Title Page **SEMINARS IN FETAL AND NEONATAL MEDICINE**

Title: Long-term Effects of Neonatal Pain

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ABSTRACT

Pain experienced during neonatal intensive care management can influence neurodevelopmental outcome and the somatosensory and/or emotional components of pain response in later life. Alterations in biological factors (e.g. peripheral and central somatosensory function and modulation, brain structure and connectivity) and psychosocial factors (e.g. gender, coping style, mood, parental response) that influence pain have been identified in children and young adults born very preterm or extremely preterm. Earlier gestational age at birth and cumulative pain exposure from tissue-breaking procedures and/or neonatal surgery influence the degree of change. In neonatal rodents, repeated needle insertion or hindpaw incision identify developmentally-regulated and activity-dependent long term alterations in nociceptive processing, and the efficacy of novel or current analgesic interventions can be compared. As prior neonatal experience and sex may influence current pain experience or the risk of persistent pain, these factors should be considered within the biopsychosocial assessment and formulation of pain in later life.

Keywords: newborn; premature; pain; neurodevelopment; somatosensory

1. Introduction

Exposure to physiological and psychosocial stressors in early life can influence a range of health outcomes in later life, with adverse effects on mental and physical well-being, and alterations in the risk for future disease (eg. cardiovascular, respiratory, and gastrointestinal disorders) [1]. The need to identify and understand the mechanisms underlying effects of early-life exposures on the experience and risk of persistent pain in later life is increasingly recognized [2]. Advances in neonatal intensive care unit (NICU) management have significantly improved survival following preterm birth, but the degree and range of environmental exposures and necessary medical interventions may alter the normal development of the immature nervous system. This review will summarize clinical data reporting associations between neonatal pain exposure and neurodevelopmental outcome, somatosensory function and current pain report in childhood and late adolescence, and risk of persistent pain in later life. Laboratory studies in rodent models of tissue injury relevant to procedural and surgical interventions in NICU (repeated needle prick and hindpaw incision) that identify age-dependent mechanisms and potential preventive interventions will also be discussed.

2. Factors influencing pain sensitivity following neonatal intensive care and/or surgery

2.1 Biopsychosocial formulation of pain

The long-term impact of neonatal pain and tissue injury cannot be simply summarized as a subsequent increase or decrease in sensitivity. While nociception is the neural process of encoding noxious stimuli, pain is a complex and unpleasant sensory and emotional experience. Therefore, pain response encompasses biological factors (eg. changes in somatosensory function and nociceptive signaling), environmental and psychosocial factors (eg. sex, coping style, mood and parental response)(Figure 1).

2.2 Population

Long-term effects of neonatal pain have predominantly been studied in NICU cohorts, but the populations vary. Infant groups may be described in terms of gestational age at birth (preterm

<37 weeks gestational age, GA) and compared with term-born 'healthy' control groups. However, the degree of prematurity has a significant impact (eg. very preterm, VP <32 weeks GA or extremely preterm, EP <28 weeks GA). Alternatively, size may be the primary descriptor (eg. very low birth weight, VLBW; small for gestational age, SGA; intra-uterine growth restriction, IUGR), and while these populations are likely to overlap with earlier gestational age, additional co-morbidities may contribute to impaired growth and adverse outcome [3].

2.3 Pain exposure

As the developing nervous system is vulnerable to alterations in activity, the degree of pain exposure and associated nociceptive afferent input may be expected to influence outcome. However, cumulative pain exposure during neonatal intensive care is difficult to categorize and quantify. Duration of mechanical ventilation or NICU stay have been used as retrospective proxy measures of pain exposure [4, 5]. More recently, the numbers of tissue breaking procedures have been prospectively counted and shown to correlate with subsequent outcome [6]. The increased tissue injury and perioperative pain associated with prior neonatal surgery may also indicate increased pain exposure [7]. Infants born extremely preterm are a high-risk group as physiological systems are immature and management often requires prolonged intensive care, with significant pain exposure if multiple procedures or surgery are required as part of monitoring and care or for management of complications [8].

2.4 Confounding factors

The specific effects of pain are difficult to separate and distinguish from associated co-morbidities in clinical cohorts. The most immature and sickest neonates are likely to require additional procedural and/or surgical interventions, and potential confounders include infection or sepsis, physiological instability and stress, environmental factors and pharmacological treatments. Risks associated with the 'need for surgery' may also reflect disease severity, perioperative physiological instability, or effects of anaesthesia. Different types and dose of analgesic and sedative drugs, such as opioids and benzodiazepines, can have positive and/or negative effect on outcome, as

detailed in a recent review [9]. Glucose can modulate acute behavioural responses to procedural interventions, but increased numbers of tissue-breaking procedures and higher cumulative doses of glucose/sucrose have been associated with poorer neurodevelopmental outcome and altered brain structure and connectivity [10]. While it is now widely acknowledged that untreated pain can influence neurodevelopmental outcome, and adequate analgesia is required for significant painful procedures and surgery, there is currently wide variability in the use of sedative and analgesic drugs in neonatal units [9]. The most effective and safe regimens for controlling both acute responses to noxious stimuli and for preventing adverse long-term outcome are yet to be determined.

2.5 Follow-up age and outcome assessed

Age at time of follow-up influences the type and sensitivity of outcome that can be evaluated. In older children and adolescents, more detailed somatosensory testing, pain history, self-reported validated questionnaires and functional neuroimaging can more fully evaluate current sensory function and pain experience. However, the degree to which biological effects associated with preterm birth persist into adulthood, or are modulated by subsequent experience and psychosocial factors can also vary [8].

3. Neonatal pain exposure and subsequent outcome

3.1. Pain exposure and neurodevelopmental outcome

Increased numbers of tissue breaking procedures during NICU have been associated with poorer cognitive, motor, and behavioral neurodevelopmental outcomes in infancy [6]. In extreme preterm birth cohorts, 25-30% had required neonatal surgery [7, 11], and this was associated with increased rates of major neurosensory disability in childhood [11] and lower cognitive scores that persisted into late adolescence [7, 8]. Effects could not be related to specific surgical procedures (most commonly inguinal hernia repair, patent ductus arteriosus ligation, bowel surgery, surgery for hydrocephalus), although it was noted that the different subgroups were relatively small [11].

3.2 Somatosensory function following preterm birth and NICU

Quantitative sensory testing (QST) utilizes a range of stimulus modalities (eg. thermal and mechanical) to evaluate large-fiber (A-beta) and small-fiber (A-delta and C-fiber) somatosensory function. Tests vary in intensity and can include: static measures (eg. baseline sensory thresholds); dynamic stimuli (eg. brush allodynia, repeated stimuli and perceptual sensitization); and tolerance or sensitization/habituation to more prolonged stimuli (eg. cold pressor test or altered pain report with a sustained heat stimulus).

Associations between neonatal pain experience and somatosensory function in later life vary with the population studied, age at time of evaluation, and type and intensity of the experimental stimulus [1]. Following preterm birth and neonatal intensive care, baseline thermal static thresholds showed generalized reductions in thermal sensitivity. The degree of change was greater in children born VP who required longer hospital admission than term born NICU patients [12], and in EP born children who also required neonatal surgery [13]. However, a more intense or prolonged thermal stimulus can unmask increased sensitivity: increased self-reported pain intensity (perceptual sensitization) to a more prolonged heat pain stimulus [12]; or reduced tolerance of cold pressor testing (hand immersion in 0-5^{0}C water bath) [5, 7]. As the relative influence of neonatal biological factors and subsequent psychosocial factors may change at older ages,[8] and age and sex/gender influence sensory thresholds throughout childhood and adolescence, characterizing persistent effects requires longitudinal follow-up. In VLBW or SGA young adults, no difference in thermal sensitivity was reported [14]. However, in EP young adults we found persistent group differences that were more marked following neonatal surgery, and independent of cognitive scores. In addition, sex-dependent differences had emerged with reduced baseline sensitivity predominantly in males and increased sensitivity to prolonged cold in females [7, 15]. Associations between the degree of prematurity and altered somatosensory function could reflect increased vulnerability of the more immature nervous system and/or increased cumulative exposure to pain and tissue injury with longer duration of intensive care, more procedural interventions, and potential complications requiring surgery. Significant inter-individual variability in QST measures, in both control and

exposure groups, highlight the need for large sample sizes to further assess the degree of difference that is clinically significant and/or associated with altered current pain experience.

3.3 Prevalence of recurrent or persistent pain

Associations between preterm birth and the prevalence of chronic pain have been sought, but differences in methodology (large epidemiological studies versus clinical cohort studies), definitions, and limited details about the type, severity and impact of pain, hamper comparison across studies [1].

Epidemiological studies demonstrate associations between increased risk of chronic pain in adulthood and different forms of early life adversity or childhood somatic symptoms [16]. In the 1958 British Birth Cohort, 288 of 7382 participants were born before 37 weeks gestation, and had a borderline significant (RR 1.26, 95%CI: 0.95-1.67) increased risk of chronic widespread pain at 45 years [17]. In the Norwegian Nord-Trøndelag Health Study, 7019 adolescents (mean age 15.8 years) completed pain questionnaires, and 44% reported chronic non-specific pain (pain at least once a week during the last 3 weeks) and 10% reported daily pain. There was no consistent association between preterm birth (80 born <34 weeks GA between 1988 and 1994) and current pain report [18]. In both studies, the relative numbers of participants born very preterm was limited, and as with all studies evaluating long-term outcome, changes in clinical practice may hamper extrapolation to current cohorts. Since the introduction of surfactant therapy in the 1990s, survival at much earlier gestational ages has improved, and increased numbers of those born extremely preterm are now reaching adulthood.

An alternative approach is to focus on more detailed evaluation in smaller numbers within high-risk cohorts. Differences in definitions of recurrent or chronic pain contribute to conflicting results, and as recurrent pains are common during childhood and adolescence, large sample sizes will be required to detect significant differences. Based on limited items within quality of life or general health care questionnaires, current pain prevalence in VP or EP young adults has variably been reported as no different, decreased, or increased [1]. In VP and VLBW cohorts, self-reported pain

increased throughout the third decade [19] when chronic pain generally becomes more prevalent, particularly in women [20]. While longitudinal evaluations in extremely preterm cohorts have identified persistent effects on cognitive, mental health and system-specific health outcomes [21, 22], pain experience has not been consistently assessed. In extremely preterm young adults from the United Kingdom EPICure cohort, we found no difference in overall prevalence of recurrent pain as mild pain was common in both EP and term-born groups. However, a more detailed history identified an increased proportion of EP participants with recurrent pain of at least moderate intensity that required analgesia and interfered with activity [7].

4. Prior neonatal pain as a risk factor for future pain

Factors related to different biological and psychosocial aspects of pain experience that can influence risk of future pain can also be altered by prior preterm birth and neonatal experience. While current evidence does not support generalizations for all preterm-born children and young adults, prior experience should be included within a comprehensive pain history and form part of a personalized approach to management.

4.1 Altered somatosensory function and modulation

In the periphery, scars related to surgery or major procedural interventions in the neonatal period were associated with localized changes in sensitivity in EP young adults. Some participants reported allodynia, and QST identified both brush allodynia and sensitization to a repeated mechanical stimulus (increased pain report with a train of punctate stimuli or 'wind-up') adjacent to neonatal scars [7], that may increase the risk of persistent pain if further surgery is required in the same area. Although the impact of repeat surgery has not been assessed in children or adults, infant surgery in the same dermatome as prior neonatal surgery was associated with increased pain and perioperative analgesic requirements [23]. This is consistent with our laboratory studies demonstrating increased hyperalgesia following re-incision in adult rodents with prior neonatal

incision; an effect that is developmentally regulated and specific to an initial injury occurring in the neonatal period (see Section 5).

Conditioned Pain Modulation (CPM) assesses the ability of a noxious 'conditioning stimulus' to alter sensitivity to a 'test stimulus' at a distant body site. Descending pathways from the brainstem tend to show tonic inhibitory effects on spinal nociceptive transmission in adulthood, although a shift to facilitation is seen with acute injury and some chronic pain states [24]. Weak inhibitory effects in childhood become more robust throughout adolescence, but were absent in 7-11 year old VP children with longer NICU admission and increased procedural pain exposure [4]. While inhibitory modulation could be evoked in the majority of EP young adults, the CPM protocol also identified a high proportion of EP females with increased sensitivity to pressure (test stimulus) and noxious cold (conditioning stimulus) in whom inhibition could not be reliably detected [15]. As impaired inhibitory CPM has been suggested as a biomarker to predict persistent pain following surgery, risk of chronic pain, or individual differences in treatment response [15, 24], further evaluation in preterm cohorts is warranted, and neonatal experience should be considered when evaluating the risk of persistent post-surgical pain.

Experimental pain sensitivity has been correlated with altered structure and connectivity in central sensory-discriminative (e.g. thermal sensitivity and somatosensory cortical thickness [25]) and emotional/affective pathways (e.g. visceral sensitivity and thalamus and amygdala volume [26]). Increased procedural pain exposure in NICU and neonatal surgery have been associated with significant changes in brain structure and connectivity that include regions relevant for pain processing [27-29]. Functional MRI in children born VP who required NICU care identified increased activation in pain-relevant regions (somatosensory cortex, anterior cingulate, insula) in response to a prolonged thermal stimulus [30]. The amygdala attaches emotional significance to sensory information relayed from the thalamus, and differences in amygdala volume and connectivity influenced fear processing and emotion recognition following preterm birth [31, 32]. In EP young adults, lower amygdala volume correlated with both the degree and directionality of altered thermal

sensitivity (ie. decreased generalized thermal sensitivity in males, but increased sensitivity in females) [7].

4.2 Psychosocial factors and risk of future pain

Pain is a complex sensory and emotional experience, requiring a biopsychosocial approach to evaluation and management [33]. While some psychosocial factors can increase resilience or be protective (e.g. social support, active coping), others increase vulnerability (e.g. fear of pain, anxiety, catastrophizing) (Figure 1). Very preterm children had higher pain catastrophizing scores (increased rumination, magnification and perceived helplessness in relation to pain) and parents were more solicitous, and these factors may impair the ability to cope with or self-manage pain [34]. In EP young adults, increased anxiety and pain catastrophizing correlated with increased thermal sensitivity and more intense current pain [7, 15]. As child anxiety, child pain coping efficacy, and parental pain catastrophizing have predicted persistent postsurgical pain (which occurs in up to 20% of adolescents following major surgery) [35], earlier identification and targeted interventions may improve outcome.

It is now clear that sex and/or gender influences experimental pain sensitivity and the prevalence of chronic pain in adults [20] and neurodevelopmental outcome following preterm birth, but relatively few studies have compared pain-related outcomes in preterm-born males and females. At 18 months, more invasive procedures in NICU were associated with slower thalamic growth and reduced total brain volume, particularly in VP females [10]. At 7 years of age, increased neonatal procedural pain exposure was associated with lower cortisol, primarily in boys born preterm (24-32 weeks GA) [36]. In one study, reduced cold pressor tolerance in EP adolescents was predominantly due to shorter immersion times in males (13 males, 18 females) [5], while we found reduced tolerance predominantly in EP young adult females (38 males, 60 females) and additional sex-dependent differences in both experimental pain sensitivity and current pain report [7, 15]. Separate reporting of outcome in males and females may further elucidate differences related to sex and gender at different ages.

5. Long-term effects of neonatal injury on nociceptive processing

5.1 Laboratory evaluations in rodent models of neonatal tissue injury

Pre-clinical evaluations of age-dependent differences in pain processing are essential for understanding acute and long-term responses to early life injury; identifying safe, effective and developmentally-appropriate analgesic interventions [1]; and may also have broader potential for identifying novel pain-resolution mechanisms [2]. The normal activity-dependent development of the nervous system is vulnerable to alterations in sensory input, with the potential for long-term alterations in structure and/or function that are not seen following the same insult at older ages.

Many different laboratory models have identified persistent alterations following early life injury. Effects vary with the type and severity of stimulus, age at time of injury and assessment, and the subsequent outcome measured [1]. Here, repeated needle stick injury and hindpaw incision, which respectively model procedural pain exposure and surgical injury during the neonatal period, will be discussed. Effects of different neonatal injuries (eg. inflammation, visceral insults, traumatic nerve injury) on additional outcomes (eg. stress response) are included in recent reviews [1, 37, 38]. Studies are often performed in rodents that are born at an early developmental stage that has correlations with the preterm born human. Although variability in maturation across different regions of the peripheral and central nervous system limit the ability to directly translate age across species, there are similarities in the sequence of mammalian development, and effects of injury at different ages can be compared and followed to adulthood over shorter time periods in the rodent. In addition, specific confounders can be avoided or added, such as controlling for the degree of maternal separation, or evaluating effects of analgesic interventions [1].

5.1. Procedural pain exposure: repeated hindpaw needle insertion

Repeated needle insertions in one or both hindpaws and/or forepaws of neonatal rodents have been used to model repeated tissue-breaking procedures in NICU. Comparison groups include littermates exposed to a tactile stimulus only (stroke with a cotton-tipped swab) to control for the

effects of maternal separation and repeated handling, and/or naïve age-matched animals. Combining results across studies is difficult as reports vary in: i) size and type of needle (eg. 28 gauge automated lancet or needle of 25 to 30 gauge); ii) depth of insertion (not always reported but may be restricted to the surface, be a specific depth such as 2mm, or pass fully through the paw); iii) age and duration of exposure (daily from the day of birth throughout the first 1 or 2 postnatal weeks, i.e. postnatal day (P) 0 to P7 or P14); iv) frequency (from 4 to 30 insertions twice daily); and v) distribution of needle insertions (same unilateral hindpaw or alternate across all four paws).

While limited numbers of needle insertions in a single hindpaw (eg. 4 per day from P0 to P7) do not produce long-term changes in baseline mechanical and thermal withdrawal threshold [39], more widespread (all 4 paws) [40] and more prolonged exposures (P0 to P14) [41] have been associated with persistent sensitivity in adulthood. While one study reported no difference in adult threshold from tactile controls in both males and females [42], often the sample size is too small to evaluate sex differences [39] or males only are studied [40].

Subsequent adult incision of the neonatally-injured paw increased the duration of mechanical hyperalgesia and enhanced responses of dorsal horn neurons to pinch [39]. Paracetamol at the time of neonatal needle insertions did not alter acute hyperalgesia but reduced the duration of incision-related hyperalgesia in adulthood [43].

Following repeated needle insertion in neonatal mice (10 per day on alternate forepaws and hindpaws from P1 to P6), ex-vivo magnetic resonance imaging in adulthood found no difference in regional brain volumes between needle insertion and handling groups. However, repeated sucrose administration produced significant changes in the volume of multiple brain regions (including the hippocampus) that were exacerbated by concurrent needle prick (including somatosensory cortex, thalamus and periaqueductal gray) [44]. Functionally, repeated needle insertion has been associated with age-dependent variations in hypothalamic-pituitary-adrenal axis function and stress responsivity (as also reported in preterm ex-NICU infants) and impaired spatial memory retention in adult rats [40].

5.2 Surgical injury: plantar hindpaw incision

Incision of the skin and underlying muscle on the plantar surface of the hindpaw is an established model of postoperative pain that produces acute hyperalgesia in rodents of all ages. Alterations in withdrawal reflex sensitivity provide a measure of the degree of hyperalgesia and response to analgesia, and standardizing the length of incision to the size of the hindpaw facilitates comparison of the same relative injury at different ages [1].

Hindpaw incision in the neonatal rodent produces acute hyperalgesia that resolves within 1-2 days. Localized hyperalgesia in the previously incised paw was reported at P28-30 in males but not females [45]. Longitudinal studies have shown emergence of generalized thermal and mechanical hypoalgesia in all paws at older ages, associated with a shift in descending modulation from the normal bimodal pattern of facilitation or inhibition (depending on stimulus intensity) to predominantly inhibition [1]. This generalized distribution of reduced sensitivity has parallels with clinical QST findings in preterm-born children who required neonatal surgery and/or intensive care (Section 3.2).

Neonatal incision also has a long-term impact on the response to re-injury in later life. Incision in the first postnatal week, but not at older ages, increases both the degree and duration of re-incision hyperalgesia in adult male and female rodents. Thus, there is a 'somatosensory memory' of the early life injury [46, 47]. Spinal cord mechanisms contribute to persistent effects with alterations in synaptic signaling resulting in increased excitation and decreased inhibition [48, 49]. Interactions between neurons and glia also alter nociceptive sensitivity within the spinal cord, and priming of spinal microglia by neonatal injury contributes to increased microglial reactivity, sensitization and hyperalgesia following re-incision in adulthood [46]. While the same degree of re-incision microglial reactivity and behavioural hyperalgesia is seen in both male and female rodents, responses to microglial inhibitors are sexually dimorphic and effective in male rodents only [50].

Plantar incision allows the comparative efficacy of different analgesic interventions to be assessed. Acute hyperalgesia following neonatal incision can be dose-dependently prevented by a range of analgesic interventions [1]. Sciatic nerve local anaesthetic blockade at the time of neonatal incision has preventive effects on several outcomes including: acute hyperalgesia, alterations in spinal excitatory signaling, generalized increases in reflex threshold and altered descending modulation in adulthood, and the enhanced response to re-incision [1, 47, 49]. This supports the hypothesis that long-term alterations in nociceptive function are activity-dependent and triggered by increased nociceptive input. By contrast, systemic and intrathecal doses of morphine that effectively control acute hyperalgesia during the period of neonatal administration, do not prevent the long-term changes in reflex threshold or re-injury response [47]. Neonatal incision alone did not alter morphine efficacy in adolescence [45] or early adulthood [47], but morphine administration in the absence of tissue injury has been associated with long-term changes in efficacy [47]. This suggests that using morphine for neonatal sedation in the absence of pain or injury may produce different long-term effects than when used for analgesia. This further highlights the need for ongoing research to optimize practice protocols for analgesia and sedation during neonatal intensive care [9].

Conclusions

Preterm birth, neonatal intensive care and neonatal surgery are associated with adverse long-term effects on neurodevelopmental and somatosensory outcome, that are also influenced by gestational age at birth. Management of neonatal pain needs to consider modulation not only of acute behavioural and physiological responses, but also the potential long-term effects of pain and injury, and the relative risk-benefit of different analgesic and sedative interventions. Preclinical models of neonatal tissue injury confirm specific developmental and activity-dependent alterations in nociceptive function that persist into adulthood, and that can be modulated to varying degrees by different analgesics. Further evidence is required to achieve consensus regarding the safest and most effective interventions for pain in neonates, to minimize acute physiological and behavioural distress

and improve long-term outcome. For children and adolescents with significant early life pain exposure, recognition of risk factors for altered sensory and emotional responses to subsequent pain may identify those at increased risk of persistent pain who would benefit from targeted interventions.

Practice points

- Minimizing the number of procedural interventions where possible, regular assessment of pain and sedation, and providing procedural and perioperative analgesia are important components of management in neonatal intensive care.
- The evaluation and management of pain requires consideration of biological, environmental and psychosocial factors that influence the sensory and/or affective components of pain.
- Prior neonatal experience should be considered when assessing pain and future injury response in infants and children born preterm.

Research directions

- Further longitudinal follow-up with standardized outcomes is required to quantify the long-term impact of neonatal pain and identify subgroups of preterm-born children and adolescents at risk of persistent pain.
- In clinical cohorts, comparison of outcome in males and females is required to identify sex and/or gender differences in the biopsychosocial aspects of pain response.
- Preclinical studies are essential for understanding specific effects on nociceptive pathways, and evaluating potential mechanism-based and/or sex-dependent preventive interventions.
- Prospective clinical trials are needed to increase the quantity and quality of current evidence and develop protocols for minimizing the long-term effects of pain in early life.

Conflict of interest statement

None declared

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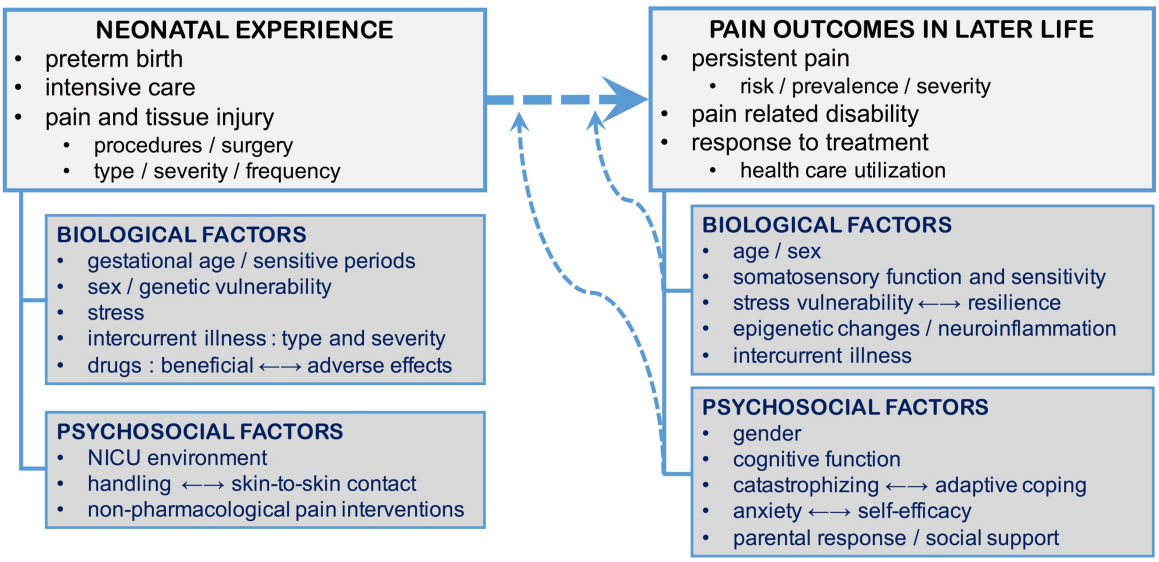
Figure Legends

Figure 1. Schematic biopsychosocial model of potential links 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 the experience or report of pain and/or modulate the long-term impact of prior neonatal experience. Factors that may have negative or positive effects on outcome are indicated with bidirectional arrows. Reproduced with permission from Walker [1].



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