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UPCOMING ISSUES

Pediatric Pain

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Fetal Pain?

Fetal pain has so many implications that it requires a scientific appraisal independent of the heated controversies regarding abortions, women's rights, or the beginnings of human life. These implications include pain perception in preterm neonates, anesthesia for fetal surgery or intra-uterine procedures, and the long-term consequences of perinatal anesthesia/analgesia on brain development. Published during the current IASP Global Year Against Pain in Children, this issue of *Pain: Clinical Updates* summarizes the evidence concerning fetal pain, evaluates recent reviews of this topic, and explores future research in this field.

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Human Brains Are Well Developed Prior to Birth

By convention, assessments of brain development are mostly based upon somatomotor development at birth, by which point the human brain has already achieved a relatively advanced stage of development. Comparisons between species[1] show that more than two months before birth, the human brain is at the developmental stage of the newborn macaque, a species considered quite precocious at birth.[2] Human newborns are capable of complex processing, including abstract processing of the shapes of objects and the properties of numbers, implying advanced prenatal development of sensory processing. Earlier arguments against the possibility of fetal pain were based upon the immaturity of, or inhibition of, cortical neurons and thalamocortical inputs in the fetus,[3,4] as these elements are considered essential for conscious pain perception. However, immaturity or hypofunction of cortical neurons are not by themselves sufficient to preclude the occurrence of fetal pain.

Neurons in the Subplate Zone Are Functional

Neurons in the subplate zone of the forebrain, which later separates to include interstitial neurons in the subjacent white matter and neurons in cortical layer I, form an intrinsic synaptic network within which synaptic communication relies upon glutamate, gamma-aminobutyric acid, acetylcholine, neuropeptides,

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and calcium-binding proteins. The somatosensory subplate zone receives distinct inputs from the thalamus and the neocortex[5] and reaches four times the width of the somatosensory cortex in the human fetus (and twice the width in the monkey). Neurons in the subplate zone initiate excitatory amino acid or peptide neurotransmission in the cortex, influencing the development of fetal cortical circuits.[6,7] Differentiation of subplate neurons at 17–25 weeks' gestation produces five cellular subtypes whose distinct dendritic and axonal patterns correspond to different functional roles in development. Changes in the subplate zone are evident in the lamination patterns of the developing human fetal cerebral cortex.[8,9]

Subplate neurons remaining in deep cortical layers have been termed "vestigial remnants," simply because subplate neurons in other areas undergo programmed cell death during normal development. Yet a high proportion of spinal cord neurons also normally die prior to maturity, with no suggestions that remaining neurons are vestigial. Maintaining "vestigial" neurons would be metabolically expensive and unlikely to occur in normal development. Subplate neurons are optimally positioned for efficient communication, with sparse connections across time and space and rich inputs from cortical and thalamic afferents. These neurons play essential roles in the formation of ocular dominance columns, sensory receptive fields, and cortical gyri. They are particularly vulnerable to preterm injuries that produce cognitive and sensory deficits during later childhood.

Apoptosis of subplate cells in superficial layers leaves behind well-connected subplate cells in deep cortical layers that form the earliest cortical circuits. Their connectivity strongly correlates with the behaviorally relevant component of evoked responses termed "N1," which represents sensory perception in primates and is initiated in cortical layer I.[10] These superficial connections, initially formed in the subplate zone, are essential components of the cognitive processing by which sensory information is primed, guided, and interpreted.[10,11]

Consciousness Occurs below the Cerebral Cortex

Half a century ago, neurosurgeon Wilder Penfield noted that large amounts of the cerebral cortex could be excised, even as extensive as hemispherectomy, while he continued to converse with his patients, who suffered no evident impairment of consciousness. Surgical removal of dysfunctional portions of the cerebral cortex that contained epileptic foci deprived these patients of stored information or discriminative capacities, but not consciousness itself. Based on findings from more than 750 patients, Penfield and Jasper proposed that "the highest integrative functions of the brain are not completed at the cortical level, but in a system of highly convergent subcortical structures supplying the key mechanism of consciousness." Electrical stimulation of various cortical areas revealed that the reflective, conscious capacities of their patients proceeded in parallel with cortical stimulation effects such as elaborate fantasies or dream-like experiences, suggesting that the observer function of consciousness is separable from its cortical content. Lesions in the reticular activating system, but not the cortex, lead to loss of consciousness.

Transient lapses of consciousness also occur in absence epilepsy, associated with distinctive electroencephalogram (EEG) patterns of synchronously evolving bilateral spike and wave discharges. These discharges show a symmetrical coincidence of even the first abnormal EEG spike bilaterally, inconsistent with epileptic spread across interhemispheric pathways, but instead resulting from paroxysmal discharges in midline subcortical structures, which are radially and symmetrically connected with both cerebral hemispheres. This EEG pattern cannot be produced by experimental stimulation of cortical areas, but is evoked by stimulation of the midline thalamus. The Nobel laureate Edelman and colleagues have also reviewed the criteria for consciousness in animal species and concluded that the mechanisms for consciousness are not exclusively cortical.

Further clinical evidence for conscious perception mediated by subcortical centers comes from infants and children with hydranencephaly.[12,13] Despite total or near-total absence of the cortex, these children clearly possess discriminative awareness. They distinguish familiar from unfamiliar people and environments and are capable of social interaction, visual orienting, musical preferences, appropriate affective responses, and associative learning.[14]

Thus, a subcortical system comprising the basal ganglia, medial and midline thalamic nuclei, substantia nigra, ventral tegmental area, superior colliculi, midbrain, and pontine reticular formation mediates the organization of consciousness.[15] In the words of Penfield and Jasper, this system does not function "by itself alone, independent of the cortex," but "by means of employment of various cortical areas." That intact forebrain commissures are not required for high levels of cognitive function[16] provides further evidence for the subcortical integration of both cerebral hemispheres, symmetrically and radially connected to this midline system.

Multiple lines of evidence thus corroborate that the key mechanisms of consciousness or conscious sensory perception are not dependent on cortical activity. Consistent with this evidence, the responses to noxious stimulation of children with hydranencephaly are purposeful, coordinated, and similar to those of intact children.[14] Further, preterm neonates or adolescents with cortical parenchymal injury mount biobehavioral responses to pain that are indistinguishable from those of normal controls. Whether consciousness is required for sensory perception has also been questioned by recent studies of adult patients in a persistent vegetative state.[17,18]

Attempts to set forth criteria for fetal consciousness create difficulties of measurement and conundrums of proof and disproof

Is the Fetus Conscious?

Attempts to set forth criteria for fetal consciousness create difficulties of measurement and conundrums of proof and disproof. As the starting point for human observation of all natural phenomena, consciousness is required to construct

proofs of the existence of anything, but it is another matter to prove that consciousness is present.[19] Fetal behavioral states are frequently described in words such as "arousal," "wakefulness," or "awareness," despite significant differences between these terms.

Fetal sleep-like states can be inferred from EEG patterns or behaviors, implying an inhibition of cortical activity in utero, mediated by cortical inhibitors such as adenosine, neurosteroids (pregnenolone, allopregnenolone), corticotrophin-releasing hormone, prostaglandins (prostaglandin D_2), or a low blood oxygen.[4] Conversely, high circulating levels of neurosteroids such as dehydroepiandrosterone during fetal life may activate excitatory NMDA receptors, resulting in neuronal activation. It remains unclear whether these hormonal changes are the cause or consequence of fetal behavioral states.

In a careful analysis of fetal behavior that relies upon memory and learning as the highest-order evidence for psychological function in utero, Hepper and Shahidullah concluded that conscious sensory perception does occur in the fetus.[20] Can the fetus perceive pain from tissue injury? Abortion or fetal surgery provoke robust behavioral and physiological responses not unlike the fetal responses to other aversive stimuli.[21]

Closer examination reveals three major flaws in the scientific rationale of recent reviews purporting to rule out the occurrence of fetal pain

Critique of Recent Reviews

Closer examination reveals three major flaws in the scientific rationale of recent reviews purporting to rule out the occurrence of fetal pain.[3,4,22] First, pain perception is presented as mediated by a hard-wired system, passively transmitting nociceptive impulses until "perception" occurs in the somatosensory cortex.[3,22] Pain research over the past 40 years, beginning with the gate control theory and extended through vast amounts of clinical and experimental data, has long outgrown this Cartesian view of pain. Based upon this progress, we can assert with confidence that nociceptive signaling in prenatal development depends not only on the context and characteristics of the stimulus, but also on the fetal behavioral state at that time. For example, fetuses undergoing intrauterine invasive procedures were reported to show coordinated responses promoting the avoidance of tissue injury.[21,23]

Second, reviewers of this literature incorrectly assume that pain perception during fetal life must engage the same neural structures as those used by adults. Lack of development of the latter areas is then used to support the argument that fetuses do not feel pain until late gestation. Clinical and animal research shows that the fetus or neonate is not a "little adult," that the structures used for pain processing in early development are unique and different from those of adults, and that many of these fetal structures and mechanisms are not maintained beyond specific periods of early development. The immature pain system thus uses the neural elements available during each stage of development to carry out its signaling role.

Third, such reviews presuppose that cortical activation is necessary for fetal pain perception.[3,4,22] Based upon this assumption, the lack of evidence for pain-specific thalamocortical connections supports their contention against fetal pain. This line of reasoning, however, ignores clinical data cited above that ablation or stimulation of the primary somatosensory cortex does not alter pain perception in adults, whereas thalamic ablation or stimulation does. The thalamus plays a pivotal role in regulating the spinal-brainstem-spinal loops that mediate context-dependent descending facilitation or inhibition, coordinated via the key mechanisms underlying consciousness. Recent studies have noted robust activation of the somatosensory cortex in preterm neonates exposed to tactile or painful stimuli, modulated by gestational maturity, postnatal age, sex, laterality, and sleep/wake states.[24,25]

The available scientific evidence makes it possible, even probable, that fetal pain perception occurs well before late gestation

Conclusions

The available scientific evidence makes it possible, even probable, that fetal pain perception occurs well before late gestation. Those attempting to deny or delay its occurrence must offer conclusive evidence for the absence of fetal pain at given levels of maturity. When developmental time is translated across animal species to humans, it is clear that functionally effective patterns of sensory processing develop during the second trimester. Thalamocortical interactions located in the subplate zone persist into maturity, thus providing a functional template for subsequent cortical processing. Several lines of evidence indicate that consciousness depends on a subcortical system and that certain contents of consciousness are located in cortical areas. These subcortical structures, which develop much earlier than the cortex, may play a pivotal role in sensory perception. Our current understanding of development provides the anatomical structures, the physiological mechanisms, and the functional evidence for pain perception developing in the second trimester, certainly not in the first trimester, but well before the third trimester of human gestation.

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