

Effects of pain, sedation and analgesia on neonatal brain injury and brain development

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ABSTRACT

Critically ill newborns experience numerous painful procedures as part of lifesaving care in the Neonatal Intensive Care Unit. However, painful exposures in the neonatal period have been associated with alterations in brain maturation and poorer neurodevelopmental outcomes in childhood. The most frequently used medications for pain and sedation in the NICU are opioids, benzodiazepines and sucrose; these have also been associated with abnormalities in brain maturation and neurodevelopment making it challenging to know what the best approach is to treat neonatal pain. This article provides clinicians with an overview of how neonatal exposure to pain as well as analgesic and sedative medications impact brain maturation and neurodevelopmental outcomes in critically ill infants. We also highlight areas in need of future research to develop standardized neonatal pain monitoring and management strategies.

Introduction

Critically ill newborns undergo painful procedures as part of life-saving neonatal intensive care. In a multi-centre study of infants admitted to the neonatal intensive care unit (NICU), infants underwent a median of 115 painful procedures in the first fourteen days of life.¹ Preterm infants are exposed to the highest number of painful procedures, and these exposures occur during a period of rapid brain maturation and growth that would typically occur *in utero*.² It was previously believed that preterm infants did not experience pain as thalamocortical pathways are still immature; thus, preterm infants were not routinely given analgesia for painful procedures.^{1,2} However, we now know that preterm infants experience pain, and repetitive neonatal exposure to pain has been identified as a contributor to abnormalities in brain maturation and neurodevelopment in this population.^{3–8}

There is considerable variability in neonatal pain management approaches across NICUs. This may be due to findings suggesting that the commonly used analgesic medications in neonates may also have a potential impact on brain maturation and neurodevelopmental outcomes.⁹ Thus, it is important to consider the risks and benefits associated with treating pain in this vulnerable population. In this article, we review the neurobiology of pain in infants, and associations of early-life

pain and analgesia exposure with alterations in brain maturation, brain injury and neurodevelopmental outcomes.

Assessment and quantification of pain in neonates

The assessment and quantification of pain in neonates is uniquely challenging given infants are non-verbal, so methods relying on self-report of pain cannot be used. Table 1 summarizes methods that have been used in the clinical setting and in research studies. The most common method of assessing pain is through neonatal pain observational scales. There have been several neonatal pain scales developed and described in the literature with variable validity and reliability.^{10,11} These scales consist of a combination of behavioural measures (ex: crying, skin colour, facial expressions), physiologic measures (ex: heart rate, respiratory rate) and factors that account for prematurity and wakefulness or sleep state. Commonly used scales include the Premature Infant Pain Profile – Revised (PIPP-R),¹² the Neonatal Facial Coding System (NFCS)¹³ and the Neonatal Pain, Agitation and Sedation Scale (N-PASS).¹⁴ Although there is no gold-standard for the assessment of neonatal pain, it is important for each NICU to implement pain scales while considering typical patient populations and ages of infants in their unit.

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Table 1
Tools to assess and quantify pain in neonates.

Tool	Examples	Advantages/ Disadvantages
Observational pain scales	- Premature Infant Pain Profile Revised (PIPP-R) ¹² - Neonatal Facial Coding System (NFCs) ¹³	+ Assess infant's behavioural response to pain + Validated for specific patient populations and types of pain - Do not assess physiologic responses to painful stimuli - Do not readily quantify cumulative exposure to pain
Neurophysiologic measures	- Near-infrared spectroscopy (NIRS) - Electroencephalography (EEG) - Functional Magnetic Resonance Imaging (fMRI)	+ Detect cortical neural activity in response to painful stimuli - Do not readily quantify cumulative exposure to pain
Endocrine/ Hormonal response	- Cortisol levels in saliva or hair	+ Assess stress response to painful stimuli - Do not readily quantify intensity or cumulative exposure to pain
Number of invasive procedures	- Number of skin-breaking and/or non-skin-breaking procedures	+ Assess cumulative painful exposures quantitatively - Do not assess pain intensity or physiologic responses to painful stimulus

Table 2
Examples of invasive procedures separated into those that are skin-breaking and non-skin-breaking.

Skin-breaking procedures	Non-skin-breaking procedures
Peripheral arterial line insertion	PICC removal
Peripheral intravenous catheter insertion	Penrose drain removal
Peripherally inserted central catheter (PICC) insertion	Ostomy change
Venous blood draw	Endotracheal intubation
Heel lance	Endotracheal tube retaping and suctioning
Intramuscular injection	Nasopharyngeal/Oropharyngeal suctioning
Subcutaneous injection	Orogastric or Nasogastric tube insertion
Chest tube insertion	Dressing change
Pleurocentesis	Repositioning and imaging
Penrose drain insertion	Eye examination
Paracentesis	Chest compressions
Suprapubic aspiration	
Circumcision	

Neurophysiologic tools have been used to investigate and characterize the neural responses to painful stimuli in infants in the research setting; however, these tools are not used in the clinical setting. Near-infrared spectroscopy (NIRS), which detects changes in cerebral oxygenation to monitor cortical activation, has also been used to characterize pain-evoked responses in the contralateral somatosensory cortex in infants.^{15,16} Electroencephalography (EEG), which assesses the brain's electrical activity, has also been used to characterize neural responses to noxious painful stimuli in infants, and can discriminate noxious from non-noxious stimuli.¹⁷ Further, in a systematic review of neurophysiologic tools, EEG was found to be the measure with the greatest methodological consistency across studies assessing neurophysiologic responses to pain in infants.¹⁸ More recently, functional MRI (fMRI) studies have demonstrated noxious-stimulus evoked activation in pain-processing brain regions in neonates.¹⁹ This method demonstrated that reduced functional connectivity between the thalamus and sensorimotor cortex was associated with greater procedural pain in very

preterm neonates.²⁰ There also appears to be a distinct pain “signature” in full-term neonates from that seen in adults as seen with fMRI.²¹ Since critically-ill neonates, such as those born preterm or with congenital heart disease, are exposed to repeated painful stimuli, these measures that go beyond overt clinical signs of effective analgesia may enable an improved understanding of pain management strategies.²²

Painful stimuli may also contribute to activation of hypothalamic-pituitary-adrenal axis and stress response in infants. Stress responses have most commonly been assessed in infants by measuring salivary cortisol, reflecting acute stress, and hair cortisol, reflecting chronic stress.²³ Increased salivary cortisol levels after painful exposures have been observed in infants.^{24,25} Further, greater painful exposures in the neonatal period have been related to altered physiologic stress responses and behavioural problems in childhood.^{26–28}

Finally, several research studies across different infant cohorts have quantified painful exposures through counting each attempt at an invasive procedure.^{29–32} Examples of invasive procedures with each attempt counted are shown in Table 2. This method allows for quantification of cumulative pain exposure in the neonatal period. However, this does not assess pain intensity or physiologic responses to pain. Future studies should consider combining this method along with other measures such as neurophysiologic tools which can characterize neural responses to painful stimuli.

Neurobiology of pain in neonates

Sensory and motor pain pathways undergo considerable maturation from the third trimester into the neonatal period, overlapping with the period of preterm birth.³³ Thus, in the past, it was believed that preterm infants did not experience pain. However, we now know that higher-level pain processing is present early. In a study of neonates between 25–45 weeks’ postmenstrual age (PMA), responses in the somatosensory cortex to painful and non-painful stimuli were assessed using cerebral NIRS, which detects hemodynamic changes, with light emitters and detectors placed on either side of the head over the somatosensory cortex. Changes in total hemoglobin concentrations were calculated by measuring changes in oxyhemoglobin and deoxyhemoglobin, with an increase in total hemoglobin concentration reflecting an increase in cerebral blood flow. They observed increases in total hemoglobin concentration over the contralateral somatosensory cortex in response to painful stimuli in infants as young as 25 weeks’ PMA. However, no cortical responses were detected after non-painful stimuli in the neonates in this cohort, although non-painful stimuli were still associated with reflex reactions and withdrawal of the limb.¹⁵ Studies using fMRI have observed similar cortical responses after painful stimuli in preterm infants highlighting that although pathways relaying sensory information are immature, pain processing pathways are present and active.²¹

Due to the immaturity of pain pathways, infants experience pain that is more intense but less spatially focused than adults. In infants, the terminals of c-fibers and a-fibers, nerve fibers carrying information about pain, overlap in the dorsal horn and are slowly pruned over the neonatal period.³⁴ This results in difficulties with differentiating between noxious and non-noxious stimuli in neonates until these two types of fibers are separated.³³ Receptive fields are regions of the skin within which a painful stimulus elicits a neural response; these are large in neonates and become more organized over time.^{35,36} This results in less spatially and temporally focused pain with excitation of many more neurons in the brain of neonates in response to a painful stimulus. Thus, neonates have less focused motor responses to painful stimuli such as movement of the whole body; these responses gradually become more localized and isolated over time.³³ The responses of sensory and motor neurons to painful stimuli are also less synchronized due to the presence of immature synaptic transmission and nerve fibers that are not fully myelinated.^{35,37,38} Infants also have an imbalance of excitatory and inhibitory synaptic transmission in the spinal cord, and this changes

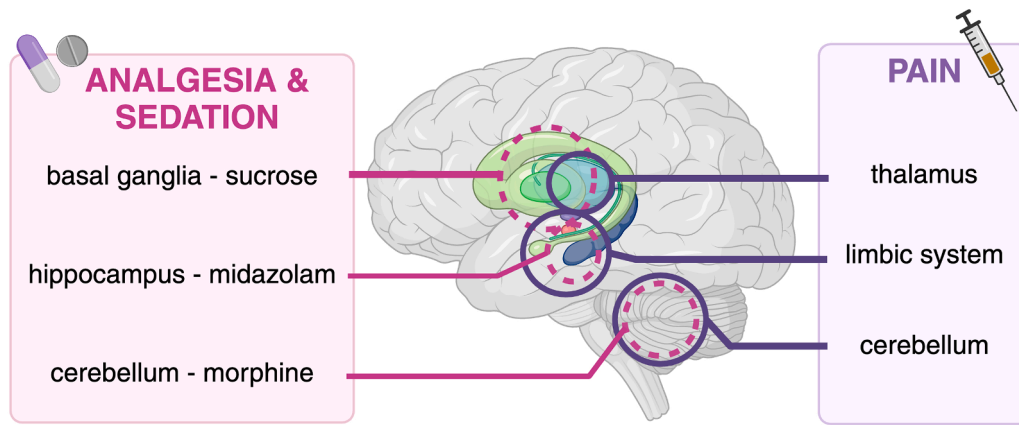


Fig. 1. Early-life pain and analgesia exposure have been associated with alterations in brain maturation with regional specificities. Created with Biorender.com.

with increasing gestational age.³³ Inhibitory fibers from the brainstem descend gradually and around 30–32 weeks, they reach the cervical spinal cord but are not yet present in the lumbar region.^{33,39} This results in differences in pain thresholds in upper compared to lower extremities at this gestational age, with greater pain sensitivity in the lower extremities. Immature descending inhibitory pathways and alterations in endogenous opioids lead to less effective inhibition of painful stimuli in neonates.³⁹ Finally, recent findings suggest that preterm infants do not habituate to repetitive painful stimuli unlike term-born neonates, which may further contribute to the harmful effects of pain on brain maturation.⁴⁰

Thus, afferent nociceptive pathways transmitting pain signals develop prior to 25 week's gestation, while descending modulatory pathways mature later, and are still immature in the term neonate; this necessitates an approach to managing pain in neonates that considers their state of brain maturation.

Early-life painful exposures and brain dysmaturation in neonates

In the neonatal period, repetitive painful exposures have been associated with brain *dysmaturation*, and poorer neurodevelopmental outcomes in preterm neonates; less is known about the effects of painful exposures on brain maturation and neurodevelopment in critically ill term-born neonates. In very preterm infants, greater exposure to pain has also been associated with poorer cognitive, motor and behavioural outcomes in early childhood, with associations observed across several independent cohorts of very preterm infants.^{3,6,7,20,29,30,41} The effects of early-life painful exposures may persist into school-age. Specifically, in a prospective cohort of very preterm infants, greater exposure to painful procedures in the neonatal period was associated with more internalizing behaviours, with this association persisting to 8 years of age.⁴² However, long-term studies of associations with outcomes in adolescence and adulthood are unknown.

Insights from neuroimaging studies of very preterm neonates suggest that brain *dysmaturation* including reduced white matter and grey matter maturation,⁵ is a key contributor to poorer neurodevelopmental outcomes seen with greater early-life exposure to pain. The associations between neonatal pain and brain dysmaturation persist to school-age with greater neonatal pain exposure associated with more immature white matter microstructure and reduced cortical thickness in the frontal and parietal lobes in 7 year old children born very preterm.^{3,29} More recent studies suggest that brain dysmaturation seen in relation to early-life painful exposures may be *regionally specific*. This is summarized in the following subsections and in Fig. 1.

Thalamic dysmaturation

The thalamus may be particularly vulnerable to the effects of early-

life painful exposures. Greater painful exposures have been associated with smaller thalamic volumes and altered microstructural maturation of thalamocortical pathways, which was related to lower cognitive and motor scores at 3 years of age in extremely preterm infants.⁶ Interestingly, this association between pain and thalamic volumes seemed to be driven by the presence of small volumes in the *lateral* thalamus, which consists of nuclei that relay somatosensory inputs.⁶ Greater pain exposure and reduced neonatal thalamic volumes have also been associated with altered sensory processing at 4.5 years of age in very preterm infants, which is important as sensory processing abnormalities may further contribute to poorer neurodevelopmental outcomes seen in children born preterm.^{43–45} Developing thalamocortical pathways, which carry information about sensory stimuli, including pain, to the cortex may be more vulnerable to the impact of environmental factors. These findings suggest that exposure to pain during the neonatal period may lead to (1) altered structural development of the thalamocortical pathways in the brain and (2) a long-lasting impact on neurodevelopment. Given this vulnerability of the thalamus to pain, a recent study examined whether leaving central lines in for longer duration was associated with a reduction in painful procedures, greater thalamic volumes, and neurodevelopmental outcomes by leveraging cross-site differences in clinical practices. Prolonged use of central lines was associated with less exposure to skin-breaking painful stimuli, larger neonatal thalamic volumes, and higher childhood motor and cognitive scores.⁴⁶ These findings highlight that procedural pain is a *modifiable risk factor* for brain dysmaturation and neurodevelopmental impairments in preterm infants, and that thoughtful consideration of each painful exposure during the NICU is necessary.

Connectome Dysmaturation

There has been a recent shift in the neonatal neuroscience literature to focus on maturation of the brain connectome as brain functions are the result of interconnected brain networks with many brain regions working together.⁴⁷ Structural brain networks consist of structural connections between brain regions derived by mapping out white matter tracts from diffusion MRI data. Functional brain networks are regions that are functionally connected, which can be assessed using functional neuroimaging methods such fMRI or EEG. Although structural and functional connections are similar, structural brain networks are believed to be “static” while functional connections are more “dynamic”.⁴⁸ Further, the development of brain networks during early-life may be influenced by environmental and sensory inputs, including exposure to pain. However, only a few studies have assessed the impact of neonatal pain exposure on structural and functional brain networks.

The findings of studies focused on early-life pain exposure suggest that networks involving the limbic system and cerebellum may be particularly vulnerable to the adverse effects of repetitive exposure to

pain in the neonatal period. Specifically, in a study of structural connectivity in very preterm infants, greater neonatal exposure to invasive procedures was associated with impaired development of connectivity from early-life to term-equivalent age in a subnetwork of connections involving limbic structures including the hippocampus and amygdala.³² Infants with more internalizing symptoms had reduced connectivity in the hippocampus and amygdala suggesting that the effects of early-life pain exposures on behavioural outcomes may be mediated through alterations in limbic pathways.³² Greater early painful exposures was also associated with decreased functional connectivity between the thalami and somatosensory cortex bilaterally, as well as between limbic structures, in an independent cohort of preterm infants.⁴⁹ Early-life exposure to pain has also been linked to atypical development of the cerebellum in very preterm infants. Greater painful exposures was associated with increased functional connectivity with the cerebellum and between the cerebellum and limbic regions at term-equivalent age in very preterm infants.³⁰ Greater cerebellar connection strength was also associated with poorer language outcomes at 18 months of age in this cohort.³⁰ As functional connectivity assesses the presence of synchronous activation between brain regions, it is possible that the hyperconnectivity observed between cerebellar and limbic structures could be due to repeated co-activation of these regions. This needs to be explored further, although greater painful exposures has been previously associated with reduced cerebellar volumes and poorer cognition and visuomotor integration at school-age in an independent cohort of very preterm infants.⁴

Collectively, these studies suggest that pain may impact the development of specific brain structures (e.g. thalamus, cerebellum) and their connectivity networks, although this warrants further study. Identifying specific regions and subnetworks that are particularly vulnerable to pain in neonates may guide treatment approaches.

Pharmacologic pain management strategies

Several medications have been used to treat pain in very preterm infants including benzodiazepines such as midazolam, opioids such as morphine and fentanyl, and sweet substances such as sucrose or oral glucose. However, it is important to understand how treatment with analgesic medications modifies the risks of adverse brain development and neurodevelopmental outcomes associated with early-life repetitive exposure to pain. There is considerable variability in the use of analgesic medications across NICUs, even after accounting for differences in clinical characteristics of newborns across centers.^{50–54} This may be due to the findings of recent studies suggesting that commonly used sedative and analgesic medications in preterm neonates may have unexpected detrimental effects on neurodevelopment and brain maturation, with regional specificities (Fig. 1).^{9,20,55–60} The following section outlines associations of analgesia and sedative exposure with brain dysmaturation and brain injury that have been described in the literature with a focus on studies that describe the use of these medications for procedural pain. Of note, in this review, we have included studies that have examined associations of neonatal benzodiazepine exposure, brain dysmaturation, and neurodevelopmental outcomes. Benzodiazepines are most often used as a sedative to manage agitation in ventilated infants, although the effectiveness and safety of these medications for sedation and analgesia warrant further study.⁶¹

Opioid analgesics

Opioids such as morphine and fentanyl are the most used analgesic medications in very preterm infants.^{51–54} Neonatal opioid exposure has been associated with brain dysmaturation, with regional specificities for the cerebellum. Purkinje cells are particularly vulnerable to the effects of morphine, as seen in preclinical models. Morphine exposure was associated with reduced Purkinje cell dendritic length and higher concentrations were associated with reduced Purkinje cell survival.⁶² Longer duration of morphine exposure was associated with a decrease in the

Purkinje cell size and the number of Purkinje cells in the cerebellum.⁶³ Findings in clinical populations of preterm infants are consistent with those in preclinical models. In a prospective cohort of very preterm infants, morphine exposure was associated with smaller cerebellar volumes.⁵⁶ Morphine exposure was also associated with poorer motor and cognitive outcomes; this relationship was attenuated when adjusting for cerebellar and cerebral volumes. These findings suggest that the link between morphine and neurodevelopmental outcomes is at least partially mediated by slower brain growth.⁵⁶ Similar findings have been observed with fentanyl exposure in preterm infants with greater cumulative dose of fentanyl associated with smaller transcerebellar diameter and poorer neurodevelopmental outcomes.^{57,64}

Morphine exposure has been associated with poorer motor, cognitive and behavioural outcomes across several independent cohorts of infants born very preterm.^{51,65–69} These associations with neurodevelopmental outcomes are still present at school-age.^{65–67} Further, morphine exposure may be a modifier of associations between early-life pain and neurodevelopmental outcomes; greater painful exposures were related to poorer neurodevelopment outcomes at 18 months of age in preterm infants who were exposed to long, but not short durations of morphine.⁵⁰ These findings suggest that dose-response relationships of morphine to neurodevelopmental outcomes warrant further study. However, it is important to note that in clinical trials of pre-emptive use of morphine infusions compared to placebo in neonates undergoing mechanical ventilation, morphine use was not associated with poorer neurodevelopmental outcomes at school-age.^{70–73} The discrepancies in findings across studies could be related to differences in morphine doses that were used, indications for morphine use, and inconsistently accounting for exposure to pain in statistical models.

Benzodiazepines

Findings from studies in newborn rodent models have observed that benzodiazepines can induce neuroapoptosis in cortical and subcortical regions.⁷⁴ Clinical trials of intravenous midazolam infusions, the most used benzodiazepine, for sedation in neonates have also shown concerning findings.⁷⁵ In the Neonatal Outcome and Prolonged Analgesia In Neonates (NOPAIN) pilot trial, a higher incidence of severe brain injury or death was seen with pre-emptive treatment with intravenous midazolam infusion compared to morphine during mechanical ventilation.⁷⁶ Greater brain injury may possibly be due to more hypotension seen with boluses of midazolam.⁷⁷ In a prospective cohort of infants born very preterm, greater cumulative midazolam exposure in the neonatal period was related to altered maturation of the hippocampus in the neonatal period with reduced hippocampal volumes and changes in hippocampal microstructure. These alterations were related to poorer cognitive outcomes at 18 months of age.⁵⁵ With longitudinal follow-up of this cohort, neonatal midazolam exposure was found to be associated with smaller hippocampal volumes at 8 years of age, with the smallest volumes observed in boys who were exposed to midazolam. These findings suggest that early-life midazolam exposure may have long-lasting effects on brain maturation, and that boys may be particularly vulnerable.⁷⁸ Collectively, the findings of these studies highlight the importance of carefully considering the use of benzodiazepines for sedation in neonates, particularly in those born preterm.

Dexmedetomidine

Dexmedetomidine is a selective alpha-2 adrenergic receptor agonist that has analgesic and sedative effects but does not cause respiratory depression. Recent studies have investigated the use of dexmedetomidine for sedation and analgesia in critically ill preterm and term infants and have found that infants treated with dexmedetomidine required less adjunctive therapy with opioids or benzodiazepines.^{79–83} Studies in preclinical injury models suggest that dexmedetomidine may have potential neuroprotective effects including possible attenuation of ischemic

injury; this may be mediated through inhibition of neuronal apoptosis and the hypoxia-inducible factor-1a pathway.^{84–87} However, the effects of dexmedetomidine exposure on brain injury and brain maturation in critically ill preterm and term-born infants are currently unknown. Further studies to determine efficacy, safety, optimal dosing, and indications of dexmedetomidine in preterm and term infants are also warranted.

Sweet solutions

Sweet solutions such as sucrose and oral glucose are commonly used for procedural pain in neonates. In a meta-analysis of randomized control trials assessing the efficacy of sucrose for procedural pain in neonates, sucrose was found to be effective in reducing the behavioural response to pain in neonates.⁸⁸ However, a recent review synthesizing findings from systematic reviews concluded that sucrose was inferior to analgesic medications or sucrose combined with analgesic medications in the treatment of procedural pain.⁸⁹ Further, in a randomized control trial of neonates assigned to receive either sucrose or sterile water, sucrose was found to reduce the behavioural response to pain but did not suppress the cortical response to pain as detected with NIRS or prevent the development of hyperalgesia.^{90,91} Collectively, these findings suggest that sucrose may not adequately treat pain in neonates.

Sweet solutions used to treat procedural pain are often categorized under non-pharmacologic interventions although warrant the same consideration as analgesic medications. Specifically, there have been concerns about potential harmful effects of repeated sucrose exposure in neonates. In mouse pups, repeated exposure to sucrose in infancy for procedural pain resulted in smaller regional brain volumes in the white matter and cerebellum in adulthood when compared to those who had received sterile water.⁹² When compared to sterile water, neonatal repetitive exposure to sucrose for procedural pain was also related to poorer spatial memory in mice in adulthood, and similar findings have been observed in clinical studies in preterm infants.⁹³ Higher cumulative doses of sucrose exposure were related to poorer motor development at term-equivalent age in preterm infants.⁹⁴ Further, greater oral glucose exposure was associated with poorer motor outcomes at 18 months, and related to smaller basal ganglia volumes from birth to term-equivalent age in female but not male preterm infants.²⁰ The potential sex-specific vulnerability of female infants to oral glucose exposure warrants further study. Together, these findings highlight the importance of considering sucrose and oral glucose as a pharmacologic treatment for pain in infants with careful consideration of when and how much sucrose is administered.

Non-pharmacologic pain management strategies

Non-pharmacologic strategies for managing pain in neonates include non-nutritive sucking, facilitated tucking, swaddling, kangaroo care, and breast milk. In a meta-analysis of more than 100 clinical trials, non-pharmacologic interventions were found to reduce behavioural responses to painful stimuli in infants born preterm and at full term.⁹⁵ However, due to wide variations in clinical populations, non-pharmacologic interventions and pain outcomes that were assessed across studies, the level of evidence remains low. Regardless, these non-pharmacologic interventions, which are largely parent-delivered are an important component of family-integrated care in the NICU.⁹⁶

Conclusions and future directions

Painful exposures in the neonatal period have been associated with altered brain maturation which have been related to poorer neurodevelopmental outcomes. Brain dysmaturation related to neonatal pain is modified by the stage of brain maturation at which these exposures occur (e.g. preterm vs. term). However, analgesic and sedative medications commonly used to treat pain in infants may also impact brain

Table 3
Summary of future directions.

Clinical populations	• Studies of pain and analgesia exposure in relation to brain development and neurodevelopmental outcomes in critically infants born at term.
Assessment and quantification of neonatal pain	• A standardized approach to the assessment of pain that also considers neurophysiologic measures that detect neural responses to painful stimuli.
Pain management	• Studies of optimal analgesic approaches in neonates that consider differences between preterm and term infants, and female and male infants.
Neurologic outcomes	• Longitudinal studies of effects of pain and analgesia on brain maturation and neurodevelopment.

maturation and neurodevelopment making it challenging to know what the best approach to the treatment of neonatal pain should be. Thus, there are several potential areas of future research that are warranted to identify optimal analgesic approaches for neonatal pain (Table 3). Future studies should consider combining quantitative pain data, such as through quantification of invasive procedures, with neurophysiologic data so that there is information about both the pain signal itself as well as cumulative exposure to pain. Most of the literature has focused on exposure of preterm infants to pain. However, given the development of pain pathways throughout the third trimester (overlapping with period of preterm birth) and beyond term equivalent age, pain management approaches should consider the gestational age of the infant. Sex-specific differences in the associations between analgesic exposure and neurodevelopmental outcomes have been observed in a few studies. This warrants further research and consideration of whether pain management strategies in neonates should differ in female and male infants. Finally, there are only a few studies of potential long-term effects of early pain and analgesia exposure, and these include follow-up visits at school-age. Longitudinal studies following children in adolescence and adulthood are needed to understand whether there are persistent effects of these neonatal exposures on brain development and neurodevelopment.

Declaration of competing interest

The authors have nothing to disclose.

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