A scientific appraisal of Fetal Pain

and Conscious Sensory Perception

Written testimony of:

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The topic of fetal pain deserves a scientific appraisal that is independent from the highly controversial and partisan issues surrounding abortion, women's rights, or philosophical projections about the beginning of human life. The implications of this appraisal extend beyond its impact on abortion, on the effects of pain in preterm neonates, on the use of analgesia/ anesthesia during neonatal surgery or intensive care, on fetal surgery and other interventions, and on the long-term effects of early experience on the developing nervous system[1]. Fetal pain was recently the subject of a systematic review, which concluded that fetal perception of pain is unlikely before 29 to 30 weeks of human gestation[2]. The vast majority of premature babies, who require neonatal intensive care or surgical care, are born before 30 weeks gestation. Before translating these findings into clinical practice, it is important to evaluate the conclusions of this multidisciplinary review.

A critique of the recent review:

Closer examination reveals three major flaws in the scientific reasoning followed by Lee and colleagues. First of all, they present pain perception 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[2]. Evidence over the past 40 years has discarded this classical Cartesian view of pain, beginning from the Gate Control Theory of pain[3] and confirmed by reams of clinical and basic science data[4-6]. 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, whereby the participation, function and neurochemical profiles of these cellular elements are constantly modified by external and internal cues[7, 8]. 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[8]. Fetuses undergoing intrauterine invasive procedures were reported to show coordinated responses signaling the avoidance of tissue injury[9].

Secondly, Lee and colleagues incorrectly assume that pain perception during fetal or neonatal development must engage the same structures involved in pain processing as those used by human adults. Lack of development of these areas is then used to support the argument that fetuses do not feel pain until late gestation[2]. Many years of careful, painstaking research shows 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[10, 11]. 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[12]. 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[13, 14].

Lastly, Lee et al. propose that activation of the sensory cortex is a necessary criterion for pain "perception" to occur in the fetus[2]. The lack of evidence for pain-specific thalamocortical connections in fetal life thus supports their claim against fetal pain. 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[15-18].

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[14, 19]. Fetal development of the thalamus occurs much earlier than the sensory cortex[20-22], but functional evidence for thalamic sensory processing will require novel neuroimaging techniques[23] or the recording thalamic field potentials[18] 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[24], which may be correlates of sensory content or its context and certainly imply conscious perception.

In addition to their scientific rationale, we question their use of systematic review methodology. Lee and colleagues report a search strategy that identified 2,106 articles in PubMed as a starting point for their review[2]. Subsequent methods, however, deviate from the evidence-based methods for systematic reviews, showing a significant disconnect between data acquisition and analysis. For example, the criteria used for selection of relevant articles (from which the evidence was extracted), independent assessments of study quality, the process used for rejecting relevant articles, or methods used for data synthesis were not stated. Methods for the systematic review of observational studies[25] were not followed and alternative methods were not described. Sixteen of their listed references could not be accessed via PubMed, whereas other relevant studies, for example, on fetal neurosensory processing were not included[26-29]. Inconsistent inclusion of evidence and ambiguous methodology used for data synthesis (such that this systematic review cannot be replicated) raises serious questions about the authors' scientific bias and the validity of their findings.

The criterion of consciousness:

To insist on the evidence for fetal consciousness[2] sets up a criterion that is difficult to measure, prove, or disprove. As the underlying substratum for all natural phenomena, it has been argued that consciousness is the proof of everything, but there can be no proof for consciousness[13, 30, 31]. Research in this area is particularly difficult because the physical basis of consciousness even in the human adult remains unknown[32]. There is also significant confusion in describing fetal behavioral states, with the frequent interposition of arousal, wakefulness, consciousness, or awareness[33-36], despite significant differences in the definition and correlates of these entities. Whereas consciousness may be abstract and difficult to measure, we recommend conscious perception as perhaps a scientifically measurable entity.

Conscious perception associated with widespread activation of brain areas[37], but the driving force for such activation comes from the reticular activating system (RAS), with inputs from the basal forebrain, locus coeruleus, substantia nigra, ventral tegmentum, and median raphe. Lesions in this system, but not in the thalamus or cortex, lead to a loss of consciousness[30, 37]. From a careful analysis of fetal behavior, with memory and learning serving as the highest order evidence for psychological function in utero, Hepper and Shahidullah infer conscious sensory perception in the fetus[34].

The question remains, however, if the fetus is "aware" of painful stimulation resulting from tissue injury. Biobehavioral data suggest that the fetus mostly remains asleep in utero[36], mediated by cortical inhibitors like adenosine, neurosteroids (pregnanolone, allopregnanolone,

corticotrophin releasing hormone), prostaglandins (Prostaglandin D_2), or low circulating oxygen[33]. Conversely, high circulating levels of neurosteroids like dehydroepiandrosterone (DHEA) during fetal life may activate excitatory n-methyl d-aspartate (NMDA) receptors, resulting in neuronal activation[38]. There is significant confusion whether these hormonal changes cause or result from sleep-like states in the fetus[33, 36]. Mild noxious stimuli are not perceived during sleep, but major tissue injury occurring as a result of abortion or fetal surgery evokes behavioral and physiologic arousal[9], not unlike the fetal responses to other aversive stimuli[34, 39]. Evidence supporting an actively maintained sleep-like state in the fetus rests on EEG and other observations indicating the inhibition of cortical activity[33]. Although evidence questioning the need for cortical activity in conscious perception is reviewed later, general considerations regarding fetal brain development are first considered as a framework for this discussion.

Human brains are well developed prior to 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[40]. Bioinformatics approaches relating brain development in animal species to the human fetus[41] show that more than 2 months before birth, the human brain is at the developmental stage of the newborn macaque, a species considered quite precocial or advanced at birth[42]. Just after birth, human newborns appear to be capable of complex processing including object transformation and rapid statistical processing[43, 44], 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[45], many of the neural circuits underlying these behaviors develop during time intervals corresponding to the second trimester of human development[40, 42].

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[46]. Neurons in the subplate zone, which later separates to include Layer I of the cortex[46-48], form an early intrinsic synaptic network that communicates using glutamate, GABA, calcium binding proteins, neuropeptides, or acetylcholine[49, 50], with distinct inputs from the thalamus and the neocortex[49].

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 that expanded during evolution to subserve important sensory functions[51]. Stimulation of the subplate region initiates large NMDA receptor-mediated EPSPs with long durations, influencing the development of cortical circuits in the neonate[52]. Subplate neurons are the source of the earliest peptidergic activity in the cortex[53]. Intensive differentiation of the subplate neurons occurs between 17 and 25 weeks of gestation, with various types of afferent fibers, 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[22, 54, 55]. Changes in the MRI lamination pattern of the human fetal cerebral cortex are predominantly caused by changes in the subplate zone[56].

A portion of subplate neurons will die during development, therefore, they were simply assigned a "shepherding" function in development, to guide other migrating neurons and to serve as a waiting zone for later, more essential connections[51, 57]. Under this conventional model, subplate cells that persist in the deep cortex till maturity are viewed simply as a vestigial neural population[58, 59]. But brain cells as vestigial developmental remnants would imply a huge waste of metabolic support – large proportions of spinal cord neurons also die prior to maturity with no suggestions that the remaining neurons are vestigal[60]. Neuronal modeling studies indicate the most efficient communication strategy might be to distribute sparse connections across time and space[61], something that the subplate neurons are optimally positioned to do[52]. 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[48-50], as pathway pioneers for corticothalamic efferents[62] and as necessary participants in the formation of ocular dominance columns[63]. They likely coordinate receptive fields with orientation maps[64] and play a role in gyrification[48]. They are particularly susceptible to the preterm injuries that trigger cognitive and sensory deficits, a susceptibility that decreases as the human fetus ages[65].

Unlike the subplate cells in the deep cortex, those in the most superficial layers of cortex will die upon maturity, leaving behind a convergence of connectivity that evolves into the first functional developmental circuits[47, 48]. This connectivity pattern strongly correlates with a unique marker for primate conscious perception, the behaviorally relevant N1 evoked response, an EEG deflection recorded following sensory stimuli. Changes in the N1 component of a ERP accurately predict sensory perception in primates[66], as a response initiated in cortical layer I[67]. These superficial connections, initially forged in the subplate zone, are components of an interactive strategy for cognitive processing, within which sensory information is primed, guided and interpreted[67, 68]. Having examined the rationale and evidence for a functional subplate zone, which is active in the second trimester human fetus, we can return to the question of whether cortical activation is necessary conscious perception.

Conscious perception can occur without the cerebral cortex:

Half a century ago, the neurosurgeon Wilder Penfield and physiologist Herbert Jasper noted that large cortical excisions, even as radical as hemispherectomy, were made while communicating with their patients and occurred without interrupting the patient's continuity of consciousness[69]. Surgical removal of the cerebral cortex deprived their patients of certain forms of information or discriminative capacities, but not of consciousness itself. Based on such findings from more than 750 patients with intractable epilepsy, they 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"* [69]. Electrical stimulation of cortical areas before excision revealed that the reflective, critical conscious capacities of their patients co-existed with stimulation-induced effects (elaborate fantasy, dream-like experiences or hallucinations), suggesting an independence of the observing function of consciousness and its cortical contents[69].

Some epileptic seizures, typically initiated with a discrete lapse of consciousness, show a symmetrical bilateral coincidence of even the first abnormal spike in the EEG, which seemed

incompatible with epileptic spread across the callosal interhemispheric pathways[70]. This suggested paroxysmal activity in subcortical regions that are symmetrically and radially connected with both cerebral hemispheres[69]. A specific and selective malfunction of consciousness occurs in seizures of absence epilepsy, associated with the distinctive EEG pattern of bilateral, synchronously evolving spike and wave discharges. This EEG pattern was not evoked by stimulation of any cortical area, but was experimentally produced by stimulation of the midline thalamus by Jasper and others[71, 72]. Edelman and colleagues have also discussed the criteria for consciousness in animal species[73, 74] and concluded that a functional cerebral cortex is not necessary for conscious perception.

A subcortical system, mediating the organization of conscious perception and volitional behavior, mainly includes the basal ganglia, medial thalamus (midline, intralaminar and reticular nuclei), ventrolateral thalamus, substantia nigra, ventral tegmental area, superior colliculus, median raphe, and the midbrain and pontine reticular formation. This system, critical for consciousness, does not function *"by itself alone, independent of the cortex"*, but *"by means of employment of various cortical areas"*[69]. That intact forebrain commissures are not required for high levels of cognitive function[75] provides further evidence for its role in the integration of bilateral cerebral cortical areas, radially and symmetrically related to this midline system[76, 77]. Additional evidence for the role of subcortical processing in conscious sensory perception comes from the Sprague effect described in cats[78, 79]. Experimental inactivation of the cortex at the junction of occipital, parietal, and temporal lobes by reversible cooling leads to unilateral neglect of stimuli from the opposite side, whereas cooling of the superior colliculus opposite to the cortical inactivation seems to "cure" this unilateral defect[80, 81]. Similar correction of the neglect caused by frontal cortical damage was observed in a human patient following midbrain damage on the opposite side[82].

Confirmatory clinical evidence for conscious perception mediated by this subcortical system comes from infants and children with hydranencephaly, with minimal or no cortical tissue[83, 84]. Despite the total or near-total absence of the cerebral cortex, these children clearly possess discriminative awareness, for example, distinguishing familiar from unfamiliar people and environments, social interaction, functional vision, orienting, musical preferences, appropriate affective responses, and associative learning[85].

Multiple lines of evidence reviewed above, in fact, conclusively present the alternative view that anatomical development or functional activity of the cortex is not required for conscious sensory perception. Consistent with this view are observations that (a) children with hydranencephaly consistently respond to pain or pleasure in a conscious coordinated manner[85-87] similar to intact children, (b) preterm neonates or adolescents with parenchymal brain injury have impaired cortical function, yet they mount biobehavioral responses to pain indistinguishable from those of unimpaired controls[88, 89], and (c) patients in a persistent vegetative state present evidence for the conscious perception of self and environment[90, 91], including the capacity to experience pain[91].

Summary and conclusions:

The conclusions of Lee and colleagues[2] regarding fetal pain are flawed, because they ignore a large body of research related to pain processing in the brain, present a faulty scientific rationale and use inconsistent methodology for their systematic review. Based on the available scientific

evidence, we cannot dismiss the high likelihood of fetal pain perception before the third trimester of human gestation. When developmental time is "translated" across experimental species to humans, it is clear that functionally effective patterns of sensory processing develop during the second trimester in the fetal thalamus. Many 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, whereas the contents of consciousness are selectively located in cortical areas. Ablation or stimulation cortical areas do not block or cause pain perception in adults, whereas thalamic ablation or stimulation does. It is likely, therefore, that thalamic nuclei play a central role in conscious pain perception. Fetal development of the thalamus occurs much earlier than the sensory cortex, providing the substrate and mechanisms for conscious pain perception during the second trimester, but not in the first trimester and before the third trimester of human gestation.

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