Defining pain in newborns: need for a uniform taxonomy?
Kanwaljeet J. S. Anand (anandam@stanford.edu)
Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA

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Correspondence
Prof. K. J. S. Anand, Department of Pediatrics, Stanford University School of Medicine, 770 Welch Road, Suite 435, Stanford, CA 94304 MC: 5876, USA.
Tel: (650) 498-6313 | Fax: (650) 736-9186 | Email: anandam@stanford.edu

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ABSTRACT
A framework for defining pain terms such as acute, persistent, prolonged or chronic pain to newborns was derived from the scientific literature on neonatal pain assessments, previous attempts to define chronic pain and the clinical and neurophysiological features of neonatal pain. This novel framework incorporates the temporal features, localising characteristics, and secondary effects of the pain experienced, as well as the behavioural and physiological response patterns of newborns.

Conclusion: Although not evidence-based, this framework provides an initial starting point for defining commonly used neonatal pain terms. It will require future revision/refinement based on the accumulating evidence for non-acute pain.

‘Ideas need to be fruitful; they do not have to be right. And, curiously enough, the two do not necessarily go together.’ (1) Peter W. Nathan, MD, FRCP (1914–2002).

A scientific rationale for pain and its effects in human newborns were first presented thirty years ago (2). Multidisciplinary efforts have since fuelled significant progress in neonatal pain (3), exploring its underlying mechanisms (4,5), describing its epidemiology in clinical settings (6,7), defining its impact on the brain and subsequent development (8,9) or devising clinical assessment and management approaches (10,11). Despite this progress, defining and identifying pain in newborns remains a major challenge. Descriptors such as acute, persistent, prolonged or chronic pain are often used interchangeably for newborns, without clear definitions for these terms. Explicit definitions may help reduce confusion and controversy among clinicians, improve assessment and management and inform study designs in neonatal pain research.

The International Association for the Study of Pain (IASP) defined pain as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage’ (IASP Committee on Taxonomy, 1969, updated in 1994 and 2002) (12). This definition requires patients to describe their pain, by default establishing the primacy of self-report as a ‘gold standard’. Although widely accepted across all healthcare professions and biomedical disciplines, this definition lacks applicability to non-verbal populations (13,14) and ignores the cognitive and social dimensions of pain (15). Indeed, pain in newborns was often discounted until the IASP...
Committee on Taxonomy added a note clarifying that, ‘The inability to communicate verbally does not negate the possibility that an individual is experiencing pain’ (16).

The question of conscious pain perception in the early preterm newborn (or foetus) has been hotly debated (17–22), mainly because of its social, ethical and legal implications (23–26). Consciousness was widely believed to reside in the cerebral cortex, thus putatively being absent or rudimentary in those without functional thalamocortical connections (20,26), although mechanisms underlying the subcortical control of consciousness (27–29) and functionality of the subplate zone (30–33) appear to challenge that default. Attempting to set forth criteria for early human consciousness would create the difficulties of ‘measuring’ consciousness and the conundrums of trying to prove or disprove whether consciousness is present at different stages of development (34,35). For the purpose of this review, it is presumed that all viable newborns are capable of consciously perceiving and responding to pain (13,14,36,37).

Given the absence of self-report, pain assessment in newborns is challenging, particularly among ventilated preterm infants with a limited behavioural repertoire. Although numerous pain assessment methods have been devised, validated and implemented in clinical care (38,39), most are focused on the acute, episodic pain resulting from clinically essential, frequently performed invasive procedures. Hartley et al. recently presented an EEG-based measure of nociceptive brain activity evoked by acute noxious stimulation and reduced by a topical anaesthetic (40). This too applies only to acute pain, requires specialised expertise, equipment and analytic capabilities and has a relatively low sensitivity (57%, 64%) and specificity (65%, 68%) to be clinically useful (40).

The need to differentiate acute from prolonged pain was first proposed at the 8th World Congress on Pain (41), and an expert panel later recognised the ability of newborns to experience prolonged/chronic pain (42). To the clinician-researcher, acutely painful events in newborns clearly appeared to cause pain-related distress and could be standardised for research. Clinical examples of prolonged or persistent pain were harder to study—they defied quantification, occurred less frequently, and did not elicit reproducible responses in newborns (43,44). Not surprisingly, therefore, only 10% of newborns in neonatal intensive care units (NICUs) received daily clinical assessments for prolonged, continuous pain (11).

Attempts to define chronic pain in the neonatal context have contributed greatly to our current understanding of pain in infancy (45,46). A few methods to assess the intensity of prolonged/chronic pain were devised and validated (Table 1), but given the absence of clear definitions, other aspects specific for chronic pain (duration, periodicity, character or secondary effects) have not been addressed. Despite these gaps, clinicians are using therapies normally reserved for chronic pain in newborns without any clear indications (47–50), or assessment of short-term and long-term risk/benefit ratios. Most clinicians can easily identify examples of persistent pain following tissue injury (circumcision, other post-operative pain) or inflammation (necrotizing enterocolitis, pyelonephritis), as well as examples of chronic pain (osteoogenesis imperfecta, epidermolysis bullosa), but a consensus for developing the taxonomy of pain terms specifically for newborns remains elusive (45,46,51).

For adults, various professional societies define acute pain as that associated with tissue injury, whereas chronic pain is defined as pain that extends beyond the period of tissue healing, with levels of pathology insufficient to explain the presence and/or extent of pain. Pain signals may remain active for months or years, causing a ‘persistent pain that disrupts sleep and normal living, ceases to have protective functions, and instead degrades health and functional capability’(12,52,53). Turk and Okifuji differentiated acute and chronic pain using criteria for duration and pathology, short-lasting pain with high physical pathology reflects acute pain, whereas prolonged durations with low pathology represent chronic pain (54). However, most chronic pain conditions in adults represent an interplay between significant nociceptive inputs and psychosocial/cognitive factors (55). The ‘expected healing period’ for defining transitions from acute to chronic pain is variably pegged at one, three or six months (12,52–54,56).

Such time-points clearly exclude newborn infants who have not lived long enough to experience chronic pain, whereas the examples for chronic pain commonly cited by clinicians (e.g. epidermolysis bullosa) usually portend some kind of ongoing tissue pathology (45,46). Also, diseases associated with prolonged pain in newborns (e.g. necrotizing enterocolitis) may have variable and undefined durations of tissue pathology. An empirical approach may be justified therefore, for defining the pain terms commonly used in neonatal care. Putative definitions for acute, prolonged, persistent or chronic pain must be explicit and relevant to the transient newborn period; they must represent the types of pain being experienced, independent of their aetiology or management.

Limited evidence supports management of chronic or persistent pain in neonates, so why do definitions matter at all? We argue that defining an infant’s pain would justify a bedside clinician’s level of concern, focus their attention towards specific assessment methods and allow them to weigh the risks/benefits of appropriate interventions. Pain definitions will also stimulate further advances to: understand the epidemiology of neonatal pain, investigate the underlying mechanisms at different levels of neurologic maturity, identify biomarkers/patterns for psychophysical or molecular phenotyping, recognise genetic, epigenetic or other factors that place infants at high risk for poor outcomes or long-term complications and lastly, develop targeted therapies for specific types of non-acute pain (15,54). Most clinical trials chose their subjects based on a few selected clinical characteristics, which may or may not match individual newborns with the therapies uniquely suited for their pain. Thus, inclusion criteria incorporating explicit pain definitions may improve homogeneity in
Table 1: Previous studies on persistent or chronic pain in newborns

| Authors, Year | Study design | Number of subjects | Number of observations | Age group(s) | Male/Female | Comparators | Assessment method | Stimulus studied | Parameters/Findings | Validation | Reliability | Internal consistency |
|---------------|-------------|--------------------|------------------------|--------------|-------------|-------------|-------------------|-------------------|---------------------|------------|-------------|----------------------|
| Krichel & Bildner, 1995 (86) | Observational study | 24 | 76 | 32–60 weeks PCA | N/A | None | CRIES Pain Scale | Various surgical procedures (Ipsplacement to PDA closure) | Facial expression (grimace) | Convergent: $R_s = 0.73$, $p < 0.0001$ | N/A | Interm: $R_s = 0.72$, $p < 0.0001$ | Cronbach’s $x$ coefficient = 0.92 |
| Debillon et al., 2001 (93) | Staff survey, observational study | 76 | 89 | 25–36 weeks GA | N/A | N/P | NEOPAIN Scale | Mechanical ventilation, NEC, surgical closure of PDA | Facial activity | Discriminant: scores decreased 4.4 (0.4) pre- vs. post-analgesia, $p < 0.0001$ | N/A | Interm: weighted $x$ coefficients = 0.59–0.74 (0.69) | N/A |
| Boyle et al., 2006 (43) | Staff survey, within an ongoing RCT | 46 | 72 | 23–32 weeks GA | N/A | N/P | N/P | Mechanical ventilation | Facial expressions | Discriminant: scores decreased 3.0 pre- vs. post-analgesia, $p < 0.0001$ | N/A | Interm: weighted $x$ coefficients = 0.59–0.74 (0.69) | N/A |
| Hummel et al., 2008 (87,94) | Observational study | 286 | 3600 | 23–40 weeks GA | N/A | N/P | N/P | Mechanical ventilation, various surgical procedures | Facial expressions | Discriminant: scores decreased 3.05 pre- vs. post-analgesia, $p < 0.0001$ | N/A | Interm: weighted $x$ coefficients = 0.59–0.74 (0.69) | N/A |
| van Dijk et al., 2009 (95) | Observational studies, survey | 246 | 525 | 21/25 | N/A | N/P | N/P | Acute procedural | Facial activity | Discriminant: scores decreased 4.4 (0.4) pre- vs. post-analgesia, $p < 0.0001$ | N/A | Interm: weighted $x$ coefficients = 0.59–0.74 (0.69) | N/A |
| Lundqvist et al., 2014 (96) | Observational study | 86 | 294 | 23–29 weeks GA | N/A | N/P | N/P | Acute procedural | Facial activity | Discriminant: scores decreased 3.0 pre- vs. post-analgesia, $p < 0.0001$ | N/A | Interm: weighted $x$ coefficients = 0.59–0.74 (0.69) | N/A |
| van Ganzewinkel et al., 2014 (45) | Delphi survey, three rounds | N/A | N/A | N/A | N/A | N/P | N/P | Post-operative or mechanical ventilation | N/A | N/A | N/A |

ALPS-Neo = Astrid Lindgren’s Children’s Hospital Pain Scale; BP = Blood pressure; CRIES = Crying, Requires oxygen, Increased vital signs, Expression, Sleepless; EDIN = Echelle Douleur Inconfort Nouveau-Né; GA = Gestational age; HR = Heart rate; ICC = Intraclass correlation coefficient; NEC = Necrotizing enterocolitis; N-PASS = Neonatal Pain, Agitation and Sedation Scale; N/A = not available; PCA = Post-conceptional age; PDA = Patent ductus arteriosus; $R_s$ = Spearman rank correlation coefficient; $r$ = Pearson moment correlation coefficient; RCT = Randomised controlled trial; RR = Respiratory rate; SpO$_2$ = Peripheral oxygen saturation.
clinical trials. As an initial starting point for defining the different pain terms used for newborns (Table 2), we should consider the following:

**Temporal features**

Any painful experience is defined by its onset and duration, exemplifying the salient differences between acute and non-acute pain. Acute pain occurs immediately with the onset of tissue injury or stimulation of an inflamed area, and it usually lasts for the duration of the stimulus or for brief periods thereafter (some infants experience a slower decay of pain compared to others). However, the durations assigned for acute, prolonged, persistent or chronic pain are arbitrary at best. In adults, some experts classify pain lasting longer than one month as chronic pain, whereas others consider pain as chronic only if it lasts for longer than three or six months (12,52–54). Similarly, variable criteria are used for children (56,57). Given the temporal characteristics of painful conditions in newborns, the length of the neonatal period, as well as time-courses for developing long-term effects of pain, tolerance to analgesic drugs or other systemic effects, we posit that pain lasting longer than seven days be considered as chronic pain in newborns. This should prompt further diagnostic efforts, re-evaluation of current analgesic strategies, use of alternative therapies and longer-term plans for preventing disability, promoting rehabilitation and restoring function.

**Character of pain**

For obvious reasons, precise descriptors cannot be chosen for the character of pain (e.g. burning, piercing and shooting) that newborns experience, but clinicians may attempt to discern how well it is localised, or whether it is associated with clear boundaries or not. In the developing nervous system, two features characterise neonatal pain processing: (i) the immature peripheral and central nervous systems are biologically primed towards lower thresholds for activation, excitation and transmission of nociceptive stimuli as compared to older ages; this feature is further accentuated in preterm infants (5,51); (ii) dorsal horn neurons in the spinal cord have large, overlapping cutaneous receptive fields; stimulation of these receptive fields heightens nociceptive signalling and can evoke a long-lasting excitability within the spinal cord (58–60). Indeed, inhibitory signalling in the spinal cord is weak or absent in newborns and develops gradually during infancy (61,62). These features are likely to promote poorer localisation of pain in newborns, while also heightening its secondary effects.

**Secondary effects**

Tissue injury or inflammation leads to secondary effects such as hyperalgesia (increased pain to a stimulus that is normally painful) and allodynia (pain due to stimuli that do not normally provoke pain). Primary hyperalgesia localises to the area of tissue damage, whereas secondary hyperalgesia occurs in normal areas remote from the site of tissue damage. Despite their biological plausibility (5,61,63,64), limited clinical evidence supports these phenomena in human newborns. Fitzgerald et al. reported primary hyperalgesia following heel lances in newborns and its reversal with topical anaesthetic cream (65), whereas Taddio et al. reported secondary hyperalgesia to venipuncture in one-day-old newborns of diabetic mothers, who had received multiple heel lances for monitoring blood glucose levels (66). Similarly, Andrews et al. reported signs of visceral and somatic hyperalgesia in infants undergoing abdominal surgery (67,68). Allodynia has not been investigated in neonates with prolonged or

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**Table 2** Suggested starting point for defining the pain terms used for neonatal pain

| Pain term      | Onset          | Duration               | Charactera                       | Primary hyperalgesia                      |
|----------------|----------------|------------------------|-----------------------------------|------------------------------------------|
| Acute episodic | Immediate      | 0–120\(^b\) minutes   | Sharp, well-localised             | Present, mild, short-lasting             |
| Acute recurrent| Immediate      | variable               | Sharp, well-localised             | Present, moderate or severe              |
| Prolonged\(^c\) | Rapid, may be gradual | One hour to 24\(^b\) hours | Sharp, diffusely localised       | Present, moderate or severe              |
| Persistent\(^f\) | Rapid or gradual, cumulative | one to seven days | Dull/sharp, diffusely localised | Present, moderate or severe              |
| Chronic        | Usually gradual | Eight days or longer   | Dull, diffusely localised         | May be present or absent, mild if present |

| Pain term      | Secondary hyperalgesia | Allodynia | Behavioural phenotype | Physiological phenotype |
|----------------|------------------------|-----------|-----------------------|-------------------------|
| Acute episodic | Probably absent         | Probably absent | Strongly reactive and reflexive | High peak, sympathetic activation |
| Acute recurrent| Present, mild or moderate | Probably absent | Weakly reactive or reflexive | Prolonged peak, sympathetic activation |
| Prolonged\(^c\) | Mild or absent          | Probably absent | Strongly reactive on stimulation | High plateau, sympathetic activation |
| Persistent\(^f\) | Present, mild or moderate | May be present, mild/moderate | Hyperreactive initially, later hyporeactive | Normal or low sympathetic activation |
| Chronic        | Present, moderate or severe | May be present, moderate/severe | Hyperreactive more often, could also be hyporeactive | Normal or suppressed sympathetic drive |

\(^a\)Based on descriptions in adult patients, but may be discerned by a careful physical examination.

\(^b\)Some infants with increased sensitivity to pain may have a slower decay of the acute pain following an invasive procedure, thus justifying some overlap in the durations of acute episodic pain and prolonged pain.

\(^c\)Continuous pain may be characterised as either ‘prolonged’ or ‘persistent’.
persistent pain, although it may be more likely in infants with neurologic impairment (47–50) or in those experiencing opioid withdrawal (69,70). A developmental allodynia appears to exist in preterm neonates (71–75) (but not term neonates (76)), manifesting as similar responses to non-noxious and noxious stimuli. Standardised tests for allodynia need to be developed and performed in newborns with persistent or chronic pain.

Response patterns
The physiological and behavioural responses to acute pain are well characterised in newborns and used for pain assessments (38). Assessment methods developed from models of prolonged or chronic pain also show considerable overlap in the parameters chosen (Table 1), and some of these are different from acute pain (77). In older children, chronic pain is often associated with fatigue, insomnia, impaired cognition or executive function, physical disabilities and mood disturbances (56,57,78). These may be absent or difficult to assess in newborns, particularly among those receiving neonatal intensive care (45,46,51). Behavioural responses generally manifest as ‘distress’ (38,79), varying in severity and incorporating facial expressions (80), gross body movements (81,82) and subtle movement of hands, fingers or toes (81,83). Physiological responses are incorporated into most assessment scales for acute pain, measuring increased sympathetic activity (38) (and lower parasympathetic tone? (84,85)). Although scales such as CRIES (86) and N-PASS (87) do include changes in vital signs, it is arguable whether neonates facing acute procedural pain versus chronic pain will show similar changes in vital signs. An increased sympathetic drive may not occur in chronic or persistent pain. Heart rate variability, for example, increases during acute pain but is diminished in response to persistent or chronic pain (88,89).

Could the spectrum of rehabilitative interventions used for adult chronic pain be analogous to the behavioural and environmental interventions advocated for newborn care? These include everything from relationship-based models of nursing to management of temperature, light, sound, and circadian rhythms, kangaroo care, sensorial saturation and other interventions (90). As with adults in chronic pain, many drug-based interventions may have unforeseen benefits and potential harms in newborns. Because of their greater potential for short-term and long-term adverse effects in infants (91,92), we should consider the importance of investigating behavioural and environmental interventions for infant chronic pain as possibly safer than drug therapies (47–50). Although future research will determine novel ways for assessing acute versus non-acute pain in newborns, an empirical framework is proposed to help define various types of neonatal pain. Putative criteria may evolve from this framework, eventually leading to more accurate methods for studying the diverse types of pain experienced by human newborns.

CONFLICT OF INTEREST
The author has no conflicts of interest related to this article.

References
1. Nathan PW. The gate-control theory of pain. A critical review. Brain 1976; 99: 123–58.
2. Anand KJS, Hickey PR. Pain and its effects in the human neonate and fetus. N Engl J Med 1987; 317: 1321–9.
3. Walker SM. Neonatal pain. Paediatr Anaesth 2014; 24: 39–48.
4. Fitzgerald M. The development of noiceptive circuits. Nat Rev Neurosci 2005; 6: 507–20.
5. Walker SM, Beggs S, Baccei ML. Persistent changes in peripheral and spinal nociceptive processing after early tissue injury. Exp Neurol 2016; 275(Pt 2): 253–60.
6. Carbalaj R, Rousset A, Danan C, Coquery S, Nolent P, Ducrocq S, et al. Epidemiology and treatment of painful procedures in neonates in intensive care units. JAMA 2008; 300: 60–70.
7. Lago P, Boccuzzo G, Garetti E, Pirelli A, Pieragostini L, Merazzi D, et al. Pain management during invasive procedures at Italian NICUs: Has anything changed in the last five years? J Matern Fetal Neonatal Med 2013; 26: 303–5.
8. Schwaller F, Fitzgerald M. The consequences of pain in early life: injury-induced plasticity in developing pain pathways. Eur J Neurosci 2014; 39: 344–52.
9. Vinall J, Grunau RE. Impact of repeated procedural pain-related stress in infants born very preterm. Pediatr Res 2014; 75: 584–7.
10. Carbalaj R, Eriksson M, Courtos E, Boyle E, Avila-Alvarez A, Andersen RD, et al. Sedation and analgesia practices in neonatal intensive care units (EUROPAIN): results from a prospective cohort study. Lancet Respir Med 2015; 3: 796–812.
11. Anand KJS, Eriksson M, Boyle EM, Avila-Alvarez A, Andersen RD, Sarafidis K, et al. Assessment of continuous pain in newborns admitted to NICUs in 18 European countries. Acta Paediatr 2017; 106: 1248–59.
12. Merskey H, Bogduk N. Task force on taxonomy: classification of chronic pain: descriptions of chronic pain syndromes and definition of pain terms, 2nd Edition. Seattle, WA: IASP Press, 1994.
13. Anand KJS, Craig KD. New perspectives on the definition of pain. Pain 1996; 67: 3–6; discussion 209–11.
14. Anand KJS, Rovnaghi C, Walden M, Churchill J. Consciousness, behavior, and clinical impact of the definition of pain. Pain Forum 1999; 8: 64–73.
15. Williams AC, Craig KD. Updating the definition of pain. Pain 2016; 157: 2420–3.
16. IASP. Pain terms, a current list with definitions and notes on usage. IASP task force on taxonomy. Seattle, WA: IASP Press, 2002.
17. Anand KJS, Maze M. Fetuses, fentanyl, and the stress response: signals from the beginnings of pain? Anesthesiology 2001; 95: 823–5.
18. Bellieni CV. Pain assessment in human fetus and infants. AAPS J 2012; 14: 456–61.
19. Lagercrantz H, Changeux JP. The emergence of human consciousness: from fetal to neonatal life. Pediatr Res 2009; 65: 255–60.
20. Lee SJ, Ralston HJ, Drey EA, Partridge JC, Rosen MA. Fetal pain: a systematic multidisciplinary review of the evidence. JAMA 2005; 294: 947–54.
21. Reissland N, Francis B, Mason J. Can healthy fetuses show facial expressions of "pain" or “distress”? PLoS ONE 2015; 8: e65530.
22. Derbyshire SW. Foetal pain? Best Pract Res Clin Obstet Gynaecol 2010; 24: 647–55.
23. Williams C. Framing the fetus in medical work: rituals and practices. Soc Sci Med 2005; 60: 2085–95.
24. Cohen IG, Sayeed S. Fetal pain, abortion, viability, and the constitution. J Law Med Ethics 2011; 39: 235–42.
25. Brugger EC. The problem of fetal pain and abortion: toward an ethical consensus for appropriate behavior. Kennedy Inst Ethics J 2012; 22: 263–87.
26. Lagercrantz H. The emergence of consciousness: science and ethics. Semin Fetal Neonatal Med 2014; 19: 300–5.
27. Anand KJS. Fetal pain? Pain Clin Updates 2006; XIV: 1–4.
28. Merker B. Consciousness without a cerebral cortex: a challenge for neuroscience and medicine. Behav Brain Sci 2007; 30: 63–81; discussion -134.
29. Aleman B, Merker B. Consciousness without cortex: a hydranencephaly family survey. Acta Paediatr 2014; 103: 1057–65.
30. Perkins L, Hughes E, Srinivasan L, Allsop J, Glover A, Kumar S, et al. Exploring cortical subplate evolution using magnetic resonance imaging of the fetal brain. Dev Neurosci 2008; 30: 211–20.
31. Moore AR, Zhou WL, Jakovcevski I, Zecevic N, Antic SD. Fetal pain, abortion, viability, and the constitution. J Law Med Ethics 2011; 39: 235–42.
32. Kostovic I, Jovanov-Milosevic N, Rados M, Sedmak G, Benjak V, Kostovic-Srzentic M, et al. Perinatal and early postnatal reorganization of the subplate and related cellular compartments in the human cerebral wall as revealed by histological and MRI approaches. Brain Struct Funct 2014; 219: 231–53.
33. Gatti MG, Becucci E, Fargnoli F, Fagioli M, Aden U, Buonocore G. Functional maturation of neocortex: a base of viability. J Matern Fetal Neonatal Med 2012; 25(Suppl 1): 101–3.
34. Hudson AJ. Consciousness: physiological dependence on rapid memory access. Front Biosci (Landmark Ed) 2009; 14: 2779–800.
35. Goupil L, Kouider S. Behavioral and neural indices of metacognitive sensitivity in preverbal infants. Curr Biol 2016; 26: 3038–45.
36. Bartocci M, Bergqvist LL, Lagercrantz H, Anand KJS. Pain activates cortical areas in the preterm newborn brain. Pain 2006; 122: 109–17.
37. Bartocci M, Anand KJS, Lagercrantz H. Response to David Bowsher’s comment: the hump from cerebral neurovascular events to the subjective experience of pain in neonates. Pain 2006; 126: 320–2.
38. Hatfield LA, Ely EA. Measurement of acute pain in infants: a review of behavioral and physiological variables. Biol Res Nurs 2015; 17: 100–13.
39. Stevens B, Gibbins S. Clinical utility and clinical significance in the assessment and management of pain in vulnerable infants. Clin Perinatol 2002; 29: 459–68.
40. Hartley C, Duft EP, Green G, Mellado GS, Worley A, Rogers R, et al. Nociceptive brain activity as a measure of analgesic efficacy in infants. Sci Transl Med 2017; 9: pii: eaah6122.
41. Anand KJS. Long-term effects of pain in neonates and infants. In: TS Jensen, JA Turner, Z Wiesenfeld-Hallin, editors. Proceedings of the 8th World congress on pain. Seattle: IASP Press, 1997: 881–92.
42. Anand KJS, Aranda JV, Berde CB, Buckman S, Capparelli EV, Carlo W, et al. Summary proceedings from the neonatal pain-control group. Pediatrics 2006; 117: S9–22.
43. Boyle EM, Freer Y, Wong CM, McIntosh N, Anand KJS. Assessment of persistent pain or distress and adequacy of analgesia in preterm ventilated infants. Pain 2006; 124: 87–91.
44. Fitzgerald M. What do we really know about newborn infant pain? Exp Physiol 2015; 100: 1451–7.
45. van Ganzewinkel CJ, Anand KJS, Kramer BW, Andriessen P. Chronic pain in the newborn: toward a definition. Clin J Pain 2014; 30: 970–7.
65. Fitzgerald M, Millard C, McIntosh N. Cutaneous hypersensitivity following peripheral tissue damage in newborn infants and its reversal with topical anaesthesia. *Pain* 1989; 39: 31–6.

66. Taddio A, Shah V, Gilbert-MacLeod C, Katz J. Conditioning and hyperalgesia in newborns exposed to repeated heel lances. *JAMA* 2002; 288: 857–61.

67. Andrews K, Fitzgerald M. Wound sensitivity as a measure of analgesic effects following surgery in human neonates and infants. *Pain* 2002; 99: 185–95.

68. Andrews KA, Desai D, Dhillon HK, Wilcox DT, Fitzgerald M. Abdominal sensitivity in the first year of life: comparison of infants with and without prenatally diagnosed unilateral hydronephrosis. *Pain* 2002; 100: 35–46.

69. Sweitzer SM, Allen CP, Zissen MH, Kendig JJ. Mechanical allodynia and thermal hyperalgesia upon acute opioid withdrawal in the neonatal rat. *Pain* 2004; 110: 269–80.

70. Zissen MH, Zhang G, McKelvy A, Propst JT, Kendig JJ, Sweitzer SM. Tolerance, opioid-induced allodynia and withdrawal associated allostody in infant and young rats. *Neuroscience* 2007; 144: 247–62.

71. Slater R, Fabrizi L, Worley A, Meek J, Boyd S, Fitzgerald M. Premature infants display increased noxious-evoked neuronal activity in the brain compared to healthy age-matched term-born infants. *NeuroImage* 2010; 52: 583–9.

72. Fabrizi L, Slater R, Worley A, Meek J, Boyd S, Olhede S, et al. A shift in sensory processing that enables the developing human brain to discriminate touch from pain. *Curr Biol* 2011; 21: 1552–8.

73. Cornelissen L, Fabrizi L, Patten D, Worley A, Meek J, Boyd S, et al. Postnatal temporal, spatial and modality tuning of nociceptive cutaneous flexion reflexes in human infants. *PLoS ONE* 2013; 8: e76470.

74. Goksan S, Hartley C, Emery F, Cockrill N, Poorn R, Moultrie F, et al. fMRI reveals neural activity overlap between adult and infant pain. *eLife* 2015; 4: e06356.

75. Holsti L, Grunau RE, Oberlander TF, Whitfield MF. Prior pain induces heightened motor responses during clustered care in preterm infants in the NICU. *Early Hum Dev* 2005; 81: 293–302.

76. Verriots M, Fabrizi L, Lee A, Cooper RJ, Fitzgerald M, Meek J. Mapping cortical responses to somatosensory stimuli in human infants with simultaneous near-infrared spectroscopy and event-related potential recording. *eNeuro* 2016; 3: pii: e0026-16.2016.

77. Hadjistavropoulos HD, Craig KD, Grunau RE, Whitfield MF. Judging pain in infants: behavioural, contextual, and developmental determinants. *Pain* 1997; 73: 319–24.

78. Kashikar-Zuck S, Carle A, Barnett K, Goldschneider KR, Sherry DD, Mara CA, et al. Longitudinal evaluation of patient-reported outcomes measurement information systems measures in pediatric chronic pain. *Pain* 2016; 157: 339–47.

79. Valitato PA, van Dijk M, Krekels EH, Gibbins S, Simons SH, Tibboel D, et al. Pain and distress caused by endotracheal suctioning in neonates is better quantified by behavioural than physiological items: a comparison based on item response theory modelling. *Pain* 2016; 157: 1611–7.

80. Heiderich TM, Leslie AT, Guinsburg R. Neonatal procedural pain can be assessed by computer software that has good sensitivity and specificity to detect facial movements. *Acta Paediatr* 2015; 104: e63–9.

81. Morison SJ, Holsti L, Grunau RE, Whitfield MF, Oberlander TF, Chan HW, et al. Are there developmentally distinct motor indicators of pain in preterm infants? *Early Hum Dev* 2005; 72: 131–46.

82. Holsti L, Grunau RE, Oberlander TF, Osioch H. Is it painful or not? Discriminant validity of the Behavioral Indicators of Infant Pain (BIIP) scale. *Clin J Pain* 2008; 24: 83–8.

83. Grunau RE, Holsti L, Whitfield MF, Ling E. Are twitches, startles, and body movements pain indicators in extremely low birth weight infants? *Clin J Pain* 2000; 16: 37–45.

84. Weissman A, Aranowitch M, Blazer S, Zimmer EZ. Heel-lancing in newborns: behavioral and spectral analysis assessment of pain control methods. *Pediatrics* 2009; 124: e921–6.

85. Franck LS, Boyce WT, Gregory GA, Jemerin J, Levine J, Miaskowski C. Plasma norepinephrine levels, vagal tone index, and flexor reflex threshold in premature neonates receiving intravenous morphine during the postoperative period: a pilot study. *Clin J Pain* 2000; 16: 95–104.

86. Kerek J, Sander J, Deppe F, et al. N-PASS assessment tool with acute pain. *Clin J Pain* 2010; 26: 55–60.

87. de Jesus JA, Tristao RM, Storm H, da Rocha AF, Campos DJ, Hendricks J, et al. Heart rate, oxygen saturation, and skin conductance: a comparison study of acute pain in Brazilian newborns. *Conf Proc IEEE Eng Med Biol Soc* 2011; 2011: 1875–9.

88. De Jonckheere J, Rakza T, Logier R, Jeanne M, Jounwaz R, et al. Are there developmentally distinct motor indicators of pain in preterm infants? Discriminant validity of the Behavioral Indicators of Infant Pain (BIIP) scale. *Pain* 2005; 81: 293–302.