rev Neurosci.* 2019;20(11):667–85. doi:10.1038/s41583-019-0218-1.
126. Gutierrez S, Hayashida K, Eisenach JC. The puerperium alters spinal cord plasticity following peripheral nerve injury. *Neuroscience.* 2013;228:301–08. doi:10.1016/j.neuroscience.2012.10.039.
127. Nelson LH, Saulsbery AI, Lenz KM. Small cells with big implications: microglia and sex differences in brain development, plasticity and behavioral health. *Prog Neurobiol.* 2019;176:103–19. doi:10.1016/j.pneurobio.2018.09.002.
128. Mapplebeck JC, Beggs S, Salter MW. Sex differences in pain: a tale of two immune cells. *Pain.* 2016;157(Suppl 1):S2–6. doi:10.1097/j.pain.0000000000000389.
129. Mapplebeck JCS, Dalgarno R, Tu Y, Moriarty O, Beggs S, Kwok CHT, Halievski K, Assi S, Mogil JS, Trang T, et al. Microglial P2X4R-evoked pain hypersensitivity is sexually dimorphic in rats. *Pain.* 2018;159(9):1752–63. doi:10.1097/j.pain.0000000000001265.

130. Taves S, Berta T, Liu DL, Gan S, Chen G, Kim YH, Van de Ven T, Laufer S, Ji RR. Spinal inhibition of p38 MAP kinase reduces inflammatory and neuropathic pain in male but not female mice: sex-dependent microglial signaling in the spinal cord. *Brain Behav Immun.* 2016;55:70–81. doi:10.1016/j.bbi.2015.10.006.
131. Paige C, Maruthy GB, Mejia G, Dussor G, Price T. Spinal inhibition of P2XR or p38 signaling disrupts hyperalgesic priming in male, but not female, mice. *Neuroscience.* 2018;385:133–42. doi:10.1016/j.neuroscience.2018.06.012.
132. Megat S, Ray PR, Moy JK, Lou TF, Barragan-Iglesias P, Li Y, Pradhan G, Wangzhou A, Ahmad A, Burton MD, et al. Nociceptor translational profiling reveals the regulator-Rag GTPase complex as a critical generator of neuropathic pain. *J Neurosci.* 2019;39(3):393–411. doi:10.1523/JNEUROSCI.2661-18.2018.
133. Perry VH, Holmes C. Microglial priming in neurodegenerative disease. *Nat Rev Neurol.* 2014;10(4):217–24. doi:10.1038/nrneurol.2014.38.
134. Burke NN, Fan CY, Trang T. Microglia in health and pain: impact of noxious early life events. *Exp Physiol.* 2016;101(8):1003–21. doi:10.1113/EP085714.
135. Beggs S, Currie G, Salter MW, Fitzgerald M, Walker SM. Priming of adult pain responses by neonatal pain experience: maintenance by central neuroimmune activity. *Brain.* 2012;135(Pt 2):404–17. doi:10.1093/brain/awr288.
136. Schwaller F, Beggs S, Walker SM. Targeting p38 Mitogen-activated protein Kinase to reduce the impact of neonatal microglial priming on incision-induced hyperalgesia in the adult rat. *Anesthesiology.* 2015;122(6):1377–90. doi:10.1097/ALN.0000000000000659.
137. Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med.* 2017;23(9):1018–27. doi:10.1038/nm.4397.
138. Salter MW, Beggs S. Sublime microglia: expanding roles for the guardians of the CNS. *Cell.* 2014;158(1):15–24. doi:10.1016/j.cell.2014.06.008.
139. Hanamsagar R, Alter MD, Block CS, Sullivan H, Bolton JL, Bilbo SD. Generation of a microglial developmental index in mice and in humans reveals a sex difference in maturation and immune reactivity. *Glia.* 2017;65(9):1504–20. doi:10.1002/glia.23176.
140. Palermo TM, Walco GA, Paladhi UR, Birnie KA, Crombez G, de La Vega R, Eccleston C, Kashikar-Zuck S, Stone AL. Core outcome set for pediatric chronic pain clinical trials: results from a Delphi poll and consensus meeting. *Pain.* 2021;162(10):2539–47. doi:10.1097/j.pain.0000000000002241.