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Long-term consequences of pain in human neonates

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KEYWORDS

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Summary The low tactile threshold in preterm infants when they are in the neonatal intensive care unit (NICU), while their physiological systems are unstable and immature, potentially renders them more vulnerable to the effects of repeated invasive procedures. There is a small but growing literature on pain and tactile responsivity following procedural pain in the NICU, or early surgery. Long-term effects of repeated pain in the neonatal period on neurodevelopment await further research. However, there are multiple sources of stress in the NICU, which contribute to inducing high overall 'allostatic load', therefore determining specific effects of neonatal pain in human infants is challenging.

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Introduction

With advances in medical care over the past two decades, survival of infants born extremely premature, infants with life-threatening medical conditions and infants with congenital malformations has increased substantially. However, as part of this life-saving care, these infants are exposed to multiple stressors in the neonatal period. Extremely preterm birth results in lengthy hospitalization of infants who are physiologically unprepared for the stress outside the protective intrauterine environment.¹ Such stress includes extended exposure to light and noise,

acute and chronic illness, maternal separation, invasive procedures, handling, and multiple medications, for each of which the long-term effects are unclear. At the same time, there has been growing concern that the invasive procedures that are intrinsic to management in the neonatal intensive care unit (NICU) and the pediatric intensive care unit (PICU), such as endotracheal intubation, repeated blood tests, insertion of peripheral lines and surgery, might induce changes to the CNS.^{2,3} It is well established that preterm neonates show greater sensitivity to pain compared to full-term infants.⁴ For infants with extremely immature physiological and neurobehavioural systems, continual adaptation to repeated challenges induces long-term alterations in pain sensitivity,^{4,5} might affect generalized stress-arousal systems,^{6,7} and potentially affects the developing cytoarchitecture of the brain.^{2,9,10} Pain-related stress during many weeks or months in the NICU might in turn be one contributing factor to

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alterations in neurodevelopment and behavior in extremely preterm infants who escape major neurosensory impairment, although this link remains largely speculative at this point.

The neurobiology of pain in the developing organism is addressed in Chapter 1 of this volume, and pain while infants are in the NICU is covered in Chapter 3. This chapter first presents the overall context of pain-related stress; second, it addresses potential links between neonatal pain and brain development; and third, it examines long-term effects of procedural pain and surgery on later pain sensitivity. The animal literature on effects of neonatal pain has recently been reviewed elsewhere,⁴ therefore we primarily address pain in human infants.

Prematurity and allostatic load

Recently, the concepts of 'allostasis' and 'allostatic load' have been developed to define more clearly the cumulative effects of exposure to repeated stress from any source.¹¹ 'Allostasis' applies to systems that maintain homeostasis, integrating responses of the hypothalamic–pituitary–adrenal (HPA) axis, the immune system and the autonomic nervous system, which constantly adapt to variations in response to perceived and anticipated environmental demands. In the long term, high demands on these systems can have adverse effects on the body. 'Allostatic states' occur when the systems involved in allostasis remain elevated over time.¹² 'Allostatic load' is the resulting wear and tear on the body from repeatedly adapting to adverse situations.¹³ This is a useful framework for considering effects of multiple procedures and other stressors on preterm infants, especially given their immature neurophysiology early in postnatal life. However, it is important to note that while pain is stressful, stress is not necessarily related to pain.

For the preterm infant, allostatic load can occur under the following three conditions: (1) when stress response mediators are heightened or do not turn off when recovering from the stressor exposure; (2) when they do not turn on adequately; or (3) when they are overused by exposure to multiple stressors.¹²

Alterations during and following pain and/or stress exposure

Although allostasis is usually applied to physiological systems, behavioural responses to painful procedures contribute to the overall energy expenditure of preterm infants and, as such, constitute additional modulators of stress response systems.¹⁴ It is well established that preterm infants have heightened tactile sensitivity⁴ and react behaviorally and physiologically to invasive procedures (see Chapter 3). Moreover, acute invasive procedures prime preterm infant biobehavioral response systems to subsequent handling, producing heightened responses to routine handling.¹⁶ In fact, just as exposure to painful procedures sensitizes preterm infants to subsequent handling, even routine handling before a skin-breaking procedure leads to similarly heightened responses. Importantly, we observed this sensitization even when a 20-min rest period

was provided between conditions (unpublished data). Thus both skin-breaking procedures and handling induce an 'allostatic state', through the mechanism of central sensitization.¹⁸ This leads to heightened ongoing stress, or perhaps chronic pain, for the preterm infant who might perceive non-skin-breaking events, such as diaper change, as painful. Indeed, in some situations, diapering produces greater physiological and/or behavioral changes than heel-lance.^{19,20} Thus the effects of inherently nociceptive events cannot be separated from stresses from other sources, which might have either additive or synergistic effects.

Although responses during painful procedures might be heightened, inability to modulate recovery is also evident in preterm infants. Recently, when behavioral responses were recorded over a 20-min period during recovery from heel-lance, preterm infants observed at 32 weeks post-conceptual age (PCA) showed sustained body movement responses indicative of stress that lasted 4–18 min after the last contact of the laboratory technician.²¹ Altered recovery to skin-breaking procedures in preterm infants continues beyond the neonatal period. When assessed at 4 months corrected age (CA, i.e. adjusted for prematurity), extremely preterm infants exhibited subtle differences in ability to recover from finger-lance (pain applied to a pain-naïve site) compared to full-term controls; however, few of these differences reached statistical significance.²² Importantly, at 8 months CA, the preterm infants showed significant hypersensitivity immediately after finger-lance but significantly faster dampening of facial and heart rate responses during recovery.⁵ Interestingly, the differences were most pronounced in the recovery phase. When parents reported lower sensitivity to pain in their extremely preterm infants at 18 months CA,²³ they were probably observing faster dampening or response during recovery. Furthermore, our findings from 4 to 8 months CA suggest that differences might become more marked over time. Beyond infancy, adolescents born preterm showed greater sensitivity to pressure points,²⁴ and a combined sample of preterm and full-term children who had early surgery showed increased pain sensitivity.²⁵ We speculate that both heightened pain sensitivity, and/or rapid recovery likely reflect changes to more generalized stress as well as nociceptive systems.

Failure to activate stress responses systems adequately

Although preterm neonates born >30 weeks gestational age (GA) generally show plasma cortisol levels which are similar to those of full-term newborns,^{26,27} earlier-born (<30 weeks GA) preterm infants in the NICU might have either lower basal levels of cortisol than they need to respond appropriately to stressors in the NICU,^{28,29} or response levels of cortisol that do not reflect the levels of stress to which they are exposed.^{30,31} Grunau and colleagues found that in infants born ≤28 weeks gestational age and assessed at 32 weeks PCA, a higher number of skin-breaking procedures since birth was associated with dampened cortisol responses to a clustered series of routine nursing procedures.³² In a similar sample, one-fifth of the infants produced extremely low

levels (<15 pg/ml) of adrenocorticotrophic hormone (ACTH) following clustered nursing procedures. These infants had experienced greater numbers of painful procedures in the 24 h preceding the clustered care than infants who produced detectable ACTH levels. Therefore repeated pain in the NICU possibly influences basal and stress hormone responses.

Clinicians are concerned that dampened HPA responses in extremely preterm infants might reflect adrenal insufficiency, thereby adversely affecting other physiological systems that might be critical to survival of extremely ill newborns.³³ However, since chronic exposure to high levels of glucocorticoids, including cortisol, can have adverse long-term effects on brain development,³⁴ the lower cortisol levels in extremely preterm infants could be viewed as adaptive, protecting the brain and other systems. Consequently, if down-regulated HPA responses might be a positive adaptation that protects neural structures, this possibility, coupled with the requirement of clinicians to optimize perfusion to support survival further, complicates difficult clinical decisions in the management of sick, small infants.

Overuse of stress response systems

Exposure to repeated skin-breaking events is associated with alterations in a number of biobehavioral systems in the short term, which then persist after preterm infants have been discharged from the NICU. For example, in follow-up studies of different cohorts, at 8 months CA infants born extremely preterm showed a higher basal heart rate⁵ and higher salivary cortisol levels⁷ than full-term controls. When early illness severity and intravenous morphine exposure were controlled statistically, the cumulative number of skin-breaking procedures among infants born ≤ 28 weeks GA was associated with higher basal and response to novelty cortisol levels at 8 months CA. Up-regulation of basal cortisol levels in infants born at extremely low gestational age is evident up to at least 18 months CA. Importantly, high pain exposure, low gestational age, and length of time on mechanical ventilation are all highly inter-related, therefore it is very difficult to isolate specific effects of neonatal pain.

In summary, stress of pain and handling in the NICU, together with other factors, such as chronic lung disease requiring prolonged mechanical ventilation, induce an allostatic state. Preterm infants show alterations in their ability to modulate stress response systems during and following painful events and intrusive handling. Moreover, in some cases they fail to activate stress responses, or display delayed responses. In infants born at the earliest gestational ages, down-regulated stress hormone responses in the NICU appear to be followed by up-regulated basal levels many months after NICU discharge. Although the mechanisms of the shift from down-regulation of cortisol in the NICU to later up-regulation are not yet known, a multiplicity of factors is thought to be involved. For example, mothers presenting with preterm delivery receive glucocorticoids (betamethasone or dexamethasone) to enhance infant respiratory development and thereby prevent severe chronic lung disease. However, animal models have shown that antenatal glucocorticoids,

as well as prenatal exposure to stress, are associated with permanent reprogramming of endocrine function, and changes to the brain (for review see ref. 35), even when administered in doses comparable to or below those used in humans. Importantly, gestational stress itself is linked to increased risk of preterm delivery.³⁶ In human infants, it is a major challenge to disentangle effects of these (and other) factors, in addition to pain and stress in the NICU, all of which can be compounded by physiological immaturity and prolonged mechanical ventilation. Cumulative evidence from animal models underscores the importance of timing of stress³⁵ and pain exposure³⁷ and the importance of follow-up at multiple ages, since effects change across time.

Vulnerability of the developing preterm brain

The etiology of neurobehavioral problems in preterm infants who escape major sensory, motor and cognitive impairments is unclear. However, these problems are probably attributable, at least in part, to disturbances in the expected organizational events in brain development, and/or injury to basal ganglia or hippocampus,³⁸ and/or subtle white matter changes, which are far more common than previously thought among infants who escape periventricular leukomalacia or severe intraventricular hemorrhage.³⁹ Lengthy hospitalization of the extremely preterm neonate occurs during a period when the brain is undergoing major development, including the establishment and differentiation of subplate neurons, alignment, orientation and layering of cortical neurons, elaboration of dendrites and axons, formation of synapses, selective pruning of neuronal processes and synapses, as well as proliferation and differentiation of glial cells. Experimental manipulations in animal studies provide abundant evidence that positive or negative early life experiences can alter both the structure and function of the developing brain, including altered number or pattern of synaptic connections, numbers of glia, and the degree of capillary branching that augments the blood and oxygen supply (see refs 9 and 10). The rate and extent of commitment of synapses is thought to be regulated by neurochemical and hormonal systems, particularly stress hormones.⁴⁰ Moreover, immature autoregulation of cerebral blood flow results in vulnerability to either hypotension or hypertension.⁴¹ Multiple components of the NICU experience (e.g. pain, illness severity, medication exposure) probably interact, cumulatively producing a negative impact. Mechanisms have been proposed whereby neonatal pain in preterm infants might disrupt normal brain development and thereby impact neurodevelopment, including excitotoxic damage leading to altered apoptosis (programmed cell death) and neuronal survival,¹⁰ and high basal endogenous glucocorticoid exposure due to 're-setting' to up-regulation of cortisol levels. Compromised brain function is likely to be due to many factors, and compensation for brain compromise might in part occur by other areas of the brain taking over processes for which they were not intended, thereby reducing integrity of specific information processing systems.

Stress and vulnerability of the hippocampal and prelimbic prefrontal regions

The HPA axis and cardiovascular, metabolic and immune systems respond to external and internal threat.⁴² As we have described above, one type of allostatic load is the inability to shut off responses after a stress is terminated. The mechanisms of the shift from down-regulation of cortisol in the NICU³² in preterm infants born at extremely low gestational age (ELGA; <28 weeks gestation) to sustained up-regulation later long after discharge home⁷ are unknown. However, high basal cortisol, as we have found in extremely preterm infants at 8 and 18 months CA, might at least partially reflect compromised ability to shut down stress. The hippocampal formation is involved with reaction to novelty, plays a role in comparing novel incoming information with stored information, and is involved with the ability of an organism to suppress irrelevant stimuli.⁴³ We found that at 3 months CA, altered capacity to regulate arousal may interfere with novel learning in preterm infants (unpublished data). In an independent sample, we found basal heart rate (HR) was higher in extremely preterm than in full-term infants later at 8 months CA, and that cumulative neonatal procedural pain was associated with higher basal HR.⁵

Importantly, in another study we found that higher maternal stress, together with higher infant cortisol levels, were associated with poorer cognition (as indexed by visual attention) in infancy.⁴⁵ Later in childhood, behaviorally from 3 to 9 years we have found that extremely preterm children, even those with normal intelligence, back-off from novelty, showing uncertainty and anxiety when dealing with novel cognitive challenges.^{6,46}

Together, these studies suggest that 'high risk' preterm infants show 'resetting' of basal physiology, and that these changes alter capacity to interact with novelty stimulation. Individual differences in behavioral traits related to response to novelty have been related to cell proliferation in the hippocampal formation.⁴⁷ Moreover, higher exposure to stress hormones in the neonatal period in rat pups impeded neurogenesis in the hippocampal region.⁴⁸ Chronic up-regulation of the HPA axis has been found in rats that were highly reactive to novelty.⁴⁹

The hippocampal region is a vulnerable link in the regulation of the HPA axis and cognition. According to the 'glucocorticoid cascade hypothesis', wear and tear in the hippocampal region of the brain leads to dysregulation of the HPA axis and cognitive impairment. The evidence for this connection has been established in animal models of aging, with rats⁵⁰ and humans^{51,52} showing hyperactivity of the HPA axis associated with impaired episodic, declarative and spatial memory. Findings such as these are relevant for children born preterm who have been shown to have smaller hippocampal volumes.^{53–56}

Neuroimaging, electrophysiology and prematurity

Imaging studies are beginning to describe structural differences in the brains of children born before term.

Using advanced volumetric MRI, preterm children have smaller brain volume in specific regions at age 7 years,⁵⁵ and poorer cognitive outcome was correlated with reduced brain volume.⁵⁷ There are regions of particular vulnerability in the developing brain. For example, adolescents born <30 weeks gestation had comparable head circumference and neurologic exams (compared to term-born controls) but had smaller hippocampal volumes^{53–56} and decreased volume of temporal lobe cortex.⁵⁶ Morphometric analyses identified disproportionately smaller volumes in specific cortical (sensorimotor, premotor, midtemporal, parieto-occipital, subgenual) and subcortical (corpus callosum, amygdala, hippocampus, basal ganglia) regions. Perinatal risk factors (e.g. hemorrhage, hypoxia, severity of illness) and sociodemographic factors (e.g. minority status, maternal education) did not explain these findings. Pervasive influences of neonatal repetitive pain exposure might be at least in part responsible for changes in brain development of preterm infants;² however, this remains speculative at this point. Mechanisms that might lead to neuroanatomic differences include the fact that immature neurons show enhanced vulnerability to excitotoxic stress⁵⁸ and repetitive pain during NICU care might impact altered neuronal survival.^{9,10} However, in addition, neurodegenerative mechanisms in the immature brain show increased susceptibility to numerous adverse events, including hypoxia and infection. Extremely preterm children likely have multiple diffuse brain insults, leading to altered patterns of macro- and microstructure of the brain,⁵⁹ with different parts of the brain acquiring functions for which they were not intended. Neonatal pain might be one factor in a complex multifaceted process.

Pre-emptive analgesia in the NICU

A critical question continues to be whether analgesics play a role in long-term changes to the CNS.⁶⁰ Pre-emptive morphine might ameliorate, have no effect, or potentially even exacerbate adverse neurodevelopment associated with prematurity. Pharmacologic treatment of neonatal pain was reviewed recently⁶¹ and is addressed elsewhere in this volume, therefore we will only touch on these issues here.

Analgesic agents directly suppress neuronal activation, and reduce extracellular concentrations of excitatory neurotransmitters, thus it was hypothesized that pre-emptive analgesia in infants receiving mechanical ventilation would prevent major sequelae prior to NICU discharge.⁶² Contrary to expectation, results from two recent multisite randomized controlled trials (RCTs) of pre-emptive morphine did not show beneficial effects in relation to adverse neonatal sequelae.^{62–65} To our knowledge, only one RCT of pre-emptive morphine administration in the NICU examined neurodevelopment in childhood (age 5–6 years). However, results were inconclusive due to the low sample size of 20 children per group.⁶⁶ Whether pre-emptive morphine prevents altered pain sensitivity has not yet been addressed in human infants.

Apart from RCTs, the daily dose of intravenous morphine (adjusted for daily weight) has been documented in a few

studies and examined in association with later outcomes. Initially, with infants born in the 1990s, morphine appeared to ameliorate effects of cumulative neonatal invasive procedures since birth on later pain sensitivity in the NICU.⁶⁷ However, among infants born more recently, this was not replicated.³² One major change over this period in neonatal medical management of preterm infants was the shift to much less use of postnatal corticosteroid administration. In the subsequent cohort, where the morphine effect was not replicated,³² infants with any exposure to postnatal corticosteroids were excluded, which might account for the different findings. Importantly, follow-up of this recent cohort (including or excluding the few infants exposed to postnatal dexamethasone) showed that higher neonatal intravenous morphine exposure did not prevent the high cortisol levels found at 8 or 18 months CA in infants born ≤ 28 weeks GA.⁷

It is very challenging to study effects of morphine or other analgesics or sedatives used pre-emptively in the NICU, even in RCTs, because humane care of infants currently requires physicians to treat those thought to be in pain, despite the knowledge gaps of long-term risks and benefits of these medications.

Surgery

Relatively few studies have assessed long-term effects of early surgery on pain sensitivity later in life. Although a large body of literature has shown that analgesics prevent pain and blunt the physiological effects of pain and stress at the short term (see, for example, refs 68 and 69) their capability to prevent hypersensitivity in the long term is not clear. In one of the most cited studies, term-born males who had undergone unanesthetized neonatal circumcision, responded more intensely to immunization at age 4–6 months than uncircumcised infants.^{70,71} Pre-treatment with EMLA-cream partially attenuated this hypersensitivity.⁷¹ Recent findings suggest that hypersensitivity following surgery is primarily restricted to the area of tissue damage, and that this adverse effect might develop even when adequate perioperative analgesia was administered.^{72,73} For example, Peters and colleagues found that infants who had undergone surgery within the first 3 months of life in combination with adequate analgesia⁶⁹ demonstrated higher sensitivity to subsequent surgery in the same dermatome. These infants needed more intraoperative fentanyl, had higher pain scores, had greater (nor)epinephrine [(nor)adrenaline] plasma concentrations, and needed more morphine than did infants with no prior surgery. Developmental alterations in spinal and supraspinal processing were the proposed mechanisms for this higher sensitivity. By contrast, infants who previously underwent surgery in another dermatome had significantly higher postoperative analgesic requirements and norepinephrine (noradrenaline) plasma concentrations but did not require higher intraoperative analgesia, nor did they have higher pain scores than infants with no prior surgery. The differences between groups were attributed to the more subtle/transient changes resulting from altered supraspinal processing,

which might be suppressed by the general anesthesia during surgery. Hypersensitivity is not restricted to the ipsilateral side of tissue damage but extends to the contralateral side. Neonates suffering from unilateral hydronephrosis 3 months after pyeloplasty demonstrated greater tenderness to mechanical stimuli both in the area of incision and on the unaffected contralateral side of the body than age-matched controls.⁷⁴ Most interesting was the fact that hyperalgesia did not differ between infants who were treated conservatively or by surgical intervention, suggesting that the visceral nociception might be responsible for the long-term effects. Preliminary findings from the Rotterdam group,^{72,73} as well as from Fitzgerald and colleagues,^{25,75} show that this localized hyperalgesia might even persist for 8–10 years after abdominal or thoracic surgery in early infancy, both on the ipsilateral and contralateral side. Both groups also demonstrated the existence of hypoesthesia for thermal and mechanical detection thresholds in the dermatome of tissue damage. Experimental models in rats confirm the findings in humans. Neonatal tissue damage induced by nerve ligation dramatically lowered sensory mechanical thresholds in the wounded area when animals grew older.⁷⁶ Conversely, following neonatal laparotomy in a mouse model, visceral nociception in adulthood to subsequent pain exposure was reduced.⁷⁷ Besides tissue damage, surgery is associated with inflammatory pain. Repetitive formalin injections in newborn rats resulted in hyposensitivity as adults.⁷⁸ Injection of carrageen also led to hyposensitivity in adulthood, however, importantly, when re-exposed to inflammation pain adult rodents showed hypersensitivity.^{37,79,80} The effects of neonatal inflammation are complex and depend on the timing, type and dose of inflammatory agent used, as well as whether tissue is completely healed, or re-inflamed at follow-up testing.^{4,37} The animal findings have confirmed and helped to resolve the apparently contradictory results of human studies, showing hypersensitivity and hyposensitivity under different conditions in the long run following neonatal pain. The results of early pain exposure are more complex than initially expected in this challenging area of research.

At least in the first year following discharge from the NICU, preterm infant pain systems appear to be surprisingly robust and adaptable, and even among infants born ≤ 800 g effects of neonatal pain exposure on later pain sensitivity are subtle rather than extreme.^{5,22} This is unexpected, given the sheer number of skin-breaking procedures that these infants undergo at a time of increased tactile sensitivity and development of their neurophysiology at all levels of the CNS.

Although children who underwent surgery in infancy show altered tactile sensation many years later, especially at the site of incision, Fitzgerald has pointed out that this has not been studied in patients who had surgery as adults, and might be a feature of healing postsurgery *per se*, rather than any indication of unique sequelae of infant pain. It is noteworthy that although 17.5% of children who were hospitalized, especially younger children who had more invasive treatment, displayed clinically significant medical fears many weeks or months later,

importantly the vast majority (more than 80%) did not.⁸¹ Thus, for this minority of young children with persisting problems following hospitalization, factors such as child temperament, family context, and social modeling are likely to be the most salient reasons, rather than a direct result of pain itself. Similarly, most children did not display self-injurious behavior in a follow-up of children who had brachial plexus birth injury.⁸² Thus the majority of children exposed to early pain do not display severely aberrant behavioral sequelae later.

It has also been proposed that pain syndromes might be initiated by early pain, however, we found no differences in somatization (pain of unknown cause) later in childhood (age 9 years)⁴⁶ or adolescence (17–19 years),⁸³ compared to socially comparable full-term controls.^{7,46} This is not to underestimate the importance of humane and appropriate pain management for young children, or the fears instilled if pain is not controlled, but rather to urge caution in overstatement of causal effects specific to infant pain based on the existing evidence in humans.

Notwithstanding these cautions against overstating long-term effects of infant pain on later pain sensitivity, a great deal more remains to be learned about pain and its effects in infancy. Moreover, we propose that as part of the overall allostatic load induced by all sources of stress, repeated pain probably contributes substantively to altered stress systems. Having said that, it is important to recognize that there are multiple pathways to altered generalized stress systems in infancy, including long-term effects of maternal stress during pregnancy, antenatal glucocorticoid treatment, in addition to other sources of neonatal stress (e.g. maternal separation), all of which together might compound effects of pain-related stress in the NICU.

Summary

Causal effects of neonatal pain on later pain sensitivity have been established through animal models. However, the findings are complex and show that outcomes vary in relation to timing, type and extent of insult. In human infants, there is a growing body of work on pain sensitivity in infants exposed to neonatal pain and/or surgery. The animal findings are essential for interpreting and confirming human studies, due to the difficulties of establishing causality in follow-up of human infants. However, the differences in complexity between species, and in the opportunities for modulating early changes, must be acknowledged in the protracted development of humans. The profound effects of parenting even in rodents⁸⁴ underscores the need to study long term effects of pain in the caregiver context in humans.

In terms of changes to the brain, there are multiple factors with similar sequelae, which might be interactive in their effects or might suggest that multiple causes lead to similar end points. For example, stress at varying points in prenatal and postnatal development can have long-term effects, thus specific effects of neonatal pain are difficult if not impossible to isolate in the human preterm infant.

Practice points

- Differences in pain reactivity between extremely low birth weight preterm and full-term infants, although present, are subtle, suggesting few clinically important long-term changes to nociception in human preterm infants.
- Hypersensitivity at the site of surgery persists, although this might apply to surgery at any age.
- Repeated invasive procedures and routine handling might contribute to important long-term alterations in more generalized stress systems. High basal cortisol levels found in ELGA infants in the first 2 years of life might impact neurodevelopment and might – at least partially – reflect compromised ability to shut down stress response systems.
- Effective management of sick infants with low cortisol levels in the NICU presents a difficult dilemma. On the one hand, cortisol is important in supporting blood pressure and perfusion, whereas on the other hand, exogenous cortisol might contribute to disturbances in pathways of brain development.
- Long-term effects of pre-emptive opiates on neurodevelopment are largely unknown.

Research agenda

- Long-term studies of neurodevelopment in relation to neonatal pain and opiate exposure in the NICU.
- Tactile sensitivity following surgery in adults, as well as infants and children.

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