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Assessing pain in preterm infants in the neonatal intensive care unit: moving to a 'brain-oriented' approach

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Summary

Preterm infants in the neonatal intensive care unit undergo repeated exposure to procedural and ongoing pain. Early and long-term changes in pain processing, stress-response systems and development may result from cumulative early pain exposure. So that appropriate treatment can be given, accurate assessment of pain is vital, but is also complex because these infants' responses may differ from those of full-term infants. A variety of uni- and multidimensional assessment tools are available; however, many have incomplete psychometric testing and may not incorporate developmentally important cues. Near-infrared spectroscopy and/or EEG techniques that measure neonatal pain responses at a cortical level offer new opportunities to validate neonatal pain assessment tools.

More than 12 million premature infants are born worldwide each year [101]. Preterm newborns shift abruptly from the protective intrauterine environment to the neonatal intensive care unit (NICU), where they undergo essential life-saving, invasive care-related procedures. For example, an infant born at less than 29 weeks gestational age may experience 300 or more painful procedures over a 3-month stay in the NICU [1]. Despite national and international guidelines that call for minimizing painful procedures in these neonates [2], the high rate of exposure to these procedures continues [3]. To increase awareness of the importance of assessing and managing pain, some suggest that pain should be considered an adverse event [4].

Since the rapidly developing nervous system of immature preterm neonates differs from term infants, preterm infants are particularly vulnerable to the effects of pain and stress. In the neonatal period they are at risk of enhanced pain sensitivity (for a review see [5]). For these infants, poorly managed pain and stress may have important consequences. Continual adaptation to repeated pain appears to induce functional changes in stress and pain

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processing systems [6–12]. Furthermore, repeated neonatal pain may contribute to long-term changes in generalized stress systems [13], including altered programming of primary human stress hormone (cortisol) levels in infants born extremely preterm, long after NICU discharge [14,15]. Altered programming of the hypothalamic–pituitary–adrenal axis has implications for the health and neurodevelopment of these infants as they grow older [16,17].

To protect the brain, and to promote optimal long-term development, using accurate pain assessment tools is essential for mitigating pain. Given the vulnerabilities of tiny babies, pain assessment must be as accurate as possible to ensure that there are no 'unintended negative consequences' of pharmacologic pain management or other forms of humane care [18].

Current pain assessment tools for both pre- and full-term infants have been reviewed extensively [19,20]. Given the lack of a 'gold standard' for pain in nonverbal infants, we will describe technologies developed to measure cortical responses to pain, the use of which offer novel ways to validate pain indices in neonates. With these new techniques, improved accuracy of assessment of pain in these infants is expected. In addition, a 'brain-oriented' approach is needed to embed pain assessment in NICU care, but with an emphasis on balancing risks and benefits related to pain management, so that potential iatrogenic effects of both pain and analgesic/sedative management are considered.

Models of pain/stress processing early in development

The evaluation and validation of pain assessment parameters in this specialized population should be founded upon appropriate developmental theories or models. For preterm infants in the NICU, the two most relevant developmental models that place these infants' pain responses in a broader 'brain-oriented' developmental context are the synactive theory of development and, the more recently proposed, early life stress model. The synactive theory of development, a systems-based theory, assumes that the process of development is species specific and is driven by the CNS [21]. The infant alternates between stabilizing and integrating behavioral and physiological response systems to allow more complex behaviors to emerge. The central hypothesis posited at the time this theory was developed was that early exposure to stress in the NICU involved a mismatch between the external environment and the preterm infant's immature CNS and that this mismatch was linked to the developmental impairments reported in these children at school age [22]. In many NICUs, this theory is applied through a prescribed model of care called the Neonatal Individualized Developmental Care and Assessment Program (NIDCAP) [23]. Therefore, for the premature neonate, any unexpected experiences, including those that are painful, would disrupt the stability of the infant, thereby potentially impacting development. The strength of this model is its dynamic integration of multiple systems including sleep/wake states, motor behavior, physiological responses and attention/interaction systems. In addition, this model provides specific directions for caregivers in the NICU to provide humane care that maximizes stable infant–caregiver interactions. This model has been used as the basis for a new pain assessment tool, the Behavioral Indicators of Infant Pain (BIIP), which included developmentally relevant, specifically defined behaviors identified and validated as stress cues from the NIDCAP [24,25].

The more recently developed early life stress model conceptualizes stimulation within a caregiver–gene–environment context [26]. Here, ongoing activation of both the stress and threat–response systems, in the absence of a consistent, responsive and comforting adult, induces epigenetic changes that, in the long-term, are maladaptive. With contingent care giving, the systems are able to reorganize 'adaptively' allowing the infant to become better

regulated. The strength of this model is its integration of the stress–threat systems with care giving. Furthermore, this model is broad and applicable to both infants and older children. Although this model does not specifically direct care, with respect to pain assessment, it directs caregivers and researchers to consider the context of early stress exposure on pain responses. We propose that a combination of the two theoretical models provides an important foundation to guide accurate, reliable and valid pain assessment for preterm infants, particularly since they highlight the importance of early life stress and environmental/developmental care, an approach that shows much promise for protecting the infant's brain and development.

Pain assessment

Over the past 10–20 years, much work has been carried out to develop tools with which to evaluate pain in the NICU. Unfortunately, rather than starting with a developmentally relevant theoretical framework, extrapolating pain responses in full-term infants has been the most commonly used strategy for developing pain assessments for preterm infants (e.g., Neonatal Facial Coding System [NFCS] [27–30]; Premature Infant Pain Profile [PIPP] [31–33] and Neonatal Infant Pain Score [NIPS] [34,35]). This approach is limited because assessing pain in preterm infants is more complex than in full-term infants owing to the immaturity of premature regulatory systems at every level and to the ongoing maturation of the CNS. Preterm infants may respond to acutely painful stimuli with behavioral and physiological responses that are of smaller magnitude, particularly in infants at younger gestational ages [36–39]. In addition, preterm infants at earlier gestational ages may display different pain behaviors from those born at later gestational ages [40]; therefore, these behaviors may not be captured by pain scales based on pain cues observed in full-term infants. Complexities such as these have led to the recommendation that the most promising pain scales for preterm infants should incorporate developmentally relevant pain indicators [41].

Types of pain indicators

Identifying the presence or absence of pain requires the use of reliable and valid pain measures that can be used for both research and clinical assessment. The tools that are currently available can be divided into two categories: unidimensional measures and multidimensional measures. Unidimensional measures of pain use either a single type of variable, such as facial activity, or single dimensions of pain, such as behavioral parameters [20]. The most common behavioral indices include changes in anatomically defined facial actions, in cry, in general or specific body movements, in muscle tone, in color, and in sleep/wake states. Currently, a number of behavior-based pain assessments are available for use in both research and in a clinical setting; however, as recent reviews have described, many lack full testing of their psychometric properties and/or have only been used in research settings [20,42].

Multidimensional measures combine both behavioral and physiological pain indicators and may include other contextual factors. Combined with one or more of the previously mentioned behavioral indices, physiological indicators include heart rate, heart rate variability, respiratory rate or pattern, oxygen saturation and blood pressure.

The greatest increase in the number of available pain assessments is the addition of many multidimensional scales. These scales, while convenient to use for clinicians, also come with a significant limitation. The findings that behavioral and physiological responses to pain are divergent, including in preterm infants, are well-documented [43,44]. A single multivariate score precludes analysis of important pain response information both for research and for clinical purposes. For example, following a pain stimulus and/or intervention, behavioral

responses may be diminished while physiological indices remain unchanged. While this well-established divergence of behavioral and physiological responses is part of the rationale for multidimensional scales, a problem arises when these responses are combined into a single score. When interventions reduce the behavioral response without concomitant control of the activated cardiovascular and other stress response systems, these infants are left vulnerable to the possible physiological effects of uncontrolled pain [45]. Therefore, although using a pain scale that combines behavioral with physiological indices into a single score may be simple, clinicians and researchers should take into account each domain of an index separately to ensure that the individual components of the pain response are adequately managed. Conversely, when univariate behavioral scales are used, physiological recordings add important complementary information.

Brain-oriented pain assessment

One of the most significant limitations of assessing pain in a preterm population is that, until recently, all indicators were proxy measures, since infants are preverbal. No ‘gold standard’ exists for pain in infants. However, advances in technology allow more direct assessment of cortical processing. Near-infrared spectroscopy (NIRS) evaluates acute changes in cerebral blood flow, volume and oxygenation. EEG records electrical activity reflecting cortical neuronal activity. These two methods provide indices of activity in the somatosensory cortex and have been used to evaluate cortical responses to painful stimuli. Although these brain-based methods provide a new dimension for understanding pain, the complex question of whether cortical activation is a direct indicator of pain experience is, of course, unknown. Nevertheless, the landmark work demonstrating a high correlation between cerebral blood flow and facial expression of pain is a promising beginning to research aimed at addressing this question [46].

Near-infrared spectroscopy

Near-infrared spectroscopy has been available for bedside clinical use for many years [47]. The technology is based on the properties of infrared light passing through human tissue. Infrared light is differentially absorbed by hemoglobin and cytochrome oxidase aa3 (the terminal enzyme of the respiratory chain of the mitochondria that catalyzes transfer of electrons to oxygen) depending on their oxygen saturation. By calculating changes in hemoglobin oxygenation, changes in cerebral blood flow can be calculated.

Bucher and colleagues were the first to use NIRS to evaluate the effects of oral glucose for treating heel lance in preterm infants [48]. Although significant effects of glucose on clinical pain indices were observed, no significant changes in cerebral blood volume, oxy- and deoxyhemoglobin were found. However, in this study, the NIRS optode (sensor) was placed over the temporal area. More recently, in two seminal studies, Bartocci *et al.* [49] and Slater *et al.* [50] demonstrated changes in cerebral hemodynamics of preterm infants over the somatosensory cortex. In the first study, in infants born as early as 28 weeks gestation, an increase in cerebral blood volume was demonstrated in the contralateral somatosensory cortex after hand venipuncture. The magnitude of the response was inversely correlated with gestational age and directly correlated with postnatal age. In addition, the response was more pronounced in male than in female infants. Similar changes were not found in the occipital area, implying that these changes reflected responses related to the painful stimulus [49].

In the second study, increased cerebral blood volume in the contralateral somatosensory cortex was demonstrated after heel prick in infants born as early as 25 weeks gestation [50]. As in the first study, the response increased with conceptional age. In both studies, no significant changes were noted after a nonskin-breaking tactile stimulation. Together, these

studies demonstrated that preterm infant pain responses are not purely reflexive, but are processed at cortical levels.

Considerations for using NIRS for pain assessment

Using NIRS for clinical bedside pain assessment remains challenging because movement artifacts can interfere with the signal [51]. However, with secure optode placement, movement artifacts can be minimized. In addition, to maximize the likelihood of an accurate reading with NIRS, environmental factors that can induce changes in cerebral oxygenation should be controlled. Although activating alternative cortical areas than those of pain, odors have been demonstrated to alter oxy- and deoxyhemoglobin in full- and preterm infants [52,53], as have human voices [54]. Furthermore, clinical conditions that affect blood flow/oxygenation can influence NIRS recordings. When measuring a single painful event, infants who have higher birth-weights [55], are on morphine or midazolam [56], have a patent ductus arteriosus [57], have an infection, have been exposed to chorioamniotitis [58], are on pressor support [59], have abrupt changes in supplemental oxygen delivery during the observation [60], or have early parenchymal ultrasound abnormalities [55] may have altered hemodynamic changes during procedures. In addition, any significant changes in ventilator settings may influence results.

EEG

EEG recording has been used extensively to evaluate neurological cerebral function in infants. This recording technique is characterized by evolving features of frequencies and amplitude reflecting maturation of the neonatal brain (reviewed recently by André *et al.* [61]). Amplitude-integrated EEG, a compressed limited channel EEG, has gained acceptance in NICUs for continuous brain monitoring in at-risk neonates at full term (for review see [62]). Normal and abnormal activity have also been explored in preterm infants [63]. These modalities have been used for assessing the CNS maturation of the infant, for identifying the effects of cerebral insults and for evaluating prognosis [64–66].

Reactivity to somatosensory stimuli is central to clinical neurological assessment of neonates. Somatosensory evoked potentials enable direct assessment of the neural pathways from the skin through to the cortex. Somatosensory evoked potentials responses have been evoked most commonly by electrical or tactile stimulation [67]. New approaches, time-locking the stimulus and EEG, have enabled a relatively simple way to obtain somatosensory evoked potentials in the premature infant using the raw EEG signal acquired from amplitude-integrated EEG.

Until recently, EEG responses to procedural pain have received little attention, but with the surge of interest in monitoring pain in this population, and the availability of EEG recorders and monitors, this technique might be promising in this field. Frontal EEG asymmetry has been viewed as an index of emotional response, both in adults [68], and in healthy full-term infants and toddlers [69], an approach that may be relevant to pain experience. In healthy full-term neonates, repeated heel strokes (aversive, but not nociceptive stimulation) evoked changes in the symmetry of frontal EEG activity, but were attenuated in infants given sucrose [70]. Norman *et al.* used EEG to evaluate pain in full-term infants, only demonstrating a significant increase in the higher frequency band components of the EEG in frontal regions, but not somatosensory or other regions [71]. Therefore, these researchers were cautious in their conclusions. However, Slater *et al.* demonstrated an evoked response after a single painful stimulus using a time-locking technique [7,72,73]. However, no differential responses were evident in infant EEG somatosensory reactivity when sucrose was administered compared with water during a heel lance [73]. Much of the aforementioned work in pain has been performed in full-term infants or in preterm infants

after discharge from the NICU. Owing to the relative proximity of the motor cortex to the somatosensory cortex, isolating sensory responses from motor contractions of the limbs may be difficult in tiny infants. Therefore, more research is needed to explore the field of pain assessment with EEG for clinical and for research purposes.

Considerations for choosing pain measures for preterm infants

While choosing the type of pain assessment may be driven by NICU-specific needs, many of the scales published have had inadequate psychometric testing. In addition, many include indicators that are too generally defined, and/or are not based on developmentally relevant theories or models for the population, thereby limiting their accuracy. Improvements in methods of measuring central pain responses in the brain now permit evaluation of specific behavioral and autonomic pain indicators as they relate to changes in cortical pain processing. These technologies offer tremendous potential advantages that will allow further validation of pain cues, and may provide clinicians and researchers with clearer directions in decision-making, regarding which pain scales to use in the NICU.

For the purposes of determining which indicators measure pain, the most compelling research to date evaluated the relationships between behavioral and physiological pain responses in conjunction with NIRS monitoring in preterm infants undergoing heel lance [46]. In this study, three anatomically defined facial actions from the PIPP correlated most highly ($r = 0.74$) with cortical activity and, although the total multidimensional score was significant, the relationship was less strong ($r = 0.57$). Findings such as these are supported by others who have demonstrated that, over time, crying, changes in sleep/wake states and facial grimace account for most of the variance in pain expression in preterm infants [38].

In the Slater *et al.* study, adding physiological indices did not improve upon the relationship between cortical activation and the other indicators on the PIPP. However, including adjustment for contextual factors for infants born at earlier gestational ages or for infants in deep sleep states lowered the correlations [46]. It is worth noting that almost a third of infants in the study showed cortical activation to pain, but did not show facial responses. Typically, the lack of facial grimacing is associated with extremely low gestational age at the time of assessment. Therefore, the PIPP scale adjusts for low gestational age in assessing pain. However, preterm infants who have been in the NICU longer and, as a result, have had repeated exposure to noxious stimuli, show dampened facial responses even at 32 weeks postconceptual age, long after the very early period when behavioral responses are less frequently observed [6,74,75]. Research with NIRS or EEG, together with behavioral and autonomic recordings, is expected to shed light on whether dampened reactivity to acute pain is an adaptive response to maintain physiological stability or is a suppression of facial behaviors only.

The BIIP scale was developed to include hand movements, developmentally relevant for the infants at early gestational ages who often have diminished facial responses [24,25]. Research is needed to determine at a central brain level whether or not these specific hand movements will identify pain in those infants who have reduced facial responses, thereby adding precision to the assessment of pain. In addition, although changes in physiological indices did not correlate as strongly with cortical activation [46], measuring physiological along with behavioral indices to capture rapid shifts in autonomic regulation that reflect instability is essential. With the immature autoregulation of cerebral blood flow in these infants, recording shifts in cardiac rate that can accompany acute pain should be a key part of pain assessment. However, it is surprising but important that the NIRS response was largely independent of cardiac changes. Furthermore, inclusion of behavioral and physiological parameters that are measured separately is critical since there is compelling

evidence that behavioral but not physiological responses are decreased by some types of pain management, such as sucrose, which suggests sedative but not analgesic effects [76]. Finally, careful consideration of the context of the assessment is important in the interpretation of activation in the somatosensory cortex when evaluated by NIRS. As mentioned previously, the context of the assessment is vital because, as has been recently demonstrated, hemodynamic changes during a painful event may be related to factors other than pain. For example, in adults undergoing cardiac surgery under anesthesia, changes in regional oxygen saturation were observed during sternotomy [77]. These changes were likely to have been the result of changing chest wall dynamics, which affected blood pressure.

Conclusion & future perspective

Over the past 20 years, a multitude of pain assessment tools have been developed for measuring pain in infants cared for in the NICU. Unfortunately, the enthusiasm to develop the scales has not been maintained to ensure that complete psychometric testing is performed. Furthermore, many studies have not used appropriate theoretical models to determine the developmentally relevant, relatively specific pain indicators in this population. Until recently, researchers and clinicians have relied upon recordings of behavioral and physiological responses that are proxy measures for pain. Further improvements in both NIRS and EEG technology will enable more accurate measurement of cortical somatosensory activation. However, a major gap exists in our understanding of what brain activation means. We have yet to determine whether or not activation in the neonatal brain in different locations is similar to that of adult brain activation. In older children and adults, compelling evidence shows that perceived pain does not directly reflect physiologic reactivity; indeed, cognitive and emotional factors are key for the self-description of pain. For preterm infants, the primary objective is to protect the brain from damaging neuronal excitation that may impact neurodevelopment. In this context, NIRS and EEG can provide important adjuncts to the assessment of cortical pain activation. However, evidence that some somatosensory activation occurs in adults who are appropriately anesthetized during surgery (as reflected by NIRS) should caution us from making definite conclusions [77]. However, despite the lack of definitive data describing whether or not somatosensory responses mirror pain perception in the neonate, given the limited capacity of the immature preterm infant to self-regulate blood flow to the brain and the vulnerability to brain insult, further exploration of the neonatal somatosensory response using NIRS or EEG has important potential for the assessment of developmentally relevant behaviors and of autonomic indicators of pain.

With respect to clinical practice and research, brain-based assessment such as NIRS and EEG will not replace bedside tools to measure pain. As of yet, no substitute exists for the judgment of an experienced clinician who can take into account the full context of the assessment including previous medical history, current physiological status and the impact of the environment. Further work is needed to determine the specificity and sensitivity of these technologies for measuring acute pain. Then these technologies can be evaluated for their potential to measure pain in different contexts, such as postoperative pain and other ongoing pain conditions.

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Practice Points

- Pain assessment in preterm infants is complex because their responses can differ from those of term infants.
- Pain assessment tools can be classified as either uni- or multidimensional depending on the type of indicators included in each scale.
- A number of uni- and multidimensional pain assessments are available for use in the neonatal intensive care unit, but in addition to inadequate psychometric testing, most do not incorporate developmentally relevant cues for preterm infants.
- Near-infrared spectroscopy and EEG are technologies that may allow complementary assessment of pain processing at a cortical level.
- Complementary use of these brain-oriented technologies with assessment measures will permit evaluation of pain parameters, providing an additional way to test the validity of pain indices.
- More accurate pain assessment tools will help in devising strategies to reduce pain in premature infants.
- The first steps will be to validate acute pain measures. While prolonged pain is more challenging, applying these technologies during postoperative pain will lead to evaluation of indices for sustained pain.