

Neurodevelopmental Changes of Fetal Pain

Curtis L. Lowery, MD,* Mary P. Hardman, MD,* Nirvana Manning,* R. Whit Hall, MD,† and K. J. S. Anand, MBBS, DPhil‡

Pain in the developing fetus is controversial because of the difficulty in measuring and interpreting pain during gestation. It has received increased attention lately because of recently introduced legislation that would require consideration of fetal pain during intentional termination of pregnancy. During development, sensory fibers are abundant by 20 weeks; a functional spinal reflex is present by 19 weeks; connections to the thalamus are present by 20 weeks; and connections to subplate neurons are present by 17 weeks with intensive differentiation by 25 weeks. These cells are important developmentally, but decline as a result of natural apoptosis. Mature thalamocortical projections are not present until 29 to 30 weeks, which has led many to believe the fetus does not experience emotional "pain" until then. Pain requires both nociception and emotional reaction or interpretation. Nociception causes physiologic stress, which in turn causes increases in catecholamines, cortisol, and other stress hormones. Physiological stress is different from the emotional pain felt by the more mature fetus or infant, and this stress is mitigated by pain medication such as opiates. The plasticity of the developing brain makes it vulnerable to the stressors that cause long-term developmental changes, ultimately leading to adverse neurological outcomes. Whereas evidence for conscious pain perception is indirect, evidence for the subconscious incorporation of pain into neurological development and plasticity is incontrovertible. Scientific data, not religious or political conviction, should guide the desperately needed research in this field. In the meantime, it seems prudent to avoid pain during gestation.

Semin Perinatol 31:275-282. © 2007 Published by Elsevier Inc.

The issue of fetal pain is clouded by complex scientific, political, social, and religious issues, which have driven national groups into debate over their opinions regarding this emotionally charged controversy. Unfortunately, political and religious considerations have clouded scientific reasoning on this important subject; it is paramount that scientific discussion remains dispassionate from other considerations. The scientific discourse as to whether a fetus feels pain should be divided into two discussions: 1) the perception of pain and 2) the physiological stress response.

The stress response may or may not be associated with the cortical perception of pain. As demonstrated through the works of Dr. Anand and others, the neonate experiences a physiological response to pain, which may be described as

activation of the fetal hypothalamic pituitary adrenal axis. Although the stress response is well-described in the fetus and newborn, some controversy remains as to whether the fetus or newborn infant can perceive noxious stimuli at the cortical level as painful during mid-term gestation. For obvious reasons, the evidence is indirect, and cannot be confirmed except by indirect methodology. This discussion does not preclude the harmful effects of stress stimuli on the developing fetus, regardless of whether the stimuli can be perceived at the cortical level.

What is "pain?" The most commonly accepted definition of pain is presented by the Committee on Taxonomy of the International Association for the Study of Pain:

*"An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage Activity induced in the nociceptor and nociceptive pathways by a noxious stimulus is not **pain**, which is always a psychological state, even though we may well appreciate that **pain** most often has a proximate physical cause."*¹

The Institute of Medicine Committee on Pain, Disability, and Chronic Illness Behavior reported "the experience of pain is more than a simple sensory process. It is a complex perception involving higher levels of the central nervous sys-

*Department of Obstetrics and Gynecology, University of Arkansas for Medical Sciences, Little Rock, AR.

†Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR.

‡Department of Pediatrics, Arkansas Children's Hospital, Little Rock, AR.

Address reprint requests to Curtis L. Lowery, MD, University of Arkansas for Medical Sciences, Department of Obstetrics and Gynecology, 4301 W. Markham Street, Little Rock, AR 72205. E-mail: LoweryCurtisL@uams.edu

tem, emotional states, and higher order mental processes.” This definition would imply a cortex with connections from the peripheral sensors capable of detecting this stimulus and relaying it to the central nervous system. This also requires the cortex to be developed to the point where it is able to perceive this stimulus as noxious.

Since it is not possible for the fetus to communicate with us, researchers have used the activation of the hypothalamic-pituitary–adrenal axis as a surrogate indicator of fetal pain.²⁻⁵ This so-called stress response has its limitations, since this response does not involve or require the cortex. Another factor to consider is the type and duration of pain stimulus presented to the fetus. When considering anesthesia for the fetus, priorities should be given as to whether the fetus will experience pain for a short time (eg, from a needle stick for fetal injection) or a long time (eg, during an operative procedure or in utero fetal surgery). Each procedure should be addressed differently and each could have dramatic short-term and long-term consequences on fetal development.

Background: The Abortion Controversy

Primarily because of controversy regarding pain relief to the human fetus during abortion, there has been renewed interest in fetal pain. Two recent reviews on fetal pain have argued against providing fetal pain relief during abortion, and they argue that insufficient scientific evidence supports such legislation.^{6,7} One review concluded that pain perception is unlikely before 29 to 30 weeks of human gestation.⁶ Unfortunately, many of the patients who require neonatal intensive care are born before 30 weeks of gestation and require multiple painful procedures to survive. The scientific rationale and methods leading to these conclusions must be examined, particularly in relation to other aspects of pain research, because changes in clinical practice based on those conclusions will have a significant public health impact.

Pain Perception

Pain perception has been described as a “hard-wired” system in which pain impulses are passively transmitted along sensory nerves, spinothalamic and thalamocortical pathways, until “perception” occurs, via activation of the primary somatosensory cortex.⁶ Evidence over the past 40 years has discarded this classical Cartesian view of pain, beginning from the Gate Control Theory of pain⁸ and confirmed by reams of clinical and basic science data.⁹⁻¹¹ Pain perception, instead, involves multi-layered networks of nociceptors, nerve fibers, neurons, and glia, distributed in multiple spinal and supraspinal areas, forming diverse feed-back and feed-forward loops. The participation, function, and neurochemical profiles of these cellular elements are constantly modified by external and internal cues.^{12,13} Moreover, the neurons, nociceptors, and nerve fibers participating in the perception of pain mature and begin to function at varying times. It would be a mistake to view the onset of pain perception, or

any other neural function, as we view assembly of computer parts. There is no scientific evidence that function in the multi-layered networks underlying pain perception wait for some cue to be “turned on.” The developing neural elements may be immature, but they are NOT inactive; they demonstrate plasticity. Neurons migrate, become excitable, produce axons and dendrites, and begin to synthesize neurotransmitters shortly after DNA synthesis stops, at time intervals corresponding to the first trimester of human development.¹⁴ Signaling of pain at any stage of development depends not only on the context and characteristics of the painful stimulus, but also on the behavioral state and cognitive demands at that time.¹³ Fetuses undergoing intrauterine invasive procedures, definitely illustrative of pain signaling, were reported to show coordinated responses signaling the avoidance of tissue injury.¹⁵

Pain perception during fetal or neonatal development does not engage the same structures involved in pain processing as those used by human adults. Lack of development of these areas is often used to support the argument that fetuses do not feel pain until late gestation.⁶ Many years of careful, painstaking research have shown that the fetus or neonate is not a “little adult,” that the structures and mechanisms used for pain processing during fetal or neonatal life are unique and completely different from those used by adults, and that many of these structures/mechanisms are not maintained beyond specific periods of early development.^{16,17} The immature pain system thus plays a signaling role during each stage of development and may use the neural elements available at that time to fulfill this role.¹⁸ Evolutionary theory posits that emotions necessary for survival will develop as early as possible during ontogeny. If starvation and injury are the greatest threats to newborn survival, then hunger and pain may be the earliest homeostatic emotions to develop in the fetus.^{19,20}

Some argue that activation of the sensory cortex is a necessary criterion for pain “perception” to occur in the fetus, citing the lack of evidence for pain-specific thalamocortical connections in fetal life.⁶ This line of reasoning, however, ignores clinical data showing that ablation or stimulation of the primary somatosensory cortex does not alter pain perception in adults, whereas thalamic ablation or stimulation does.²¹⁻²⁴ Pain is now viewed as a homeostatic emotion, with the thalamus playing a central role in pain processing and regulating the spinal–brainstem–spinal loops that mediate descending facilitation or inhibition depending on the context of pain.^{20,25} Fetal development of the thalamus occurs much earlier than the sensory cortex,²⁶⁻²⁸ but functional evidence for thalamic sensory processing will require novel neuroimaging techniques²⁹ or the recording of thalamic field potentials²⁴ from fetuses. If cortical activity is not required for pain perception in adults, why should it be a necessary criterion for fetuses? Despite this caveat, robust cortical activity occurs in preterm neonates exposed to tactile or painful stimuli,³⁰ which may be correlates of sensory content or its context and certainly imply conscious perception.

Human Brains are Well Developed Before Birth

By convention humans are considered an altricial species, underdeveloped at birth, but this notion is based on aspects of human somatic and motoric development and it belies the relatively advanced state of the human brain at birth.³¹ Bioinformatics approaches, which use statistics, mathematics, and computer science to relate brain development in animal species to the human fetus,³² show that more than 2 months before birth, the human brain is at the developmental stage of the newborn macaque, a species considered quite advanced at birth.³³ Just after birth, human newborns appear to be capable of complex processing, including object transformation and rapid statistical processing,^{34,35} a strong indication that the neural circuits necessary for perception are functional before birth. With the exception of a surge in connectivity that occurs just before birth,³⁶ many of the neural circuits underlying these behaviors develop during time intervals corresponding to the second trimester of human development.^{31,33}

A Functional Role for Neurons in the Subplate Zone

The cortex is accepted as the main participant in cognitive function, and subplate neurons are the first cells to populate this region.³⁷ Neurons in the subplate zone, which later separates to enclose cortical neurons as the subjacent white matter (interstitial) neurons and the superficial cortical Layer I,³⁷⁻³⁹ form an early intrinsic synaptic network that communicates using glutamate, GABA, calcium binding proteins, neuropeptides, and/or acetylcholine,^{40,41} with distinct inputs from the thalamus and the neocortex.⁴⁰

The subplate zone appears earlier in the somatosensory than in the visual area and reaches four times the width of the somatosensory cortex in the human fetus (2:1 in the monkey), implying that this embryonic structure expanded during evolution to subservise important sensory functions.⁴² Stimulation of the subplate region initiates large NMDA receptor-mediated electric potentials with long durations, influencing the development of cortical circuits in the neonate.⁴³ Subplate neurons are the source of the earliest peptidergic activity in the cortex.⁴⁴ Intensive differentiation of the subplate neurons occurs between 17 and 25 weeks of gestation, with at least five neuronal types (polymorphous, fusiform, multipolar, normal, and inverted pyramidal neurons), large dendritic sizes, and axonal patterns supporting a functional role during development.^{28,45,46} Changes in the MRI lamination pattern of the human fetal cerebral cortex are predominantly caused by changes in the subplate zone.⁴⁷

A portion of subplate neurons will die during development; therefore, they were simply assigned a “transient” function in development, to guide other migrating neurons and to serve as a waiting zone for later, more essential connections.^{42,48} Under this conventional model, subplate cells that persist in the white matter fibers subjacent to the cortex throughout maturity were viewed simply as a vestigial neural population.^{49,50} But brain cells as vestigial developmental

remnants would imply a huge waste of metabolic support. In addition, large proportions of spinal cord neurons also die before maturity with no suggestions that the remaining neurons are vestigial.⁵¹ Neuronal modeling studies indicate that the most efficient communication strategy might be to distribute sparse connections across time and space,⁵² something that the subplate neurons are optimally positioned to do.⁴³ The persistence of subplate cells through maturity, their location in the cortical fiber tracts, and their connections throughout the cortical layers indicate their vital role in mature cortical function.

During development, subplate neurons serve as targets for cortical and thalamic afferents,³⁹⁻⁴¹ as pathway pioneers for corticothalamic efferents⁵³ and as necessary participants in the formation of ocular dominance columns.⁵⁴ They likely coordinate receptive fields with orientation maps⁵⁵ and play a role in gyrification.³⁹ They are particularly susceptible to the preterm injuries that trigger cognitive and sensory deficits, a susceptibility that decreases as the human fetus ages.⁵⁶

Unlike the subplate cells in the deep cortex, those in the most superficial layers of cortex will die on maturity, leaving behind a convergence of connectivity that evolves into the first functional developmental circuits.^{38,39} This connectivity pattern strongly correlates with a unique physiological marker for primate conscious perception, the behaviorally relevant N1 evoked response, an EEG deflection recorded following sensory stimuli. Changes in the N1 component of an event-related potential accurately predict sensory perception in primates,⁵⁷ as a response initiated in cortical layer I.⁵⁸ These superficial connections, initially forged with neurons of the subplate zone, are components of an interactive strategy for cognitive processing, within which sensory information is primed, guided, and interpreted.^{58,59} Clearly, the subplate zone is active in the second-trimester human fetus.

Other Neurodevelopmental Considerations

Pain perception requires two distinctly different components: 1) **nociception** the sensation of the stimuli and 2) **perception with emotional reaction** which is the unpleasant feeling that occurs in reaction to the noxious stimuli. These distinct components are processed by the brain in areas anatomically and physiologically distinct from one another (see Fig. 1).⁶⁰⁻⁶² Human development occurs as an analog rather than digital process. The neurodevelopment milestones, as defined, are strictly arbitrary and have been developed for research and scientific quantification rather than strictly definable unique steps. Human development can more appropriately be classified as a continuum with neuro-anatomic structures forming, developing, and maturing during fetal development, throughout childhood, and the teenage years. Embryological dating and clinical gestational age dating are often confused in studies relating neurodevelopment. Gestational age (GA) is calculated from the first day of the women’s last menstrual period, roughly equivalent to 2

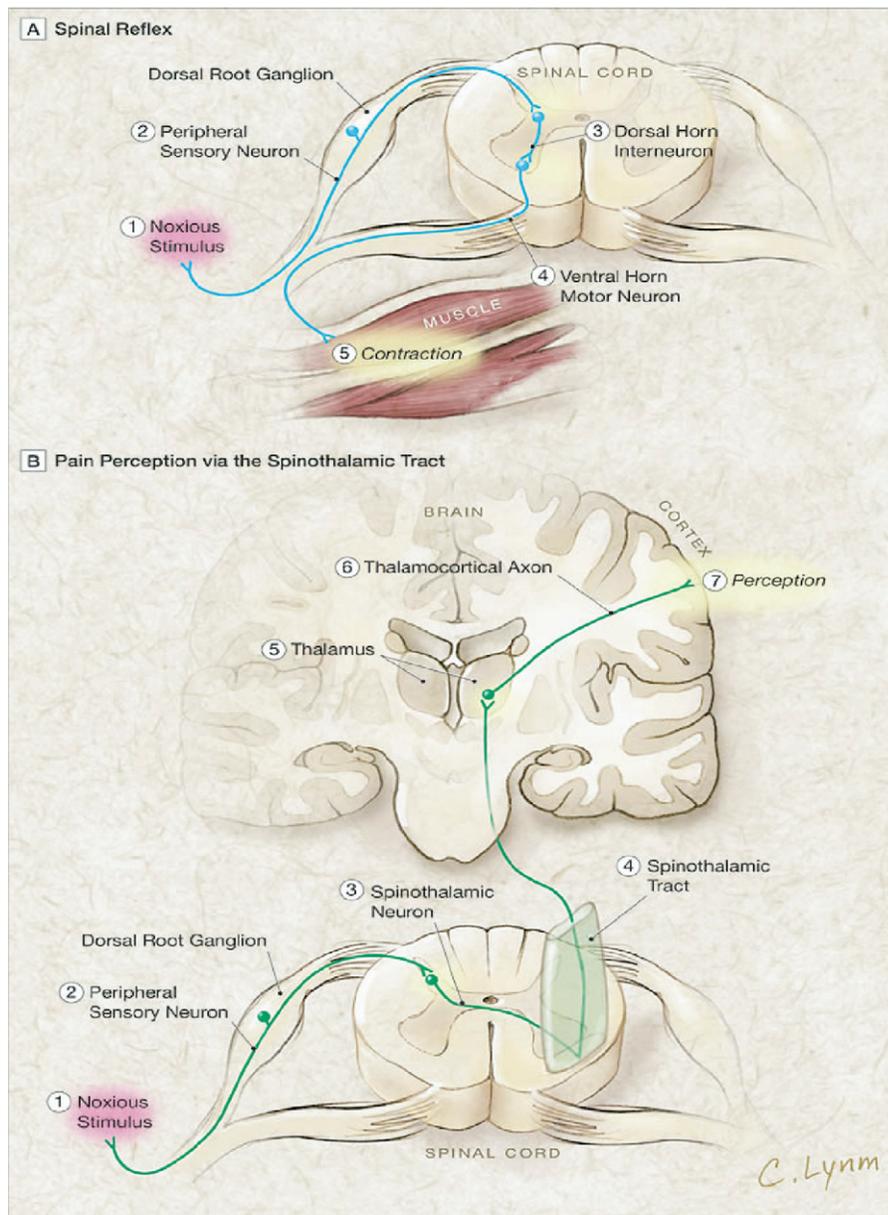


Figure 1 Spinal reflex and pain perception pathway. (A) Reflex responses to noxious stimuli occur early in development, before thalamocortical circuits are functional; noxious stimuli trigger reflex movement without cortical involvement. Activated by a noxious stimulus (1) a peripheral sensory neuron (2) synapses on a dorsal horn interneuron (3) that in turn synapses on a ventral horn motor neuron (4), leading to reflex muscle contraction and limb withdrawal (5). (B) Later in development, noxious stimuli (1) activate peripheral sensory neurons (2) that synapse on spinothalamic tract neurons (3), the axons of which extend up the spinal cord as the spinothalamic tract (4) to synapse on neurons of the thalamus (5). From here, thalamocortical axons synapse on subplate and cortical neurons, resulting in the conscious perception of pain. (Color version of figure is available online.)

weeks less than the embryo's age from the day of conception. The conscious perception of pain requires peripheral pain receptors, connections to the spinal cord through an afferent system, fibers that connect the spine and the thalami, and most important, connections between the thalamus and the subplate zone or cerebral cortex. It is also important to know pain impulses may be processed in other subcortical structures, including the hypothalamic pituitary system, amygdala (important for the emotional modulation of pain), basal ganglia, and brain stem.^{60,63}

Anatomical and functional perception of pain develops throughout the gestational process (see Table 1). Peripheral receptors develop very early and may be seen by the seventh gestational (9th week GA) week and are abundant by the 20th week (22nd week GA). These receptors are present on most of the fetal body.⁶⁴⁻⁶⁶ Starting at 10 to 13 weeks (12-13 weeks GA), the afferent system located in the substantia gelatinosa of the spinal cord's dorsal horn is developing.^{66,67} Connections between peripheral receptors and afferent fibers ending in the dorsal horn start as early as 8 weeks gestation,

Table 1 Development of Nociception and Pain Perception Pathway by Gestational Age

Anatomical and Functional Development of Nociception and Pain Perception Pathways			
Anatomical/ Functional Characteristic	Description	Gestational Age, wk	Source
Peripheral cutaneous sensory receptors	Perioral cutaneous sensory receptors	7.5	Humphrey, ¹³ 1964
	Palmar cutaneous sensory receptors	10–10.5	
	Abdominal cutaneous sensory receptors	15	
Spinal cord	Spinal reflex arc in response to nonnoxious stimuli	8	Okado and Kojima, ¹⁴ 1984
	Neurons for nociception in dorsal root ganglion	19	Konstantinidou et al, ¹⁵ 1995
Thalamic afferents	Thalamic afferents reach subplate zone	20–22	Kostovic and Rakic, ¹⁶ 1990 Hevner, ¹⁷ 2000
	Thalamic afferents reach cortical plate	23–24	Kostovic and Rakic, ¹⁸ 1984 Kostovic and Goldman-Rakic, ¹⁹ 1983
Cortical function*	Somatosensory evoked potentials with distinct, constant components	29	Klimach and Cooke, ²⁰ 1988 Hrbek et al, ²¹ 1973
	First electrocardiographic pattern denoting both wakefulness and active sleep	30	Clancy et al, ²² 2003 Torres and Anderson, ²³ 1985

*Earliest evidence of functional thalamocortical connections required for conscious perception of pain.

Reprinted with permission from Lee et al: Fetal pain: a systemic multidisciplinary review of the evidence. *JAMA* 294:947–954, 2005. (Copyright ©2005, American Medical Association. All rights reserved.)

and the myelination of these fibers begin after the completion of the connections and continue during development. A functional spinal reflex circuit develops simultaneously with the in-growth of the peripheral fibers toward the spinal cord.^{61,63} Connections to the thalamus begin at 14 weeks and are completed by 20 weeks, and thalamocortical connections are present from 13 weeks and are more developed by 26 to 30 weeks.⁶⁸ However, it is not possible to measure evoked potentials from the cortex before 29 weeks. Thus, many scientists suggest that it is not until 29 weeks gestational age that there is objective evidence that a peripheral stimulus can cause cortical activation.

The neurons of the cerebral cortex begin a migration from the periventricular zone at 8 weeks gestation, and by 20 weeks, the cortex has acquired a full complement of neurons, with glial perforation active throughout childhood.⁵ Synaptic formation begins at 12 weeks and peaks in the last trimester of pregnancy. Electroencephalographic activity appears for the first time at 20 weeks, becomes synchronized at 26 weeks, and reveals wake sleep cycles at 30 weeks.^{5,60} The adult conscious perception of pain is a complex process and requires mature cortical processing across wide areas of the brain. Although this process clearly began in utero, we should be careful not to apply our adult information regarding pain to that of the immature developing fetal brain.

Autonomic and Endocrine Responses to Noxious Stimuli

It is known that when the fetus is exposed to noxious stimulation, there is activation of the hypothalamic pituitary and adrenal axis. This so-called “stress response” has been used to imply

a fetal pain response. There are important reasons that solely the fetal stress response must not be used to imply that the fetus perceived pain at a conscious level. Giannajoulopoulos and co-workers have demonstrated the activation of the fetal hypothalamic pituitary and adrenal axis during fetal blood sampling in utero.⁶⁹ In this study, noradrenaline, cortisol, and β -endorphin were obtained just after entering the fetal hepatic vein and again on completion of the fetal transfusion. During this procedure, the needle traversed the fetal abdomen and was in place during the time required to transfuse the fetus. During a transfusion, the median increase in β -endorphin was 590%, cortisol 183%, and noradrenaline 196%. This result was compared with fetuses in which the hepatic vein was sampled for a short period of time simply to obtain blood. Findings showed no significant increase in hormone levels.

Similarly, when fetal blood sampling and transfusions are accomplished through needle directed umbilical cord sampling (no pain fibers present), there are no demonstrated changes in stress hormone levels. The same group demonstrated that invasive procedures may alter brain blood flow as early as the 18th week of pregnancy, which would imply that stimuli may trigger large-scale responses in the central nervous system without ever reaching the cortex.⁷⁰ This implies that noxious stimuli have the potential to affect neural development even though the cortical system is presumably too immature to appreciate conscious pain perception.

It has been demonstrated that autonomic and metabolic reflexes can be suppressed by analgesics. Fentanyl, when used during surgical operations at 28 weeks of gestation, reduced hormonal and anatomic reactions.^{71,72} The premature newborn and fetus have exhibited a stress reaction in

response to painful stimulation. Conversely, the stress reaction has been shown to be suppressed through the appropriate administration of pain medication.

Long-Term Developmental Impacts of Pain Exposure

The effect of pain on the developing fetus or infant will vary dramatically depending on gestational age, the duration of exposure, and nature of the noxious stimulus. It is not necessary that the thalamocortical connections be fully developed for effects to be witnessed. Changes in blood flow distribution have been seen as early as the 18th week of gestation, and premature infants have shown habituation to painful stimuli during the 25th week of gestation.^{70,73} In studies of premature human fetuses and rat pups, constant and repetitive painful stimuli have been shown to result in permanent spinal cord level sensitization.⁷³ Fetal brain development and organization is shaped by input from external stimuli.

Strong and recurring stimuli may result in the formation of abnormal synapses; once formed, these aberrant connections may remain and result in hyperactive responses to stimuli. Preterm infants exposed to 4 weeks of neonatal intensive care units have shown increased cardiovascular responses during the pain of heel prick when compared with infants born at 32 weeks.⁷⁴ Differences in response patterns were correlated with the number of invasive procedures performed on the infants after birth, rather than demographic factors such as Apgar scores, birth weight, or severity of illness.

The plasticity of the developing brain can lead to an alteration of the pain response center, which may make these infants at risk for stress disorders and anxiety-mediated adult behavior. Infants exposed to stressful birth conditions have demonstrated an increase in salivary cortisol response at 6 months of age. Furthermore, when circumcision is performed only on unanesthetized infants, long-term alterations in pain-related behavioral response have been demonstrated at 4 and 6 months of age.^{75,76} Long-term follow-up studies on children exposed to neonatal pain and stress have shown correlations to prolonged stay in the ICU and altered pain thresholds and abnormal pain-related behavior in later childhood.⁷⁷

Conclusion

For adults, pain is an emotional experience. We define pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.” We should keep in mind that the noxious stress response that activates the hypothalamic-pituitary and adrenal axis is linked to the emotional pain response. Activation of the hypothalamic-pituitary-adrenal axis can occur in the absence of cortical activation, and fetuses have exhibited this response in advance of maturation of the thalamocortical connections. However, stressful stimuli affect the subplate neurons and other developmental elements in the maturing fetus, which is one mechanism by which repetitive pain can lead to persistent neurological sequelae in the developing fetus.

Exposure of the fetus and premature newborn to pain has been associated with long-term alterations in pain response thresholds, as well as changes in behavioral responses related to the painful stimuli. Anesthesia has been shown to reduce the stress response to painful stimuli in the fetus and newborn infant. It is important to consider the long-term effects of the noxious stimuli on neurophysiological development when painful procedures are planned.

For older infants and children, the conscious perception of pain is a complex process requiring large areas of the cortex and well-developed connections to the thalamic and spinal thalamic tracks. It is likely that this maturation process begins at a very early gestational age and continues into the third trimester. Although the thalamocortical connections are not complete before 24 weeks, other pathways are present in the developing nervous system and demonstrate robust connections to the subplate neurons. The fetus or newborn may not be able to perceive pain from a cortical level; however, he may be able to perceive noxious stimuli, processing the information, and model the developing nervous system in response to the pain. Thus, it is important to reduce pain exposure in the fetus and newborn, since pain exposure has been shown to induce significant adverse long-term neural-developmental changes.

References

1. Merskey H: Logic, truth and language in concepts of pain. *Qual Life Res* 3:569-576, 1994 (suppl 1)
2. Clancy GT, Anand KJ, Lally P: Neonatal pain management. *Crit Care Nurs Clin North Am* 4:527-535, 1992
3. Anand KJ, Coskun V, Thiruvikraman KV, et al: Long-term behavioral effects of repetitive pain in neonatal rat pups. *Physiol Behav* 66:627-637, 1999
4. Anand KJ, Scalzo FM: Can adverse neonatal experiences alter brain development and subsequent behavior? *Biol Neonate* 77:69-82, 2000
5. Anand KJ, Hickey PR: Pain and its effects in the human neonate and fetus. *N Engl J Med* 317:1321-1329, 1987
6. Lee SJ, Ralston HJP, Drey EA, et al: Fetal pain: a systematic multidisciplinary review of the evidence. *JAMA* 294:947-954, 2005
7. Derbyshire SWG: Can fetuses feel pain? *Br Med J* 332:909-912, 2006
8. Melzack R, Wall PD: Pain mechanisms: a new theory. *Science* 150:971-979, 1965
9. Nathan PW, Rudge P: Testing the gate-control theory of pain in man. *J Neurol Neurosurg Psychiatry* 37:1366-1372, 1974
10. Dickenson AH: Gate control theory of pain stands the test of time. *Br J Anaesth* 88:755-757, 2002
11. Defrin R, Ariel E, Peretz C: Segmental noxious versus innocuous electrical stimulation for chronic pain relief and the effect of fading sensation during treatment. *Pain* 115:152-160, 2005
12. Woolf CJ, Salter MW: Neuronal plasticity: increasing the gain in pain. *Science* 288:1765-1768, 2000
13. Price DD: Psychological and neural mechanisms of the affective dimension of pain. *Science* 288:1769-1772, 2000
14. Bates E, Thal D, Finlay B, et al: Early language development and its neural correlates, in Rapin I, Segalowitz S (eds): *Handbook of Neuropsychology Child Neurology* (ed 2). Amsterdam, Elsevier, 2002
15. Williams C: Framing the fetus in medical work: rituals and practices. *Soc Sci Med* 60:2085-2095, 2005
16. Fitzgerald M: The development of nociceptive circuits. *Nat Rev Neurosci* 6:507-520, 2005
17. Narsinghani U, Anand KJS: Developmental neurobiology of pain in neonatal rats. *Lab Animal* 29:27-39, 2000
18. Glover V, Fisk N: We don't know: better to err on the safe side from mid-gestation. *Br Med J* 313:796, 1996

19. Anand KJS, Rovnaghi C, Walden M, et al: Consciousness, behavior, and clinical impact of the definition of pain. *Pain Forum* 8:64-73, 1999
20. Craig AD: A new view of pain as a homeostatic emotion. *Trends Neurosci* 26:303-307, 2003
21. Brooks JC, Zambreanu L, Godinez A, et al: Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging. *Neuroimage* 27:201-209, 2005
22. Craig AD: Interoception: the sense of the physiological condition of the body. *Curr Opin Neurobiol* 13:500-505, 2003
23. Nandi D, Aziz T, Carter H, et al: Thalamic field potentials in chronic central pain treated by periventricular gray stimulation: a series of eight cases. *Pain* 101:97-107, 2003
24. Nandi D, Liu X, Joint C, et al: Thalamic field potentials during deep brain stimulation of periventricular gray in chronic pain. *Pain* 97:47-51, 2002
25. Craig AD: Pain mechanisms: labeled lines versus convergence in central processing. *Annu Rev Neurosci* 26:1-30, 2003
26. Erzurumlu RS, Jhaveri S: Thalamic axons confer a blueprint of the sensory periphery onto the developing rat somatosensory cortex. *Brain Res Dev Brain Res* 56:229-234, 1990
27. O'Leary DD, Schlaggar BL, Stanfield BB: The specification of sensory cortex: lessons from cortical transplantation. *Exp Neurol* 115:121-126, 1992
28. Ulfing N, Neudorfer F, Bohl J: Transient structures of the human fetal brain: subplate, thalamic reticular complex, ganglionic eminence. *Histol Histopathol* 15:771-790, 2000
29. Chung HW, Chen CY, Zimmerman RA, et al: T2-weighted fast MR imaging with true FISP versus HASTE: comparative efficacy in the evaluation of normal fetal brain maturation. *AJR Am J Roentgenol* 175: 1375-1380, 2000
30. Bartocci M, Bergqvist LL, Lagercrantz H, et al: Pain activates cortical areas in the preterm newborn brain. *Lancet* 2005
31. Clancy B, Darlington RB, Finlay BL: The course of human events: predicting the timing of primate neural development. *Dev Sci* 3:57-66, 2000
32. Finlay BL, Darlington RB: Linked regularities in the development and evolution of mammalian brains. *Science* 268:1578-1584, 1995
33. Clancy B, Darlington RB, Finlay BL: Translating developmental time across mammalian species. *Neuroscience* 105:7-17, 2001
34. Damon W: *Handbook of Child Psychology*. New York, NY, J. Wiley, 1998
35. Gulya M, Rovee-Collier C, Galluccio L, et al: Memory processing of a serial list by young infants. *Psychol Sci* 9:303-307, 1998
36. Rakic P, Bourgeois J-P, Eckenhoff MF, et al: Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. *Science* 232:232-235, 1986
37. Bayer SA, Altman J: Development of layer I and the subplate in the rat neocortex. *Exp Neurol* 107:48-62, 1990
38. Marin-Padilla M: Dual origin of the mammalian neocortex and evolution of the cortical plate. *Anat Embryol* 152:109-126, 1978
39. Chun JJ, Nakamura MJ, Shatz CJ: Transient cells of the developing mammalian telencephalon are peptide-immunoreactive neurons. *Nature* 325:617-620, 1987
40. Hanganu IL, Kilb W, Luhmann HJ: Functional synaptic projections onto subplate neurons in neonatal rat somatosensory cortex. *J Neurosci* 22:7165-7176, 2002
41. Sarnat HB, Flores-Sarnat L: Role of Cajal-Retzius and subplate neurons in cerebral cortical development. *Semin Pediatr Neurol* 9:302-308, 2002
42. Kostovic I, Rakic P: Developmental history of the transient subplate zone in the visual and somatosensory cortex of the macaque monkey and human brain. *J Comp Neurol* 297:441-470, 1990
43. Clancy B, Silva-Filho M, Friedlander MJ: Structure and projections of white matter neurons in the postnatal rat visual cortex. *J Comp Neurol* 434:233-252, 2001
44. Kostovic I, Stefulj-Fucic A, Mrzljak L, et al: Prenatal and perinatal development of the somatostatin-immunoreactive neurons in the human prefrontal cortex. *Neurosci Lett* 124:153-156, 1991
45. Mrzljak L, Uylings HB, Kostovic I, et al: Prenatal development of neurons in the human prefrontal cortex. I. A qualitative Golgi study. *J Comp Neurol* 271:355-386, 1988
46. Mrzljak L, Uylings HB, Kostovic I, et al: Prenatal development of neurons in the human prefrontal cortex. II. A quantitative Golgi study. *J Comp Neurol* 316:485-496, 1992
47. Kostovic I, Judas M, Rados M, et al: Laminar organization of the human fetal cerebrum revealed by histochemical markers and magnetic resonance imaging. *Cereb Cortex* 12:536-544, 2002
48. Ghosh A, Shatz CJ: Pathfinding and target selection by developing geniculocortical axons. *J Neurosci* 12:39-55, 1992
49. Judas M, Milosevic NJ, Rasin MR, et al: Complex patterns and simple architects: molecular guidance cues for developing axonal pathways in the telencephalon. *Prog Mol Subcell Biol* 32:1-32, 2003
50. Kostovic I, Judas M: Transient patterns of organization of the human fetal brain. *Croat Med J* 39:107-114, 1998
51. Woo TU, Beale JM, Finlay BL: Dual fate of subplate neurons in a rodent. *Cereb Cortex* 1:433-443, 1991
52. Laughlin SB, Sejnowski TJ: Communication in neuronal networks. *Science* 301:1870-1874, 2003
53. McConnell SK, Ghosh A, Shatz CJ: Subplate neurons pioneer the first axon pathway from the cerebral cortex. *Science* 245:978-982, 1989
54. Ghosh A, Shatz CJ: Involvement of subplate neurons in the formation of ocular dominance columns. *Science* 255:1441-1443, 1992
55. Grossberg S, Seitz A: Laminar development of receptive fields, maps and columns in visual cortex: the coordinating role of the subplate. *Cereb Cortex* 13:852-863, 2003
56. McQuillen PS, Sheldon RA, Shatz CJ, et al: Selective vulnerability of subplate neurons after early neonatal hypoxia-ischemia. *J Neurosci* 23:3308-3315, 2003
57. Cauller LJ, Kulics AT: The neural basis of the behaviorally relevant N1 component of the somatosensory-evoked potential in SI cortex of awake monkeys: evidence that backward cortical projections signal conscious touch sensation. *Exp Brain Res* 84:607-619, 1991
58. Cauller L: Layer I of primary sensory neocortex: where top-down converges upon bottom-up. *Behav Brain Res* 71:163-170, 1995
59. Koch C, Davis JL: *Large-Scale Neuronal Theories of the Brain*. Cambridge, MA, MIT Press, 1994
60. Anand KJ, Carr DB: The neuroanatomy, neurophysiology, and neurochemistry of pain, stress, and analgesia in newborns and children. *Pediatr Clin North Am* 36:795-822, 1989
61. Fitzgerald M: The development of nociceptive circuits. *Nat Rev Neurosci* 6:507-520, 2005
62. Clancy B: Web-based method for translating neurodevelopment from laboratory species to humans. *Neuroinformatics* 5:79-94, 2007
63. Fitzgerald M: Development of pain mechanisms. 667-675, 1991
64. Vanhatalo S, van Nieuwenhuizen O: Fetal pain? *Brain Dev* 22:145-150, 2000
65. Valman HB, Pearson JF: What the fetus feels. *Br Med J* 280:233-234, 1980
66. Bijlani V, Rizvi TA, Wadhwa S: Development of spinal substrate for nociception in man. *NIDA Res Monogr* 87:167-179, 1988
67. Okado N: Onset of synapse formation in the human spinal cord. *J Comp Neurol* 201:211-219, 1981
68. Kostovic I, Goldman-Rakic PS: Transient cholinesterase staining in the mediodorsal nucleus of the thalamus and its connections in the developing human and monkey brain. *J Comp Neurol* 219:431-447, 1983
69. Giannakouloupoulos X, Teixeira J, Fisk N, et al: Human fetal and maternal noradrenaline responses to invasive procedures. *Pediatr Res* 45: 494-499, 1999
70. Teixeira J, Fogliani R, Giannakouloupoulos X, et al: Fetal haemodynamic stress response to invasive procedures. *Lancet* 347:624, 1996
71. Guinsburg R, Kopelman BI, Anand KJ, et al: Physiological, hormonal, and behavioral responses to a single fentanyl dose in intubated and ventilated preterm neonates. *J Pediatr* 132:954-959, 1998
72. Anand KJ, Sippell WG, Aynsley-Green A: Randomised trial of fentanyl anaesthesia in preterm babies undergoing surgery: effects on the stress response [Published erratum in *Lancet* 1:234, 1987]. *Lancet* 1:62-66, 1987
73. Leader LR, Baillie P, Martin B, et al: Fetal responses to vibrotactile stimulation, a possible predictor of fetal and neonatal outcome. *Aust N Z J Obstet Gynaecol* 24:251-256, 1984

74. Johnston CC, Stevens BJ: Experience in a neonatal intensive care unit affects pain response. *Pediatrics* 98:925-930, 1996
75. Taddio A, Katz J, Ilersich AL, et al: Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet* 349:599-603, 1997
76. Taddio A, Shah V, Gilbert-MacLeod C, et al: Conditioning and hyperalgesia in newborns exposed to repeated heel lances. *JAMA* 288:857-861, 2002
77. Porter FL, Grunau RE, Anand KJ: Long-term effects of pain in infants. *J Dev Behav Pediatr* 20:253-261, 1999