‘Neonates do not feel pain’: a critical review of the evidence

Amy Marchant*

Faculty of Biological Sciences, University of Leeds, UK

*Corresponding author: Email: amymarchant@ymail.com

Supervisor: Dr Anne King, Faculty of Biological Sciences; University of Leeds, UK.

Up until 1985, the nervous system of the neonate was widely considered to be underdeveloped for pain sensation. Analgesia to alleviate distress from ‘painful’ procedures in which neonates were, and still are, subject to was often considered trivial. Pain in the neonate and (in some cases) the disabled neonate is especially hard to investigate, as they are unable to verbally communicate. There is also no known direct biological marker of pain, only behavioural and stress-related physiological correlates. This critical review gives evidence for and against the hypothesis ‘Neonates do not feel Pain’. Evidence of both the neonatal response to analgesics and long-term effects of neonatal pain are also investigated, with the aim of further supporting or falsifying the hypothesis. Convergence of the observations covered in this review show that most, if not all, studies are in favour of pain-related behaviour and physiology in the neonate, both of which having a similar phenotype to that seen in the older infant and adult. The evidence investigated in this review also supports the hypothesis that cortical development appears to accommodate the subjectivity of pain, but it is not vital for pain experience. Further data and theory have the potential to bring more invaluable evidence to the table regarding whether or not the neonate is able to feel pain.

Key words: neonate, pain, behaviour, physiology, cognition, analgesia

Received 5 December 2013; accepted 13 June 2014

Introduction

Hypothesis: ‘Neonates do not feel pain’

During the vulnerable neonatal period from birth onwards in which forced immobilization, feeding tube insertion, heel lance and other such invasive procedures often take place (Carbajal et al., 2008), one would assume that pain sensitivity is greatest. Up until the late 1980s, however, it was widely considered among clinicians that neonatal pain experience was non-existent due to the belief that they were undeveloped and incapable (Owens and Todt, 1984). The 20th century appeared to be a time in which clinicians were more concerned about foetal distress. This is reflected by the significant lack of studies from 1920 until 1980 investigating pain in the neonate; curare often being used as a surgical muscular paralysis agent up until 1985, making pain-related protest or movement impossible regardless of its existence (Cote, Lerman and Todres, 2009). This dry spell in neonatal pain research was alleviated in 1980, with a study by Anand et al. (1985) leading to the observation of pain-induced responses and death due to endocrine shock during neonatal surgery, emphasizing the importance of anaesthesia. Convergence in human and animal study data has led to recent advances in the field of neonatal pain (Johnston and Walker, 2003).

Despite many findings pointing towards some kind of unpleasant sensation being felt in the neonate on administration of noxious stimuli, conflicting experimental results (potentially due to the subjective nature of whether or not we think a subject is in pain, for example) still prevail in the discussion of neonatal pain. The significant limitations of pain research such as the inability of neonates (and often the handicapped) to verbally vocalize whether or not they are in pain can often lead to contrasting ideas. In addition, only...
non-invasive, medically necessary methods of pain induction are permitted in humans (as per the ethical restrictions laid down by the International Association for the Study of Pain (2013)). Direct quantitative measurement of pain is also not possible due to the lack of pain ‘centre’ and biological marker; therefore, objective indicators such as self-report (in adults) and facial expressions (in neonates such as brow bulge, crease and furrow) are heavily relied upon (Grunau and Craig, 1987). Some physiological correlates, however, can often be indicative of the experience, such as respiration, heart rate and serum cortisol levels (Hummel and van Dijk, 2006). Promising acoustic studies such as that by Branco et al. (2007) have been questioned, with some believing outward communication and inner perception are not correlated. Modern breakthroughs such as non-invasive neuroimaging (specifically functional magnetic resonance imaging or fMRI) have brought invaluable new pain-related evidence to the table; this technology is vital for our further understanding. Recent evidence surrounding the following points will be critically analysed in this review, with the hypothesis, ‘Neonates do not feel pain’, in mind.

At what point is the switch in sensory processing from tactile to noxious sensation?

It is both a valid and common view that neonatal pain is only viable due to functional connections between brain structures obligatory for perception and the periphery. Neurons of the spinothalamic projection begin to differentiate on embryonic day 12 (E12) in rats (Altman and Bayer, 1984), with central projections of both myelinated and unmyelinated afferents fully entering the dorsal horn by E19 (Jackman and Fitzgerald, 2000), having adult-like function and morphology at P2 (Woodbury et al., 2008). Both the spinothalamic tract and free nerve endings are present at 8 weeks of gestation (Fitzgerald, 1987); these being regarded by some as the minimum necessary framework to support pain processing. This view is strengthened by reports of whole body movement away from a stimulus due to an appearance of perioral inner bursting in functional circuit formation was further emphasized by Slater et al. (2010); these bursts being thought to precede the onset of sensory function, emphasizing the critical role of the cortex in relation to pain function. In contrast to this, hydranencephaly-inflicted children aged 4–21 months, who lacked significant regions of cortex due to their condition, have also displayed pain-related behaviour (Jones and France, 1978). Nandi et al. (2002) showed that ablation of the thalamus affects pain perception. Taken together, these
findings challenge cortico-centric views of pain function and suggest a subcortical developmental route for the appearance of pain function.

According to the International Association for the Study of Pain, pain is an unpleasant sensory and emotional experience associated with tissue damage, or described in such terms (Merskey and Bogduk, 1994). Most individuals associate the word ‘pain’ with early life injury, as suggested by Craig and Korol, 2008, implying that memory has a role. The beginning of declarative memory use (due to prefrontal cortex and hippocampal development) at around 8–16 weeks of postnatal age (Richmond and Nelson 2007) allows the storing of learned information. Evidence supporting the fact
that early pain sensation is mediated subcortically is stronger than evidence for declarative pain memory in the neonate (Nandi et al. 2002), however. It is important to note that the development role of cortex and its relationship with subcortex in pain function (and consciousness) is hugely controversial. The consensus view is that 18 weeks is too early for the appearance of pain function in the healthy foetus, and it is thought to be roughly 24–26 weeks of gestation.

**Neonatal pain management**

Effective neonatal pain management remains a controversial topic, despite major advances in pharmacological, physiological and behavioural neonatal pain interventions within the last few decades. Is it reasonable to suggest that the idea of neonatal pain existence is valid if the stereotypical pain-related responses are alleviated by analgesics? Opioids are routinely used in the Neonatal Intensive Care Unit (NICU), and their pharmacokinetics and pharmacodynamics in infants have been studied intensely. An early study by Quinn et al. (1993) found morphine to evoke a significant decrease in pain-associated plasma adrenaline in pre-term neonates; however, insignificant haemodynamic and behavioural differences were found. It is important to note that the efficacy of the behavioural scale used had not yet been validated in pre-term neonates, this potentially questioning the validity of these behavioural findings. A multidimensional assessment by Guinsburg et al. (1998) used strict eligibility screening to obtain 22 mechanically ventilated pre-term infants aged ≤32 weeks with a postnatal age of 12–48 h. These infants were studied 30 and 60 min after a single administration of the opioid, fentanyl (3 mg/kg) or placebo, measuring the physiological and behavioural pain and stress indicators associated with mechanical ventilation (i.e. non-acute pain). High basal cortisol, growth hormone and lactate were present before treatment, with behavioural scales indicating pain. After fentanyl, minimum and maximum heart rate decreased (due to increased vagal tone as per most opioids (Garofalo et al. 2008)) and growth hormone level increased, with behavioural postoperative comfort score increasing and neonatal facial coding system score decreasing. Despite the fact that the behavioural findings were purely qualitative, (assessed through bedside observation, video playback and still images) and that even premature neonatal handling has been shown to induce pain, it is clear that these findings imply a decrease in non-acute pain-related responses after morphine administration. Further studies have confirmed these results and contributed to falsifying the hypothesis that neonates do not feel pain, with Alencar et al. (2012) also observing a decrease in pain-related response and insignificant differences in arterial blood gas levels after fentanyl administration. The above studies by Guinsburg et al. (1998) and Alencar et al. (2012) indicate that neonatal opioid administration may not only decrease suffering that may potentially lead to long-term adverse effects, but also stabilize blood pressure, divert energy sources to growth and have a beneficial effect on the clinical stability of critically ill pre-term neonates.

To conclude, physiological, haemodynamic and behavioural data both before analgesia and the alterations in pain-related response after analgesia indicate that neonates react to noxious stimuli, experiencing stress and displaying stereotypical pain-induced responses. More research is required (in addition to that by Segato et al. (1997)) to understand the apparent pain-alleviating mechanism of sucrose, with any adverse effects, such as that seen in paracetamol (Cuzzolin, Antoniccu and Fanos, 2013). It is reasonable to suggest that regardless of whether or not the above analgesic interventions, including opioids, are purely a distraction mechanism as opposed to a direct analgesic—widely observed stereotypical pain-related responses similar to that seen in the adult are clearly alleviated in the neonate on their administration, thus falsifying the hypothesis. In addition to this, the long-term effects of analgesia do not directly contribute to our understanding as to whether or not neonates feel pain. The long-term effects of morphine are difficult to evaluate due to the confounding factors of illness and prematurity on neurodevelopmental outcome, with some subjects having received more morphine than others as a neonate. The prevention of long-term hypersensitivity using pre-emptive morphine is unclear, with the results of the only study examining neurodevelopment after NICU pre-emptive administration in those aged 5–6 years being inconclusive due to low sample size (MacGregor et al., 1998).

**Evidence for long-term effects of the neonatal pain experience**

The role of neuronal activity and the importance of the neonatal period to sensory development have been highly documented. Significant neuronal development takes place postnatally, with both structural and functional alterations of sensory connections occurring (Walker, Tochiki and Fitzgerald, 2009). Pre-term neonates exhibit low tactile threshold—their system physiology being unstable and potentially rendering them more vulnerable to the effects of repeated invasive procedures (Grunau, 2002).

Multiple studies have observed pain-induced activation of the hypothalamic-pituitary-adrenal axis, immune system and autonomic nervous system in both the pre-term and the full-term neonate (Neveu et al., 1994; Morison et al., 2001). This often leads to a general increase in stress response mediators; their effects often being maintained beyond that which is normal, switched off prematurely or ‘overused’ due to multiple stressors. Determining the specific effects of neonatal pain is challenging due to the multiple NICU stressors contributing to high ‘allostatic load’ (the cumulative stress upon the neonate (McEwen, 1999)). Increased knowledge of the subjects’ previous medical and environmental conditions could lead to better analysis of the effects of neonatal pain.

Chu et al. (2012) analysed the adult rat following neonatal noxious insult, finding alterations in pain sensation, an increase in resting blood pressure and weakened cardiovascular...
responsiveness to nociceptive stress in adulthood. At P1, neonatal rats were administered either intraplantar saline or 0.25% carrageenan (1 µl/g). Baseline cardiovascular variables and 24-h responsiveness to Complete Freund’s Adjuvant (CFA) injection in the freely moving adults were recorded. Through the use of Von Frey Filaments, it was found that carrageenan-treated rats exhibited generalized basal hypoalgesia (in agreement with Bruehl and Chung (2004)) and localized hyperalgesia following nociception induced by adult intraplantar CFA (Fig. 2). Significantly higher basal blood pressure, baroreceptor sensitivity and parasympathetic activity after CFA injection were also found in these rats in comparison to controls. A potential theory behind these cardiovascular findings is that neonatal nociceptive stress induces a persistent hypertensive response, eventually causing the developing brain to reset and increase its basal level. The measurement of paw withdrawal threshold both 6 and 24 h after CFA injection was appropriate in comparison to previous similar studies. The telemetry technique used by Chu et al. (2012) allowed continuous cardiovascular recordings to be obtained from conscious, unstressed and freely moving animals continuously. This method is significantly more valid than tail-cuff plethysmography, which requires physical restraint of the animal that may itself affect blood pressure, a 70% reduction in the number of animals required plus no need for any additional data manipulation (Braga and Burmeister, 2011). The potential influence of circadian rhythm (an idea first investigated by Zhang, Zannou and Sannajust (2000)) was accounted for by including data at night to depict changes in autonomic activity throughout the day, increasing the relevance of the findings. Chu et al. (2012) implanted the telemetry device in the abdominal aorta of the mice studied; however, the reliability of the cardiovascular data obtained from this site has been questioned (Kaidi et al., 2007), left carotid implantation being considered far superior and more appropriate for mice and rat studies. This information may benefit future studies similar to Chu et al. (2012) by increasing the reliability and validity of pain-related cardiovascular recordings. According to some authors, evidence of hypersensitivity and loss of cardiovascular control sometime after neonatal pain-related stress supports the existence of pain sensation in the neonate (Morison et al., 2001; Beggs et al., 2012). Further replication of this recent study is required to further support these findings and to ensure that these results fully correlate to the human neonate.

Handling and early maternal separation can also result in visceral and somatic hyperalgesia as found by Coutinho et al. (2002); therefore, future studies similar to this should account for the environmental history of the rats to obtain more reliable results.

Long-term structural effects of the neonatal pain experience have also been found. Neurotrophins are vital for the development of sensory skin innervation, also controlling the survival and function of neurons both centrally and peripherally (Huang and Reichardt, 2001). NT-3 (of the Nerve Growth Factor family of Neurotrophins) has shown to be critical for cutaneous sensory nerve sprouting (Airaksinen et al., 1996). Beggs et al. (2012) built on an early study by Reynolds et al. (1997) and found, through neonatal skin wounding, that Neurotrophin-3 (NT-3) is highly regulated in the skin. A skin wound was induced in both rats and mice at P1, with regional cutaneous innervation being analysed at P7 and compared with naïve animals. The wounding induced a 3-fold up-regulation of protein gene product (PGP) 9.5 positive fibres in the skin and a 25-fold increase in release of NT-3 in comparison to control. The sensory neurite outgrowth induced by this NT-3 release was significantly reduced through the use of specific antibodies to block NT-3 activity in dorsal root ganglion and skin co-cultures. This confirmed NT-3 as a requirement for sensory neurite outgrowth, as did the absence of wound-induced hyperinnervation in heterozygous transgenic mice created by the team (NT-3 +/− lacZ). It is thought that NT-3 stimulates sensory nerve sprouting through the binding of TrkC receptors on nerve terminals, the accompanying TrkA and TrkB receptor activation sustaining neuronal life and encouraging new sensory neurons to form. The low-affinity interactions of NT-3 with TrkA and TrkB require high NT3 concentrations, explaining the dramatic decrease in innervation following neonatal skin wounding in heterozygous NT-3 mutant mice. Many precautions were taken by Beggs et al. (2012) to improve validity. PGP 9.5 immunoreactivity was compared with age-matched littermate controls to obtain as representative results as possible. Skin samples were also

Figure 2. Effects of a neonatal carrageenan injection on left hindpaw withdrawal threshold following intraplantar CFA. Six hours (CFA 6 h) and 24 h after CFA injection are shown. Saline-treated rats = 9 and carrageenan-treated rats = 9. The box and whisker plots are expressed as medians with first and third quartiles (boxes), and 10th and 90th percentiles (vertical lines), *p < 0.05. (Reprinted from Chu et al. (2012), Copyright (2012), with permission from Elsevier).
taken immediately post-wounding to avoid other confounding effects, with unwounded tissue from the contralateral side of the same animal being used for comparison to increase data validity. Despite these measures, it is important to bear in mind that neonatal injury models vary in duration, extent and location of their injury. Newborn mice and rats, such as those used in this experiment, are born at an earlier stage of development in comparison to humans; therefore, this investigation is more likely to correspond with premature infants than full-term infants. To conclude, neonatal wounding was found to increase NT-3 transcription, protein levels and release 3–7 days post-injury in both rats and mice, cutaneous hypersensitivity being the result. This study focused not as much on pain sensation (in contrast to that by Chu et al. (2012)), but on the structural and functional consequences of neonatal injury; this evidence being insufficient to support or deny the existence of neonatal pain. The results of this investigation could be considered valid due to the many precautions taken; however, a longer time frame of investigation may have resulted in increasingly reliable evidence for long-term hyperinnervation into adulthood after wounding. It is reasonable to suggest from this evidence that prevention of local NT-3 up-regulation and therefore hyperinnervation may reduce the effects of neonatal tissue trauma in NICU or through surgery.

It is thought that anti-nociceptive structures may be underdeveloped at birth, with a novel study by Brummelte et al. (2012) being the first to associate procedural NICU pain with early neurodevelopment in those very pre-term. Greater pain was found to be associated with reduced white matter fractional anisotropy (therefore white matter integrity) and reduced subcortical grey matter N-acetylaspartate/choline (increased grey matter neuronal loss), using 3D magnetic resonance spectrophotometric imaging paired with diffusion tensor imaging (DTI). This neuronal loss may have been due to excitotoxicity in overactive, immature neuronal networks. Previous DTI limitations found in other studies (the inability of the model to cope with non-Gaussian diffusion (Assaf and Pasternak, 2008)) were abolished through combination with functional brain mapping in this study, resulting in reliable and non-invasive mapping of functional anatomy, reliably indicating long-term effects of painful procedures in the neonate and indirectly falsifying the hypothesis that neonates do not feel pain.

A similar study by Vinall et al. (2012) using neuroimaging examined whether a greater number of neonatal skin-breaking events led to a decreased postnatal weight and head circumference (HC) early in life and at term-equivalent age in infants born very pre-term. It was found that greater neonatal pain led to lower body weight (ANOVA, \(P = 0.01\)) and HC (ANOVA, \(P = 0.04\)) percentiles at 32 weeks GA, independent of other medical confounds. This study suggests that successful postnatal growth is dependent on the quantity of painful procedures encountered during early NICU, showing that brain maturation is affected by neonatal affliction, rather than degree of prematurity at birth. Hohmeister et al. (2010) used fMRI to investigate changes in cerebral processing in school-aged children (11–16 years) who were born at either pre-term or full term (\(\geq 31\) weeks GA or \(\geq 37\) weeks GA, respectively) and had neonatal nociceptive input within NICU. The findings were compared with that of control children who were born at full term with no experience of NICU. This is the first neuroimaging study to depict an exaggerated neuronal response to pain in pre-term NICU children. During 30 s heat stimuli of individually adjusted moderate pain intensity, pre-term (but not term) NICU children exhibited significantly higher brain activations (through greater number of voxel activation) in regions such as the primary somatosensory cortex, anterior cingulate cortex and insula that were not significantly activated in controls; these responses being pain specific as they were not observed during non-noxious thermal stimulation. This evidence indicates that pre-term noxious stimuli exposure induces greater activation of sensory, affective and cognitive pain-related regions, the most robust alterations occurring in those implicated in affective processing (Craggs et al., 2007). The continuous pain ratings of the pre-term children revealed increased sensitization and a lack of habituation, implying neonatal pain may persistently increase the gain within pain pathways. Unfortunately, the fMRI session took place 2 years after initial psychophysical evaluation, and as no data on developmental alterations in pain sensitivity in NICU neonates were available, normalization of pain threshold may have occurred. The various strengths of this study, however, appear to outweigh the limitations such as the use of extensive subject exclusion criteria to increase validity plus the visual inspection of structural scans by the team to rule out severe morphological alterations. During stimulation, children continuously rated stimulus intensity on a computerized visual analogue scale to track changes in perceived intensity and to direct attention continuously towards the stimuli, further increasing validity. Overall, this study is an adequate evidence to both disprove the hypothesis that neonates do not feel pain and confirm the existence of long-term effects. Further studies should include larger sample sizes and fMRI sessions close to the time in which psychophysical evaluation takes place. The influence of subtle structural brain abnormalities in the NICU pre-term cannot be ruled out, and the relationship between structural abnormality and pain-related functional activation also requires further investigation.

**Conclusion**

The flurry of activity investigating the existence of neonatal pain from 1985 onwards has led to the general consensus that neonates do feel pain on the administration of noxious stimuli such as heel lance and other procedures. The emergence of fMRI has put a new slant on behavioural and physiological studies, especially through the analysis of cortical responses to pain. It is clear to see that animal models have proved essential for interpretation and confirmation of human findings, despite there being differences in complexity between species.
The investigation of analgesics has also proved to be very worthwhile in dissecting the existence of pain in the neonate, with pre- and post-analgesic responses further supporting its functional existence, the fentanyl studies by Guinsburg et al. (1998) and Alencar et al. (2012) being particularly poignant. Could it be said that morphine and other opioids merely distract the subject from the pain they are experiencing instead of directly targeting it? If this is found to be true, the use of analgesic efficacy to prove the existence of neonatal pain is questionable, emphasizing the need for further research on this class of drugs and a further awareness of the clinical factors that determine analgesic effectiveness. The importance of analgesic use is emphasized by structural studies such as that by Beggs et al. (2012), with many more contributing significant evidence of the long-term effects of pain experienced during the neonatal period showing that long-term effects exist and are not to be taken lightly. The earlier an infant is subjected to pain, it seems, the greater the potential for harm as emphasized by structural studies in the premature, such as that by Brummelte et al. (2012). These effects have proved to be dependent on the nature and timing of the insult, indicating plasticity at such a vulnerable time of life, the pain-related effects also occurring in adults—further falsifying the hypothesis that neonates do not feel pain. It is important to accept that with all premature and full-term studies, interpretation is often questionable as nociceptive events cannot be separated from other stresses such as low tactile threshold, rapid brain development, GA and severe illness which may have either additive or synergistic effects on neonatal developmental trajectories. Stress also plays a large part in our assumptions and is constantly linked to the pain response; however, while pain is stressful, it is questionable as to whether stress is related to pain and whether some results of pain assessment are pain specific.

Current evidence is pointing towards the existence of long-term effects, indirectly further proving the existence of neonatal pain and hence falsifying my hypothesis. If there are indeed cognitive, sensory and emotional elements to the overall pain experience, all of which are mandatory as hypothesized by Merskey (1986), pain can only be felt once in all parts of the hypothesized ‘pain matrix’ (Ploghaus et al., 1999) are formed, including the cortex. Convergence of data from previous studies implies this point is in fact after birth, however, how can pain perception be purely learned if it is protective from harmful stimuli? It is a reasonable assumption from previous studies that pain-related responses can partly be mediated through reflex pathways within the brainstem and spinal cord and that pain experience is possible on establishment of thalamocortical connections from gestational week 20 (Garel et al., 2001). All available evidence of cortical and analgesic response to pain, in combination with evidence of the existence of long-term effects of pain, imply that pain sensation is functional approximately at this point, therefore falsifying the hypothesis that neonates do not feel pain.

It is important to accept the fact that robust electrophysiological evidence supporting my hypothesis will be hard to obtain, if not impossible. It is reasonable to suggest that investigations questioning the idea of neonatal pain may reflect the personal spiritual or religious views of the scientists involved. However, the more likely explanation may be due to ambiguous results and techniques that make its existence slightly cloudier. Various nociceptive stimuli-induced inconsistencies emphasize the variability between individuals and the importance of repetitive single-subject analysis and sizeable study groups in pain research. Neonates with neurological lesions have typically been excluded from both pain-related studies of the premature and full term, possibly due to the vast inter-individual variation of lesions. Due to this, minimal knowledge of pain experience within these populations has been elucidated, this being a potential area for further neonatal pain research.

To conclude, given the strong evidence outlined above in favour of stress and pain-related behaviour in the neonate, it is reasonable to believe that neonates do feel some form of unpleasant sensation or pain-related stress on noxious stimuli that have the phenotype of that which is felt in the infant and adult. The evidence investigated in this review confirms that cortical development appears to modulate and accommodate the subjectivity of pain, but it is not vital for pain experience.

### Author biography

A.M. finished her undergraduate degree in Neuroscience at the University of Leeds in July 2013. Her particular field of interest stems from lectures on the topic of pain sensation and the underlying mechanisms of sleep—finding the ways in which sleep and anaesthesia are linked, fascinating. Her future aspirations include doing an MSc in Neuroscience, studying postgraduate Medicine and being involved in biomedical journalism at some point. A.M. wrote this paper and has primary responsibility for the final content.

### References


Fabrizi, L., Slater, R., Worley, A. et al. (2011) A shift in sensory processing that enables the developing human brain to discriminate touch from pain, Current Biology, 21 (18), 1552–1558.


