

Translational studies identify long-term impact of prior neonatal pain experience

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1. Introduction

A comprehensive assessment of pain extends beyond measuring the intensity of pain to also include: site and radiation of pain; onset, aggravating and relieving factors; character of pain; associated symptoms; effect on activities and sleep; treatment and response; medical history; and factors influencing symptomatic treatment, such as beliefs and expectations, coping response and presence of anxiety or mood disorders, and family expectations.¹⁷⁵ Similarly, in clinical analgesic trials for chronic pain, detailed phenotyping of patients may provide information related to factors that predict not only the risk of persistent pain, but also the response to treatment.⁵⁵ This is particularly relevant given emerging data that mechanisms and efficacy of potential interventions for neuropathic pain differ between males and females.¹²⁴ Core phenotyping domains recommended as part of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) include: pain qualities; psychosocial measures; sleep; and quantitative sensory testing, including conditioned pain modulation.⁵⁵ However, as evidence increases for long-term effects following pain and stress in early life, should early life experience also form part of a comprehensive pain history and patient phenotyping?

2. Early life stress and adversity

2.1. Contributing factors

There is robust evidence that early life stress (ELS) or childhood adversity is associated with increased vulnerability to a wide range of mental health and medical conditions. While the definition of ELS varies, it generally includes abuse (sexual, physical, emotional) and/or neglect during childhood.^{27,143} Activation of the stress response aims to promote beneficial metabolic, functional and behavioral adaptations, but excessive activation, particularly during critical periods in early life, can alter the normal developmental trajectory and have long-term effects on stress reactivity in adulthood.¹⁴⁰ Similarly,

while acute pain is an adaptive warning sign of tissue injury, excessive pain during early life can have long-term adverse effects. As the physiological responses to pain and stress overlap, and early life pain produces both acute and long-term alterations in stress responsivity,^{25,202} it is perhaps not surprising that many aspects of ELS studies have parallels with those evaluating the long-term impact of pain in early life. Increasing awareness of the ability of early life experience to alter subsequent mental health disorders, medical conditions and chronic pain in adulthood, and the level of research activity evaluating both epidemiology and underlying mechanism, is highlighted by recent reviews.^{2,27,30,39,56,143,157} Common factors relevant to the evaluation of both stress and pain in early life, with some illustrative examples related to ELS, include:

- (1) age at time of exposure. There are specific sensitive periods when the developing brain fine-tunes the system to match the needs of the environment, but inappropriate stimulation can alter subsequent phenotype.^{2,3,223} Stress or adversity during different developmental stages can produce different neuro-anatomical and behavioral consequences.² In addition, ELS at different ages can influence the risk of subsequent medical conditions, such as cardiovascular disease,¹²⁰ gastrointestinal disorders,^{157,217} and chronic pain.^{27,149}
- (2) severity of ELS. A “dose-response” has been shown between the number of childhood adversities and risk of adult chronic pain, particularly neck and back pain.¹⁸⁵ However, ELS can be difficult to quantify and many studies do not control for the nature, frequency, or duration of exposure.²⁷
- (3) type of ELS. This can influence the brain region affected and the behavioral outcome.²
- (4) alterations in central nervous system structure and connectivity. Abuse prior to puberty has more selective effects on hippocampus, while the prefrontal cortex is significantly influenced by abuse after puberty.² Amygdala function and connectivity is also significantly altered following ELS, although links between alterations in functional interactions and subsequent behavior are not fully understood.⁵⁶
- (5) subsequent socio-environmental influences. Differentiating effects of the initial insult from subsequent modifying effects can be difficult, and recall bias may influence findings from retrospective studies.
- (6) sex differences.³ Throughout this manuscript, biological dichotomous “sex” differences will be referred to, rather than the more psychosocially based continuous variable of gender.⁷³ Although often not specifically assessed,¹⁸⁸ sex-dependent differences are relevant to the presentation and severity of a number of diseases associated with ELS, including mental health and mood disorders,² cardiovascular disease,¹²⁰ and visceral pain.¹⁵⁷

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- (7) variable patterns of hyperactivity and/or hypoactivity.³⁰ Early life stress has been associated with both increased and decreased responsivity of the hypothalamic–pituitary–adrenal (HPA) axis. This has resulted in different hypotheses, including the possibility that altered stress reactivity may be beneficial in some contexts (eg, higher anxiety makes one more attentive to potential threats).³⁰ However, the vast majority of studies evaluating risk to subsequent health have reported adverse effects. In addition to an altered risk of subsequent pain conditions, both increases and decreases in sensitivity to experimental pain stimuli have been reported in association with different types of ELS.^{27,59}
- (8) altered response to subsequent treatment. In adults with depression, prior childhood trauma was associated with reduced efficacy of both pharmacotherapy and psychological therapies and longer time to remission.²¹⁶

2.2. Early life stress and chronic pain in adulthood

Associations between different types of early life stress/adversity and chronic pain conditions in adulthood are integrated with results from translational laboratory models in recent reviews.^{27,143,157} Given the potential confounding factors when assessing long-term effects in clinical cohorts, the importance of hypothesis-driven studies of underlying mechanism has been highlighted.¹

Prospective epidemiological studies have associated early life adversity^{97,141} and/or somatic symptoms^{22,98,205} in childhood and persistent pain in adulthood (see above reviews for additional references). The 1958 UK Birth Cohort found the relative risk of chronic widespread pain varies with type of childhood adversity, particularly children who experienced maternal death (RR: 2.0; 95% CI 1.08-3.7) or resided in institutional care (1.7; 1.3-2.4). Being hospitalized after a road traffic accident increased risk (1.5; 1.05-2.1), but there was no increase associated with hospitalization for childhood surgery before 7 years. As 70% of procedures were for tonsillectomy and adenoidectomy, the degree of trauma and time in hospital are likely to have been less for these surgical cases.⁹⁷ Significantly, associations between childhood adversity and chronic widespread pain in adulthood persisted after controlling for adult psychological distress or social class.⁹⁷ Preterm birth in 1958 (defined as <37-week gestational age) and very low birth weight (<1.5 kg) were associated with a modest and not statistically significant increase in adult widespread pain, but survival and management in 1958 vary greatly from more recent cohorts.¹¹⁷

The degree of risk for persistent adverse effects is influenced both by the type of initial adversity and the nature of the subsequent outcome. In addition, the variable quality of existing data limits systematic analysis and comparison of the effects of age at time of exposure is limited to broad groupings of onset during childhood (at or before 18 years) or adulthood. In a meta-analysis of 71 studies, prior psychological trauma from a wide range of causes (psychological, emotional, sexual, or combat exposure) increased the risk of a subsequent somatic syndrome (chronic fatigue, irritable bowel, or fibromyalgia) by 2.7 (95% CI, 2.27-3.10) times.¹ This analysis included both trauma during childhood or adulthood and found no significant age-related or sex-related effect, but larger associations following combat exposure than physical abuse, and higher risk for chronic fatigue than fibromyalgia.¹ An earlier meta-analysis of 23 studies focusing on sexual abuse in childhood and/or adulthood similarly found no significant impact of age at time of exposure (child vs adult) but reported an increased risk of nonspecific chronic pain

(OR, 2.20; 95% CI, 1.54-3.15) and chronic pelvic pain (OR, 2.73; 95% CI, 1.73-4.30). If restricted to studies involving rape, the risk of chronic pelvic pain was increased, and significant associations with fibromyalgia (OR, 3.35; 95% CI, 1.51-7.46) also emerged.¹⁴⁹

2.3. Mechanisms

As ELS has been associated with wide-ranging effects on medical disorders and mental health, hypothesized mechanisms should be capable of influencing multiple physiological and/or psychological outcomes and also producing persistent alterations in function and/or responsivity to future stimuli.

Due to a central role in stress responsivity, much focus has been on potential alterations in the hypothalamic–pituitary–adrenal axis and corticotrophin-releasing factor circuits,¹⁴³ and the impact of perioperative stress on outcome has long been recognized following both adult and pediatric surgery.^{99,218} Both ELS and pain have significant interactions with different endogenous transmitter systems (monoamine, opioid, and endocannabinoid mechanisms) that also have specific trophic roles in early life, and therefore alterations in levels of stimulation during early developmental periods can produce persistent effects.^{27,177,200}

Activation of the immune system and heightened inflammatory responses may contribute to long-term impacts of ELS on a range of mood disorders and somatic health conditions,^{139,143} including pain.²⁷ Early-life-stress-related alterations in levels of systemic proinflammatory and/or anti-inflammatory cytokines, and activity-dependent changes related to vagal and sensory afferent input, can also influence neuroinflammatory responses within the central nervous system.²⁸ Exposure to an immune insult during early development not only enhances the response to a subsequent immune challenge, but also has more global effects on outcomes such as learning, anxiety, and sensory thresholds in adulthood.^{21,226} Microglia populate the central nervous system early in development, have important developmental roles in synaptic pruning and plasticity, and are capable of long-term changes in phenotype that alter response to subsequent insults.^{28,102,151,172} Many laboratory models of ELS have demonstrated long-term alterations in microglial reactivity, resulting in a “two-hit” hypothesis: exposure to ELS primes central nervous system microglia, so that a subsequent challenge in later life results in an enhanced microglial response and increased susceptibility to subsequent illness (eg, mental disorder or neurodegenerative condition).^{28,151}

The role of epigenetic mechanisms mediating gene × environment interactions¹³² is increasingly evaluated in relation to ELS, including the potential for adverse effects to be transmitted across generations.^{39,143} Similarly, epigenetic mechanisms contribute to persistent pain mechanisms⁷⁰ and offer a potential treatment target.⁶⁹ For example, polymorphisms in the stress modulator FK506 binding protein 5 (FKBP5) gene alter the impact of early life adversity^{118,223} and selective inhibitors of FKBP51 have potential for treatment of stress-related psychiatric or metabolic disorders^{57,67} and persistent pain.¹²²

3. Early life pain: preterm birth, neonatal intensive care, and surgery

3.1. Preterm birth and pain exposure in neonatal intensive care unit

Preterm birth is a recognized global health priority¹²⁵ as more than one in ten infants are born at varying intervals before the normal gestational age of 40 weeks (moderate preterm, 32 to

<37 weeks; very preterm [VP], 28 to <32 weeks; extreme preterm [EP] <28 weeks), and rates are increasing in many countries.^{19,33} While survival and outcomes are improving at earlier gestational ages,^{37,137} significant health and personal/family cost may be associated with acute care and potential disability or risk of health and mood disorders in later life.^{33,96} As a result, there is a significant focus on identifying risk factors for adverse neurodevelopmental outcome and targets for intervention in preterm born children and young adults.^{50,115,170,184,227}

Management in neonatal intensive care unit (NICU) exposes the developing nervous system to a wide range of physiological and environmental stressors, and it is difficult to quantify overall pain exposure. Multiple procedures are required for NICU care and monitoring, but these produce variable degrees of pain and/or stress,²⁹ and some will be associated with tissue injury and ongoing pain (eg, chest drain insertion). Duration of mechanical ventilation and days in NICU have been used as proxy measures of likely procedural pain exposure,^{72,198} while others have prospectively documented tissue breaking procedures.¹⁵⁹ The added impact of higher numbers of tissue breaking procedures on neurodevelopmental outcome and associations with changes in brain structure and connectivity have been reported in recent reviews.^{159,191,202} The type and degree of pain exposure in neonatal care will be influenced and/or modulated by biological factors, particularly intercurrent illness and physiological instability, and environmental or social factors (Fig. 1).

3.2. Neonatal surgery

In addition to procedural pain exposure, surgery may be required during the neonatal period to correct congenital anomalies or treat complications of prematurity,³⁸ and we have shown that neonatal surgery has an added impact on somatosensory outcomes following extreme preterm birth.²¹⁰ Neonatal surgery in preterm infants adversely affects many neurodevelopmental outcomes.^{52,58,100,138} The “need for surgery” may be confounded by underlying disease severity. In a cohort born <30 weeks gestation, those requiring surgery were smaller, required more respiratory support, had longer hospital stays, and subsequently had smaller brain volume and lower Mental Developmental Index scores at 2 years of age.⁵⁸ Following preterm birth, male sex is an independent risk factor for adverse

neonatal outcomes,¹²⁷ including cognitive impairment^{94,114} and behavioral disorders.⁹⁵ As common surgical procedures (eg, inguinal hernia repair) have a strong male bias, sex-dependent effects require further evaluation.

3.3. General anesthesia

Surgery requires adequate anesthesia and analgesia. Adverse effects following exposure of the developing mammalian brain to general anesthesia has been clearly demonstrated in laboratory studies,⁹³ and there is ongoing debate regarding translation to clinical settings and the degree of associated risk.⁴⁰ Prolonged or repeated general anesthesia has been associated with adverse outcomes in some clinical studies, but further evaluation of specific effects of anesthesia is required.^{44,89,112} As there is no established phenotype of early anesthesia exposure, the most appropriate outcomes are debated,⁸⁹ with language and cognitive deficits emerging as more sensitive than behavioral outcomes or broad measures of neurodevelopmental delay or academic achievement.^{63,90} The extent to which “environmental enrichment” related to socioeconomic status may mitigate effects of early life exposure is not clear.⁸⁹ Age at time of exposure is likely to be a contributing factor, with suggested windows of vulnerability ranging from preterm through to the first 3 years of life.^{88,91} A single general anesthetic for inguinal hernia repair (median duration, 80 minutes) before 3 years of age did not alter mean IQ scores and tests of memory/learning and language at 8 to 15 years.¹⁸⁷ Comparison with unexposed matched sibling pairs enhances control for genetic and environmental factors, and assessment at older ages makes neuropsychological testing more reliable. No difference in outcome (Bayley Scales of Infant and Toddler Development) was found 2 years following neonatal hernia repair performed under general (<60 minutes) vs regional anesthesia, but the more sensitive primary outcome (Wechsler Preschool and Primary Scale of Intelligence) remains to be assessed at 5 years.⁴⁵ Risk increases with prolonged or repeated anesthetic exposure,⁶² but there is clearly a need to control for confounding factors related to illness severity, the surgical injury itself, and other concurrent drug treatments or medical conditions.⁷¹

Preterm-born neonates represent a high-risk group, not only due to potential adverse effects of anesthetic drugs on the

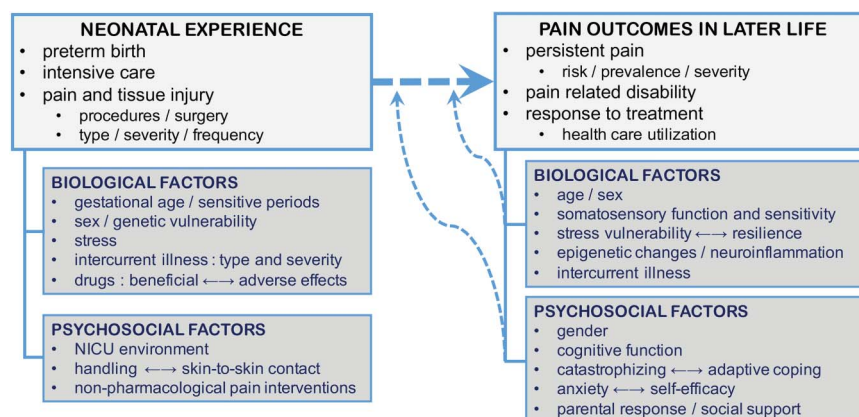


Figure 1. Schematic biopsychosocial model of potential link between early life pain in preterm neonates and adult pain outcomes. Neonatal experience is influenced by multiple biological and intercurrent clinical confounders, as well as social and environmental factors in intensive care. In adults, biological and psychosocial factors may influence pain outcome and/or modulate the long-term impact of prior neonatal experience. Factors that may have negative or positive effects on outcome are indicated with double arrows.

immature nervous system, but also because of increased vulnerability to perioperative physiological perturbations in body temperature, metabolic and cardiorespiratory status.^{126,215} In addition, the level of “unconsciousness” required by neonates is debated,⁴³ as the current algorithms and monitors used to assess depth of anesthesia in adults and older children cannot be extrapolated to use in neonates and infants.¹³⁰ Measures of relative potency of volatile anesthetic agents are based on concentrations that suppress spinal reflex movements to noxious stimuli, but this may not equate with effects in the developing brain. Intracortical recordings in somatosensory cortex of rodents during isoflurane anesthesia found greater suppression of spontaneous activity in younger animals, but resistance to noxious evoked responses that were further enhanced following hind paw incision.³¹ This further supports the need for analgesia to reduce noxious afferent input, while minimizing the excessive reductions in neuronal activity by general anesthetic agents that have been postulated to increase neuronal apoptosis. Alterations in evoked electroencephalography activity in preterm-born vs term-born infants undergoing heel lance¹⁶⁰ and in background activity during sevoflurane anesthesia during childhood (1–12 years, mean 5.2 years)¹⁵⁵ further suggest specific alterations in the immature brain.

3.4. Analgesia and sedation in neonatal intensive care unit

There is ongoing debate regarding the impact of morphine use in NICU on long-term outcome,^{131,228} with issues related to dose and duration of treatment, indication for use (ie, routine use for sedation vs titrated dosing for pain),¹⁵ associated hypotension,⁷⁶ and confounding illness factors.¹⁹³ In addition, time of assessment may influence results as adverse effects on cognitive function (intelligence quotient, IQ scores) were reported at 5 years⁴⁶ but not at 8 to 9 years following continuous morphine infusion during NICU.⁴⁷ It is not clear if this relates to compensatory recovery or changes in the sensitivity of testing at different ages. Thermal sensory thresholds at 8 to 9 years age did not differ in ventilated neonates randomized to either continuous morphine vs placebo infusion, but both groups received bolus rescue morphine.¹⁹² Midazolam sedation in NICU has also been associated with adverse neurodevelopmental outcomes,¹⁴⁴ which are greater than with morphine¹⁵ and recently were correlated with abnormal hippocampal growth.⁵³

3.5. Somatosensory function in childhood and early adulthood

Quantitative sensory testing (QST) uses a range of stimulus modalities and intensities to evaluate somatosensory and small fiber function. Standardized protocols for adults allow evaluation of potential neurological and pain disorders^{10,41,168,203} and comparison with existing reference data based on age, sex, and body site.^{121,154} Thermal stimuli of varying intensity are transduced by peripheral transient receptor potential (TRP) channels and transmitted via A-delta and C-fiber afferents.²⁰⁴ Cutaneous mechanoreceptors detect differing mechanical stimuli, with noxious pressure transmitted via A-delta and C-fiber, pricking via A-delta light touch via A-beta and brush by A-delta and A-beta fibers.^{48,220} In addition, both the degree and distribution of changes in static (eg, baseline sensory thresholds) and dynamic stimuli (eg, brush allodynia and perceptual sensitization to a prolonged or repeated stimulus) can be evaluated, with clusters of quantitative sensory testing findings associated with different pain conditions.¹²³ Quantitative sensory

testing also has utility in children over 6 to 8 years of age^{129,133} but values change with age.^{17,18,80} Alterations in sensory function have been reported in a range of pain conditions in children and adolescents, including complex regional pain syndrome,¹⁷⁹ juvenile idiopathic arthritis,³⁶ abdominal pain,²²⁴ migraine²²⁵; and sickle cell disease.^{92,147}

Quantitative sensory testing has also been used to evaluate somatosensory function following NICU and/or neonatal surgery. As sensory thresholds vary with age, and sex differences may become more apparent at older ages, longitudinal studies incorporating a range of stimulus modalities and intensities, and sample sizes sufficient to allow for individual variability in pain thresholds, are required to gain a clear picture of somatosensory profiles following preterm birth. Generalized increases in static thermal threshold (ie, reduced sensitivity) have been identified in children 9 to 14 years following neonatal intensive care and/or surgery,^{79,82,173,210} but no significant difference has also been reported in smaller samples⁷² compared to noncontemporaneous control data.^{192,194} Within individual studies, the greater degree of change in those born preterm vs term⁷⁹ and in extreme preterm (EP, <26 weeks gestational age) children requiring neonatal surgery vs those requiring NICU alone (**Fig. 2i**)²¹⁰ suggests that both gestational age and degree of tissue injury may be contributing factors. In addition, modality-specific alterations in sensory function persist for many years adjacent to neonatal scars related to surgery or major procedural interventions (**Fig. 2ii**).^{173,210}

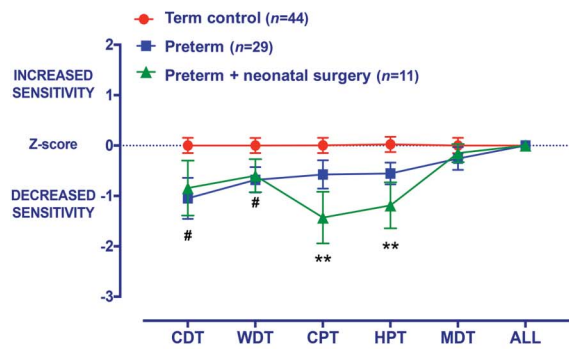
While group differences show reduced sensitivity across different intensities of static threshold (cool, warm, cold, and heat pain), more prolonged thermal stimuli can unmask increased sensitivity. A prolonged thermal heat stimulus increased perceptual sensitization (**Fig. 2B**)^{79,82} and produced a different functional magnetic resonance imaging (fMRI) pattern of cerebral activation in preterm children 9 to 14 years post NICU.⁸³ In addition, fewer extreme preterm adolescents tolerated a cold pressor test, with earlier withdrawal of the hand from an ice water bath (**Fig. 2C**).¹⁹⁸ Longitudinal evaluation at 19 years in the EPiCure cohort encompassed a range of cognitive, behavioral and health outcomes⁴⁹ and has recently been completed. Data from current pain history and a comprehensive quantitative sensory testing protocol are currently being analyzed.

Conditioned Pain Modulation (CPM) protocols assess the degree to which a noxious “conditioning stimulus” alters sensitivity to a “test stimulus” at a distant body site. Increased inhibition is reflected by either an increased threshold (if using a protocol with a variable test stimulus) or reduced pain intensity (fixed test stimulus).^{101,142,156,222} In preterm-born (24–32 weeks gestational age) children, CPM was enhanced in those with fewer painful procedures in NICU ($n = 6$), but absent in a “high-pain” group ($n = 7$) with longer NICU stay and mechanical ventilation.⁷² However, this study was performed at 8 to 11 years of age when descending modulation is less effective,¹⁸⁹ and evaluation at older ages is required. Comparing the degree of inhibition will also require adjustment for differences in baseline sensitivity and pain tolerance following NICU.

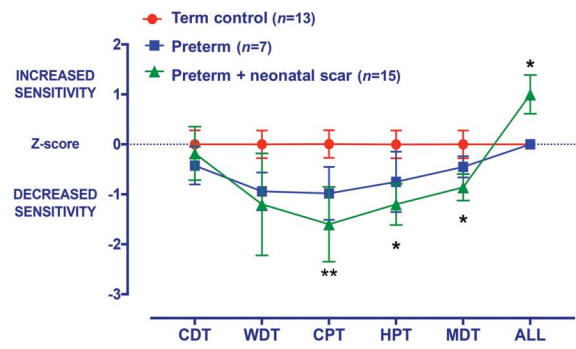
3.6. Psychosocial factors

As pain is a “sensory and emotional experience,”¹³⁴ both experimental pain sensitivity and behavioral pain responses may be modulated by social and psychological factors. A biopsychosocial approach to assessment and management of pain has been recommended for both adults⁶⁸ and children.¹¹⁶ Many psychosocial factors influence the development and

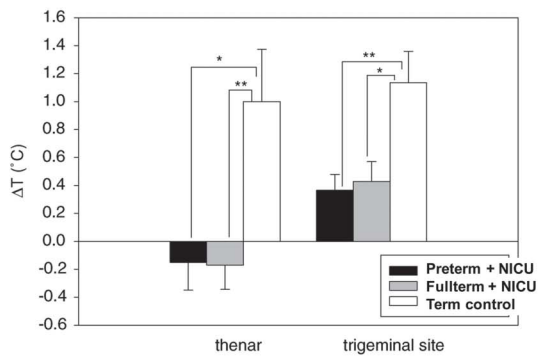
A (i) : Generalized sensory profile (thenar eminence)²¹⁰



(ii) : Localized sensory profile (± neonatal thoracic scars)²¹⁰



B Sensitization to heat⁷⁹



C Cold Pressor Test¹⁹⁸

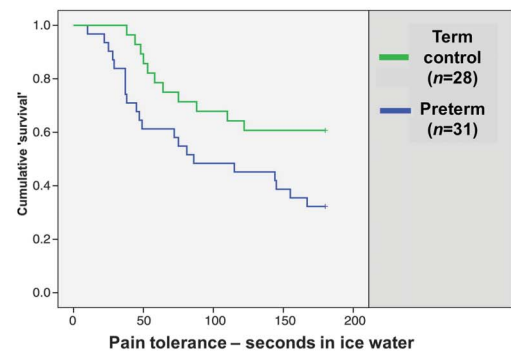


Figure 2. Quantitative sensory testing reveals modality-dependent differences in preterm born children and adolescents. (A): (i) Generalized thermal sensitivity is reduced in 11- to 12-year-old children born preterm (<26 weeks gestational age) when compared to an age-matched and sex-matched term-born control group, with a greater degree of change in those who also required surgery during the neonatal period (preterm + surgery). (ii) Localized sensory thresholds adjacent to thoracic scars related to neonatal surgery or major procedures (preterm + neonatal scar) demonstrate a mixed pattern of reduced sensitivity to static thermal and mechanical sensitivity, but sensitivity and allodynia to dynamic brush. Previously published raw data²¹⁰ Z-transformed against control data for the same body region: $Z = (\text{value}_{\text{subject}} - \text{mean}_{\text{controls}}) / \text{SD}_{\text{controls}}$. Data points = mean ± SEM. # $P < 0.05$ Term control vs Preterm * $P < 0.05$ ** $P < 0.01$ Term control vs preterm + surgery (i) or preterm + neonatal scar (ii); one way ANOVA with Dunn’s post-hoc comparisons. CDT, cold detection threshold; WDT, warm detection threshold; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; ALL, brush allodynia. B: A prolonged heat stimulus unmasks perceptual sensitization in children 9 to 14 years following neonatal intensive care (NICU). Using a computer controlled thermode, temperature was increased until pain threshold (T1) was reached then held constant for 30 seconds. At the end of stimulation, participants readjusted the temperature by lowering, increasing or leaving it such that it just felt painful (T2). Negative ΔT (T2-T1) values indicate perceptual sensitization, whereas positive ΔT values indicate habituation. Both preterms who required NICU ($P = 0.015$) and full-term infants who required NICU ($P = 0.008$) exhibited significantly greater perceptual sensitization to tonic heat.⁷⁹ Reproduced with permission. (C) In early adulthood (17-18 years), a more intense and prolonged thermal stimulus identifies increased sensitivity in subjects born preterm (mean gestational age, 26.8 weeks) vs term-born control subjects. Tolerated duration of immersion of the hand in an ice and water bath (0-2°C) is represented as Kaplan–Meier curves representing “survival” to a ceiling time of 180 seconds.¹⁹⁸ Reproduced with permission.

trajectory of chronic pain and may encompass “general” variables (eg, negative mood, childhood trauma, social support) and “pain-specific” variables (eg, pain catastrophizing, self-efficacy and coping style).⁵⁴ While some have been associated with increased risk or vulnerability to chronic pain (eg, fear, catastrophizing), others can increase resilience or be protective (eg, social support, active coping).⁵⁴ In addition, a range of biopsychosocial factors may positively or negatively modulate the association between neonatal experience and adult pain outcome (Fig. 1).

Following preterm birth, the extent to which perinatal biological effects persist to adulthood and/or are modulated by subsequent experience and social factors is debated.^{51,114} Behavioral and mood disorders have been reported in preterm born cohorts, but studies vary in the outcome measures used, and more standardized diagnostic evaluations are required to identify prognostic factors.¹¹³ Both increased procedural pain exposure in NICU³² and subsequent social factors (parental stress and education, parent–child interaction, number of children in the home) influence child behaviors relevant to pain.^{9,74,160} Preterm birth has been associated with behavioral changes that include

increased levels of anxiety, and while this may persist until adulthood, it is also modulated by subsequent social factors.^{75,96} At 9 to 14 years, children born preterm had higher pain catastrophizing scores and parents were more solicitous.⁸² Pain catastrophizing and anxiety also influence acute postoperative pain experience¹⁸¹ and the risk of persistent postsurgical pain in adults^{106,186} and adolescents.^{148,207} Catastrophizing also partially mediates sex differences in experimental pain sensitivity in healthy adults.¹⁵⁸ Inclusion of psychological and social factors is essential to fully assess potential effects of preterm birth and early life pain on subsequent pain experience.

3.7. Risk of persistent pain in adulthood

Most preterm cohort studies are not sufficiently powered to detect differences in the prevalence of chronic pain in adulthood. At 23 years, approximately 21% of 143 low birth weight survivors vs 14% of 130 term-born controls reported pain.¹⁷¹ Longitudinal evaluation in a larger VP cohort found a minor increase in self-reported pain from 19 (n = 630 responders) to 28 years (n = 314

responders).^{195,199} Pain is an included domain in several validated quality-of-life questionnaires. The Short Form 36 Health Survey (SF-36)²¹⁴ includes 2 questions that rank bodily pain intensity and interference due to pain in the last 4 weeks, and studies in young adults born preterm have reported either no statistical difference^{35,119,167} or less pain.⁴² However, point prevalence of current pain^{87,171} may not fully describe pain experience, and data related to the type, frequency, and management of pain are limited. At younger ages, recurrent pain is common¹⁵² and sample sizes tend to be too small²¹⁰ or populations too heterogenous²²⁷ to evaluate differences in pain prevalence following NICU. From a 1958 birth cohort, preterm birth (<37 weeks gestational age) had a minor impact on risk of widespread pain at 45 years of age.¹¹⁷ However, significant changes in clinical practice limit the ability to extrapolate this data to more recent NICU survivors. Infants undergoing surgery in the same dermatome as prior neonatal surgery had higher perioperative analgesic requirements and pain scores.¹⁵³ Given the constellation of long-term alterations in sensory and behavioral aspects of pain response following preterm birth, we have postulated that surgical injury in early life may be a risk factor for persistent postsurgical pain in late life.^{206,208} Defining associations between preterm birth and risk of chronic pain requires comprehensive biopsychosocial assessment and ongoing longitudinal follow-up to more fully evaluate the subsequent impact on clinical pain prevalence, intensity, and pain-related disability. Advances in neonatal care have resulted in significant improvements in survival and prognosis since 1990.¹¹³ It remains to be determined if this will be associated with improved outcome in later life as increasing numbers of survivors from high-risk groups (eg, those born extremely preterm) reach middle age in coming years.

4. Mechanisms associated with persistent effects of early life pain

4.1. Contributing factors

Long-term effects of early life stress and/or pain evaluated in a range of laboratory models are summarized in recent reviews.^{11,27,61,177,200,201,206,208} Although early life social adversity has been studied in nonhuman primates,⁶⁵ the vast majority of studies use rodents. Repeated handling and/or maternal separation during the first 2 to 3 weeks of postnatal life in the rodent is a common model of ELS, but heterogeneity of protocol and reporting can hamper comparison across studies.¹⁸⁸ Environmental manipulations such as limited bedding avoid potential confounding effects of altered temperature or nutrition and natural variations in maternal care.¹⁷⁴ As noted earlier, effects of ELS have parallels with those of infant pain, and this is also relevant in rodent studies. In addition to emphasizing the need for additional control groups with the same degree of maternal separation and handling, pain and injury studies similarly require consideration of:

- (1) age at time of exposure. Given the rapid maturation of rodents, evaluating effects following birth (postnatal day, P0) through to several months of age¹²⁸ has parallels with human development from preterm through to adulthood. Comparing responses following the same injury at different ages (assuming an age-adjusted level of stimulus) can establish sensitive periods for altered future response.
- (2) type of the initial insult.^{84,212} This can include acute noxious chemical stimuli (eg, hind paw formalin, mustard oil, capsaicin), peripheral inflammation (eg, injection of carrageenan), tissue

injury due to repeated needle stick or surgical incision (eg, hind paw plantar incision or laparotomy), nerve injury (eg, spared nerve injury), or visceral injury (eg, distension or irritant injection) to model different types of clinical pain exposure.

- (3) severity of stimulus.²¹¹ The intensity, frequency, or distribution of injury can be altered (eg, needle prick or surgical incision; volume of inflammatory injectate; single or repeated insults; ipsilateral and/or contralateral hind paw and/or forepaw injury).
- (4) sex. It is now recommended that laboratory studies include evaluation in both male and female animals^{4,136} and sexually dimorphic differences in response or mechanism can be apparent from early development.¹⁰⁵
- (5) variable patterns of hypoactivity or hyperactivity. Different types or intensities of subsequent stimuli may reveal persistent increases or decreases in sensory threshold following early life pain and injury.
- (6) efficacy of intervention. Strategies employed at the time of the early insult may vary in the ability to prevent or modify long-term effects, or the efficacy of different interventions in adulthood may be altered by prior neonatal injury.

4.2. Neonatal hind paw incision

As preterm birth and neonatal intensive care significantly alter sensory responses in childhood and early adulthood, with both generalized decreases in baseline sensitivity but enhanced responses to noxious or prolonged stimuli, our translational laboratory research has focused on the long-term impact of prior neonatal surgical injury. In particular, we aim for a mechanism-based approach¹⁹⁷ to understand both altered baseline thresholds in adulthood and altered responses to future surgical injury, and also evaluate potential preventive analgesic interventions (**Fig. 3**).

Plantar hind paw incision is a well-established model of postoperative pain,²³ with both skin and muscle injury^{103,221} contributing to subsequent sensitivity, behavioral and tissue response.^{24,103,219} Specific advantages of hind paw incision for evaluation of the long-term impact of neonatal pain include:

- (1) changes in hindlimb reflex sensitivity following plantar incision allow quantification of hyperalgesia in neonatal, juvenile, and adult rodents. Measurement includes mechanical withdrawal reflex threshold or thermal withdrawal latency in awake animals,¹⁶⁶ and quantification of electromyographic responses to threshold and suprathreshold stimuli applied in anaesthetized animals.^{12,213}
- (2) incision length can be standardized to anatomical landmarks to produce a comparable degree of tissue injury at different ages.²¹³
- (3) the degree of hyperalgesia is sufficient to allow dose-dependent effects of analgesic interventions to be assessed.
- (4) electrophysiological effects can be evaluated in dorsal root ganglia,^{20,165} spinal cord,¹⁶⁴ and somatosensory cortex.³¹
- (5) acute and persistent alterations in spinal inhibitory and excitatory synaptic signaling can be evaluated.^{7,107–110,208}
- (6) the region of tissue injury is innervated by the sciatic nerve and therefore blocking afferent input (eg, local anesthetic techniques) can assess activity-dependent alterations and evaluate clinically relevant preventive strategies.^{111,163,209,213}

4.3. Elevated sensory thresholds in adulthood

Following neonatal hind paw incision, mechanical withdrawal thresholds are elevated and thermal withdrawal latencies prolonged in both the previously injured and contralateral paw 6 to 8 weeks after the initial injury. As also seen following neonatal

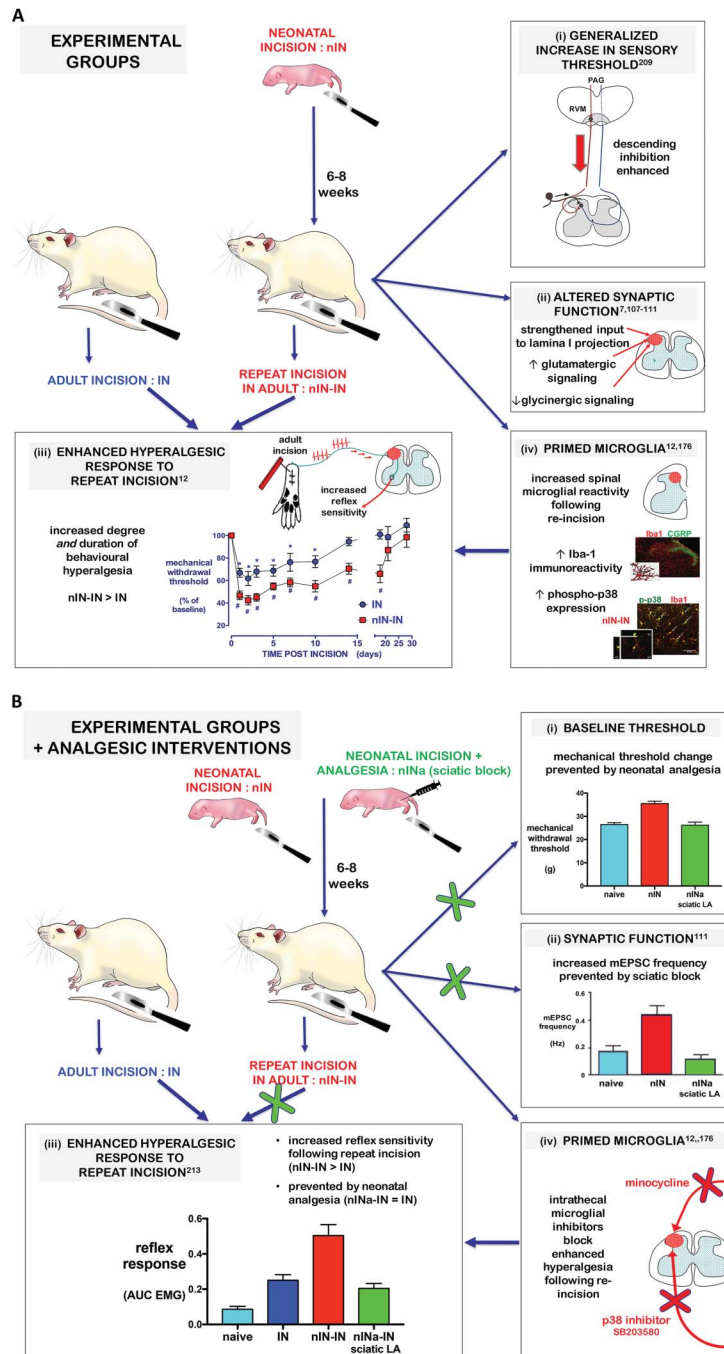


Figure 3. Schematic effects of prior neonatal surgical injury in the rodent on long-term alterations in sensory threshold and response to adult re-incision. (A) Plantar hind paw incision is performed on postnatal day 3 (neonatal incision: nIN) and the same paw re-incised 6 to 8 weeks later in adulthood (repeat incision in adult: nIN-IN). Comparison is made with adults undergoing a single incision (adult incision: IN). (A): (i) In adult animals with prior neonatal incision (nIN), sensory thresholds are raised. The pattern of descending modulation from the rostroventral medulla (RVM), which receives input from the periaqueductal gray (PAG), and sends descending modulatory pathways to the spinal cord is altered by prior neonatal incision.²⁰⁹ (A): (ii) Hindpaw incision in the neonatal rodent produces persistent changes in synaptic signaling in the ipsilateral dorsal horn.^{7,101-111} (A): (iii) Hindpaw incision in adult rodents (6-8 weeks age) increases reflex sensitivity (mechanical withdrawal threshold plotted as percentage change from baseline 0-28 days after incision). The degree and duration of mechanical hyperalgesia is enhanced in rodents with prior neonatal incision (nIN-IN > IN).¹² (A): (iv) Microglia are primed by prior neonatal injury, with increased microglial reactivity following adult re-incision confirmed by changes in morphology (increased microglial marker Iba1 immunoreactivity in the medial superficial dorsal horn)¹² and function (increased expression of phospho-p38 mitogen-activated protein kinase in microglia coexpressing Iba1).¹⁷⁶ (B) The impact of neonatal surgical injury (nIN) is altered by pharmacological interventions that prevent increased afferent activity at the time of neonatal incision or target mechanisms contributing to enhanced sensitivity in adulthood. (B): (i) Percutaneous sciatic nerve blocks with 0.5% levobupivacaine prior to neonatal incision and at 3 × 2 hourly intervals (nINa sciatic LA) prevented long-term changes in mechanical withdrawal threshold. (B): (ii) Neonatal incision increases mini excitatory postsynaptic current (mEPSC) frequency, but this effect is prevented by prolonged sciatic nerve block (bupivacaine hydroxide or tetrodotoxin microcapsules).¹¹¹ (B): (iii) Reflex sensitivity (reflex response; AUC EMG) is quantified by calculating the area under the stimulus (threshold and suprathreshold mechanical hind paw stimuli) vs response (biceps femoris electromyography recordings) relationship in anaesthetized animals. Reflex sensitivity 24 hours following incision is increased to a greater degree in nIN-IN vs IN groups, but this is prevented by neonatal sciatic block (nINa-IN sciatic LA).²¹³ (B): (iv) The enhanced hyperalgesia in nIN-IN animals is blocked by intrathecal microglial inhibitors minocycline and p38 inhibitor SB203580.^{12,176}

hind paw inflammation,¹⁶² the generalized distribution suggests a central mechanism and raised thresholds emerge only after 3 to 4 weeks of age.²⁰⁹ During this same developmental period, descending inhibitory modulation also matures,^{77,78,104,178} but this may be influenced by prior injury. In young adult animals, electrical stimulation in the rostroventral medulla (RVM) produced the typical intensity-dependent bimodal pattern of inhibition or facilitation of hindlimb reflex response.⁷⁷ However, in age-matched animals with prior neonatal incision, only inhibition was produced across all stimulus intensities (**Fig. 3A**). Importantly, perioperative sciatic nerve blockade at the time of neonatal incision (30 minutes preincision and 3 × 2 hourly percutaneous injections of 0.5% levobupivacaine) normalized both sensory thresholds in adulthood (**Fig. 3B**) and prevented the effects of neonatal injury on the pattern of descending modulation from the RVM.²⁰⁹ The common finding of raised sensory thresholds in preterm clinical cohorts and following hind paw inflammation/incision strengthens the translational validity of these early life injury models in the rodent and also identifies a mechanistic link between neonatal tissue injury and long-term alterations in sensory processing. However, the functional significance of this apparent “generalized hypoalgesia” is unclear as it is insufficient to mask the response to subsequent tissue injury (see section 4.5 below).^{34,162,213} Starting at a higher baseline could give an appearance of enhanced hyperalgesia or greater degree of change even if thresholds are only reduced to the same raw value as the previously uninjured group. Increases in reflex sensitivity to suprathreshold stimuli quantified by EMG responses and the increased duration of hyperalgesia in animals with prior neonatal injury support a more significant and sustained alteration in response to reinjury. Differences in the distribution and age of onset of raised sensory thresholds vs altered response to tissue injury further emphasize the need to incorporate a range of stimulus intensities and modalities when evaluating long-term effects of early life pain.

4.4. Spinal cord synaptic function

Prior neonatal incision has been associated with both acute and long-term alterations in excitatory and inhibitory signaling in the spinal cord and strengthening of input to lamina I projection neurons (**Fig. 3**; see reviews from Baccei for details of age-dependent and injury-dependent changes in spinal synaptic function).^{6–8,208}

In adult mice with prior hind paw incision on postnatal day 3 (P3), excitatory afferent input to lamina I projection neurons is enhanced while the efficacy of GABAergic and glycinergic inhibition is reduced.¹¹⁰ In addition, prior neonatal incision alters the temporal requirements for long-term potentiation at primary afferent synapses onto adult lamina I projection neurons, unmasks a role of calcium-permeable AMPA receptors, and thus predisposes to enhanced response to subsequent injury.¹⁰⁸ Prolonged afferent blockade prior to neonatal incision (bupivacaine hydrochloride powder or tetrodotoxin microcapsules implanted adjacent to sciatic nerve) prevented the increase in glutamatergic miniature excitatory postsynaptic currents (mEPSCs) following incision at P3 but not older ages,¹¹¹ again highlighting the vulnerability of neonatal spinal nociceptive circuits to activity-dependent change.

4.5. Enhanced hyperalgesic response to future incision

An important factor when evaluating the long-term impact of early life pain is the potential to increase the risk or severity of pain in

later life. In clinical studies, this needs to extend beyond pain severity to encompass psychosocial factors and pain-related disability, but in animal studies the degree and duration of hyperalgesia is the predominant outcome. Enhanced sensitivity to future injury has been clearly demonstrated across different rodent models or early life injury (see recent reviews).^{177,200,201,206} While neonatal inflammation enhances the response to incision in adult rodents,³⁴ we have focused on effects of repeated surgical injury, as in clinical practice many neonates with congenital anomalies or complications of prematurity require repeated surgery. Incision in the first postnatal week in the rodent, but not at older ages, increases both the degree and duration of hyperalgesia following subsequent incision, evident by decreases in behavioral thresholds, and by increased electromyographic responses to threshold and supra-threshold hind paw mechanical stimuli.^{12,213} Therefore, prior neonatal surgery may be a risk factor for persistent postsurgical pain in later life. Perioperative sciatic block prevents the enhanced response to subsequent incision,²¹³ and this has both mechanistic and potential therapeutic implications. Our ongoing studies in this model are comparing acute and long-term efficacy of different neonatal interventions.

4.6. Impact of prior incision on spinal microglia response in adulthood

In adult rodents, neuroglial interactions in the spinal cord significantly influence nociceptive signaling,^{13,14,190} with the time course and degree of response varying with type of injury (eg, nerve injury, inflammation, incision),^{145,146,169} and significant sex differences in glial signaling and response to microglial inhibitors.^{124,182,183} Microglia are derived from the mesoderm, colonize the nervous system in early development, and persist throughout life as resident macrophages capable of local proliferation.¹⁵¹ In early development, microglia have specific activity-dependent roles in the pruning, elimination, and maturation of synapses that influence network formation and function throughout the central nervous system,^{16,26,66,102,172} including the somatosensory cortex.¹³⁵ Recognition of these important developmental roles, plus alterations in microglial reactivity following a range of neonatal insults such as hypoxia, inflammation, and stress, has led to investigation as a potential therapeutic target to reduce brain injury following preterm birth.^{5,150,196} Microglia can also be primed by an initial exposure and undergo long-term changes in phenotype that result in heightened responses to future insults.^{81,151,161} Given the important role of spinal microglial reactivity in adult pain states and the potential for microglial priming to underlie long-term alterations in future response, there is increasing interest in the contribution of microglia to long-term effects following noxious early life events.²⁶ The impact of postnatal age on glial reactivity, the balance of proinflammatory and anti-inflammatory responses, and subsequent behavioral effects following nerve injury has been reviewed elsewhere.⁶⁰ Here, the focus is on spinal microglial response in a “two-hit” incision model.

In adult rats with prior neonatal incision, microglial morphology (Iba1 immunohistochemistry in the medial superficial dorsal horn) is not altered at baseline, but following a repeat incision the duration (earlier onset and prolonged), degree, and spinal distribution of microglial reactivity is increased.¹² Similarly, incision-induced expression of the active phosphorylated mitogen-activated protein (MAP) kinase p38 (p-p38) in spinal microglia occurred at an earlier time point and to a greater degree in adults with prior neonatal incision (**Fig. 3A**).¹⁷⁶

Whereas primary afferent activity at the time of neonatal injury is required to initiate long-term alterations (as evidenced by preventive effects of neonatal perioperative sciatic block) (**Fig. 3B**), it is not the sole driver of the enhanced injury response in adulthood. Electrical stimulation of the ipsilateral tibial nerve delivered the same afferent input to adult animals with or without prior neonatal incision, but produced a greater degree of hyperalgesia and spinal microglial reactivity in those with prior neonatal incision.¹² The degree and distribution of neuronal pERK expression 15 minutes after adult incision was also not significantly different in animals with and without prior incision.¹⁷⁶ While these findings suggest a centrally mediated mechanism that is independent of peripheral tissue injury, the extent to which the “memory” of early injury is determined by alterations in microglial phenotype or is secondary to enhanced synaptic signaling (see Section 4.4) is difficult to differentiate, and both are likely to play a role. Evaluating the ability of microglial inhibitors at the time of neonatal incision to prevent enhanced hyperalgesia following adult incision would further support a role for microglia, but potential sex differences in glial signaling^{124,183} also need to be considered.

Intrathecal administration of the nonspecific microglial inhibitor minocycline selectively reduced both the enhanced hyperalgesic response and microglial reactivity (Iba1 immunoreactivity) in adult rats with prior neonatal incision.¹² Much higher doses of systemic minocycline, which have an additional peripheral anti-inflammatory effect,⁸⁶ were required to reduce incision-related hyperalgesia.¹² Dose-dependent efficacy of a p38 inhibitor (intrathecal SB203850) was also enhanced in adults undergoing repeat incision.¹⁷⁶ Significantly, these experiments were conducted predominantly or solely in adult male rats, and sex-dependent differences in response to microglial inhibitors are currently being evaluated in this model.

5. Conclusions

As the rate of preterm birth and survival at earlier gestational ages increases, and advances in perioperative care and surgery allow more complex surgical interventions to be performed in neonates, evaluation of treatment “success” must extend beyond acute morbidity and mortality. Early life adversity, stress, and pain have been associated with significant long-term impacts on future health and quality of life. While association does not imply causation, many health care issues have been reliant on observational rather than randomized controlled studies, with the classic example of adverse effects of cigarette smoking. However, a significant body of carefully performed and interpreted studies that incorporate direct evidence (effect size is greater than plausible confounders, spatial and temporal proximity, dose-responsiveness), mechanistic evidence, and parallel evidence (replicability and consistency) is required.^{64,85} Specific changes in somatosensory function and associations with the degree of procedural or surgical pain exposure during neonatal intensive care suggest that long-term effects are related to pain in early life, and translational laboratory studies provide a mechanistic basis, but further evidence is required. In clinical cohorts, experimental evaluation within a bio-psycho-social framework is required to encompass factors influencing both the sensory and emotional components of pain response. While methods need to be tailored to the age at time of assessment, in adolescence and adulthood detailed assessment can include current pain, a range of somatosensory modalities and intensities, neuroimaging, and validated questionnaires to assess psychosocial function and outcomes. Sample size should be

large enough to evaluate sex differences and contributory factors in specific subgroups, with longitudinal evaluation of age-related changes in persistent effects and/or modulation by subsequent experience. Translational laboratory studies using clinically applicable injury models play a crucial role in evaluating specific age-dependent, sex-dependent, and injury-dependent changes in the structure and function of nociceptive pathways, independent of the potential confounding factors in clinical settings. In addition, laboratory-based comparisons of the relative efficacy and safety of current analgesic interventions can guide clinical choice, and identification of mechanism-based targets for intervention can inform the design of future controlled clinical studies.

Increased awareness of the adverse impact of neonatal pain has raised many important questions that will benefit from further clinical and laboratory translational research. Many relate to initial neonatal care. To what degree are acute and long-term effects of early life pain prevented by different pharmacological and/or nonpharmacological interventions in NICU? Can outcome be improved by minimizing the behavioral response to painful interventions or is it necessary to reduce associated neural activity within nociceptive pathways? In what clinical contexts and doses are opioids beneficial or detrimental? To what extent are adverse changes in brain structure and connectivity specifically related to pain and/or tissue injury, and can these be modified by alterations in management? Evaluating outcome into adulthood raises additional questions. What are the most sensitive, specific and age-appropriate outcomes for assessing the impact of neonatal pain and intensive care on long-term pain response? What is the clinical impact of changes in experimental pain sensitivity? To what extent do altered sensory and cognitive/behavioral responses to pain in later life differ in males and females, and reflect either persistent neonatal biological factors and/or modulation by subsequent experience and psychosocial factors? Given the significant advances in neonatal care, it is not yet clear if the impact of prior preterm birth will decline due to increased recognition and early intervention or escalate as increasing numbers of high-risk preterm survivors reach middle age. The field of early life pain represents not only an area of unmet clinical need, but also a major opportunity for clinical and laboratory researchers to collaborate in translational studies that have the potential to improve outcome across the lifespan.

Conflict of interest statement

The author has no conflict of interest to declare.

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