of some approaches aimed at preventing the negative impact of frequent stressors on brain development in the NICU. The stressors are sleep deprivation, pain, mother-child separation, and sensory dysstimulation.

**Stressors in the NICU**

**Sleep deprivation**

Animal studies, mostly conducted on rodents, have provided useful insights with regard to sleep deprivation. These studies have shown that sleep deprivation may result in: oxidative stress, neuroinflammation via chronic microglial activation, and the accumulation of the abnormal proteins p-Tau and amyloid-β in the cerebral cortex. These studies have also shown a neurogenesis decline via complement activation, which alters the balance of Fragile X-Mental Retardation Protein expression. In addition, the impact of chronic sleep deprivation on behavioral development has been demonstrated. Sare et al found short- and long-term changes in behaviors of sleep-deprived mice, measured by activity in an open field arena. Males demonstrated decreased sociability and increased repetitive behaviors. This data from preclinical studies show that sleep deprivation in the neonatal period has long-lasting behavioral changes, possibly modulated by gender.

**Pain**

A meta-analysis by Steinbauer et al concluded that neonatal pain has a large effect on neuronal cell death in rodents. The higher number of neonatal pain events was significantly associated with increased neuronal cell death, increased anxiety, and depressant-like behavior. Boggini et al summarized the impact of pain on preterm infants’ brain development demonstrated by MRI studies. A volume reduction of white and gray matter structures at neonatal and school ages is associated with early postnatal pain exposure. However, there is a possible bias, as the most severe clinical conditions are associated with higher exposure to painful procedures.

**Mother-child separation**

Maternal separation, an early stressful experience, can negatively impact the newborn’s nociceptive system development and pain responses at different levels (Table 1). Epigenetic mechanisms are implicated in the long-term effects of this early life stress that could also impact the next generation.

**Sensory Stimuli**

During prenatal development in mammals, the sensory systems do not become functional at the same time, but rather in a specific and invariant sequence: first tactile, then vestibular > chemical > auditory > visual. This differential timing of sensory system onset could benefit the earlier developing sensory systems as it allows them to develop without competition or interference from later developing sensory systems. In the case of preterm birth, the sensory stimuli are numerous, intense, simultaneous, chaotic, and physically different from those observed in utero. This could negatively impact synaptogenesis.

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