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COMMENT

The potential effects of NICU environment and multisensory stimulation in prematurity

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Preterm infants are at risk for poor neurodevelopmental outcomes, including deficits in learning and memory, disrupted sensory processing, attention deficit hyperactivity disorder, and autism spectrum disorder.[1,2] Prematurity leads to a situation where critical in utero steps of brain development occur in an abnormal ex utero environment. This alters the quality and intensity of sensory stimuli that the premature infant experiences, and potentially affects normal maturation of sensory systems adversely. The identification of the impact of the NICU environment on the development of sensory systems may pave the way for the establishment of a comprehensive protocol of multisensory stimulation that can potentially ameliorate sensory deficits associated with prematurity.

The establishment of accurate sensory neural networks occurs during critical periods spanning the final months of gestation and the first month after birth, during which precise patterns of neuronal activity initiate processes of refinement that underlie the establishment of accurate sensory neural networks.[3] For instance, even before birth, neighboring cells in the retina fire together (retinal waves) to sculpt the functional cytoarchitecture of the visual thalamus and cortex.[3] In the auditory system, synchronous discharge of neighboring inner-hair cells is required to form clusters of primary auditory cortical neurons and establish tonotopic auditory sensory maps.[4] There is also an extensive literature on the influence of peripheral sensory receptors on the development of somatosensory maps (see ref. [5] for review). Refinement of these processes continues through activity-dependent plasticity mechanisms during the perinatal period and early postnatal life. Consequently, exposure to inadequate and/or inappropriate visual, auditory, and somatosensory stimuli during these early development critical periods can result in long-lasting alterations in the connectivity and function of sensory cortices. For instance, disruption of visual experience can lead to amblyopia, strabismus, and alteration of the visual cortex orientation selectivity columns.[3] Similarly, exposure to environmental noise can delay the establishment of tonotopic maps in the auditory cortex.[6] In addition, there is strong evidence that abnormal somatosensory experience (i.e., painful procedures) can alter thalamocortical connectivity.[7] Taking these factors together, one may conclude that premature infants can be particularly vulnerable since the NICU environment is very different than that inside the womb.

Premature infants remain in a neonatal intensive care unit (NICU) for days to months, depending on their individual needs. During their stay in the NICU, premature babies are exposed to abnormally bright lights, highly patterned visual stimulation, and exposure to high- and mid-frequency sounds during a time of development when they would normally be inside the womb experiencing diffuse visual stimuli at very low intensities and low-frequency sounds.[8] Curiously, while most NICUs aim to have ambient sound lower than 50 dB, it has been demonstrated that the womb environment exceeds these values ranging from 70 to 90 dB.[9] Therefore, the main difference between the "noise" from the in utero environment in comparison with the NICU is not exactly the intensity of the sound, but rather its quality. Inside the womb, low-frequency sounds (i.e., heart rate, blood flow, and peristaltic movements) are dominant. In contrast, the NICU environment has many sources of high- and mid-frequency sounds (i.e., beeps from monitors, voices, and ventilators). Regarding tactile stimulation, rather than receiving constant contact of the amniotic/uterine environment, babies in the NICU are isolated in incubators, and there is contact with artificial fabrics and numerous essential medical procedures (i.e., placing intravenous lines, heel pricks). Thus, the necessary care environment that premature babies experience involves exposure to an environment that is significantly different from the womb. Therefore, the NICU environment may contribute to subtle changes in sensory cortices that could be translated into long-lasting sensory deficits. In fact, toddlers and adolescents born premature often present disabilities that are linked with disrupted development of sensory systems such as attention deficit hyperactivity disorder (ADHD), autism spectrum disorder, and learning and memory problems.[1,2] For instance, a prospective observational study showed that preterm infants presented with abnormal tactile reactivity are more likely to present poor neurodevelopmental outcome.[9]

The alterations observed in primary cortices might also reflect in associative areas that receive convergent inputs from different sensory modalities, affecting multisensory processing in particular. Multisensory processing is characterized by the transfer of information between sensory modalities. This process relies on multimodal neurons (neurons that can be driven by more than one sensory modality) and occurs at a high level of cortical processing.[10] An example of transfer of information between sensory modalities is observed as early as term when an auditory stimulus can modify the perception of a subsequent visual stimulus in newborns.[11] At 1 month of age, a baby is capable of visually recognizing an object that was previously explored orally.[12]

While newborn senses are classically viewed as separate at birth, the integration of senses increases with the accumulation of sensory-motor experience by advancing age.[13] However, findings of our group by using resting-state functional MRI suggested that two cortical areas, involved in multisensory processing and integration (intraparietal sulcus, IPS; supratemporal sulcus, STS), are already connected to unisensory cortical areas in neonates.[14]

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For example, the IPS exhibited strong functional connectivity with both visual (MT, V3) and somatosensory (S3) areas, whereas STS exhibited strong functional connectivity with visual (MT, V4), auditory (A1), and somatosensory (S2, S3) cortical regions. This could be explained by the presence of cortical areas with converging sensory inputs within the first few weeks of life. We hypothesize that the abnormal environment experienced in the NICU can alter the establishment of converging sensory inputs affecting multisensory processing.

There is a dynamic developmental reweighting of multisensory stimulus and learned associations as maturation progresses, where early infancy sensory development is characterized by broad perceptual tuning that allows young infants to bind a broader set of sensory information. Later, with increasing age, more sophisticated and specialized processing emerges, which depends critically on earlier experience.[15] Interestingly, poor IQ in adolescents who were born prior to 33 weeks of gestational age correlates with deficits in two multisensory processes, stereognosis and graphesthesia (the capacity to recognize objects or to write only based on tactile information), but not with commonly tested primary neurological problems, such as hyperreflexia and chorea.[16]

Currently, there is a great effort from multiple groups to use unisensory and multisensory stimulation in the NICU to ameliorate sensory deficits derived from prematurity. An example of unisensory stimulation is our finding on the effect of music lullaby on sleep quality and brain stimulation.[17] During the last decade, multisensory interventions (including auditory, tactile, visual, and vestibular) have been showing promising results to ameliorate sensory deficits associated with prematurity. For example, multisensory stimulation (but not tactile alone) was associated with a decrease in stress reactivity when compared with controls.[18] Moreover, infants who received behavioral cues via eye contact, infant-directed talk by a female voice, and body massaging followed by rocking showed lower salivary cortisol levels compared with controls.[18]

Recently, Filippa et al.[19] have provided an important and thorough review of the evidence supporting the behavioral orientation of the newborn to early vocal contact and music, assessed by functional neuroimaging techniques. Their review article tackled the scientific basis of plasticity and the potential benefits of maternal and organized sounds during the critical period of brain development. The authors also called attention to the importance of audiovisual synchrony between the maternal voice and face.

Neel et al. recently published a protocol for a promising interventional randomized clinical trial aiming at improving sensory processing in late preterm infants.[20] The multisensory intervention will include parent-supported, auditory–tactile–olfactory–vestibular intervention (playing of the mother's voice on the infant's pacifier, holding, and pressure containment, exposure to a parent-scented cloth, and regulated breathing by the therapist for infant vestibular stimulation). The study aims at the evaluation of sensory processing by using time-locked EEG. Language and motor functions will be measured at 2 years of corrected age by using the Bayley III.

However, a major challenge for multisensory stimulation interventions is the identification of the optimal quality (i.e., sound frequency, pattern of light stimulation, and texture of tactile stimulation) and intensity (decibels, luminescence, and pressure) of the stimulus. This is particularly important to avoid patterns of stimulation that could actually do more harm than good.

The significance of attending to multisensory stimulation is multiple. First, to adopt early interventions to minimize the effects of the NICU environment in the early stages of brain development. Second, to study the causal effects of sensory stimulation interventions on mediating neurodevelopment outcomes in well-designed clinical trials. Third, to identify subtle cognitive and sensory deficits that challenge long-term outcome perception, memory acquisition, executive functioning, and learning, which are unrecognized or underestimated by the standardized neurodevelopment evaluations such as the Bayley III. Thus, there is a strong need for incorporating multisensory perceptual mechanisms for cognitive assessment of high-risk infants.

In summary, multisensory stimulation during the NICU stay has a great potential in ameliorating sensory deficits related to prematurity. However, this field of research is still in its infancy, and there is a lot that we need to learn about the effects of the NICU environment in the development of sensory areas.

AUTHOR CONTRIBUTIONS

Both authors equally contributed to the conception, interpretation of the literature, and writing the correspondence.

ADDITIONAL INFORMATION

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