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Pain in the newborn brain: a neural signature

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No one wants to see a baby in pain. Yet, for many decades neonatal health-care providers have debated whether neonates feel pain and at what age this neural capacity emerges.[1] This is a crucial issue because neonates who require intensive care are exposed to hundreds of painful procedures as part of life-saving medical procedures. Fortunately, clinicians now recognise that neonates sense pain and that appropriate strategies for analgesia and sedation are needed for their compassionate care. In the past 10 years, in preterm neonates—a major population in neonatal intensive care units—pain has emerged as a key predictor of delayed brain maturation, which has been associated with subsequent neurodevelopmental impairments.[2]

Despite the recognition that pain management is a key aspect of care for neonates, quantifying pain in newborn babies remains challenging. Neonatal pain assessments comprise observable indicators such as physiological changes (eg, heart rate), or behavioural indicators (eg, crying), which are influenced by contextual factors (eg, gestational age).[1] Pain management with analgesics or sedatives in neonates is associated with regional brain dysmaturation in brain structures associated with memory and motor coordination.[3-5] Therefore, the identification of objective pain measures is crucial to effectively manage pain but also to promote brain health and prevent childhood disabilities.

Evidence from functional MRI (fMRI) has shown noxious-stimulus evoked activation in pain-processing brain regions in newborn babies.[6] Furthermore, functional-connectivity strength in core pain-processing regions is predicted by invasive procedures during intensive care in neonates.[7] However, defining a unique pain signature in newborn babies is challenging due to the absence of subjective reports of pain. Unique neural signatures specific for noxious stimuli (neurologic pain signature [NPS])[8] and cognitive pain modulation (stimulus intensity independent pain signature-1 [SIIPS1])[9] have been identified in adults. Whether similar signatures (NPS, SIIPS1) emerge within the first weeks of life has remained unclear due to challenges examining pain in infants.

In *The Lancet Digital Health*, Eugene Duff and colleagues[10] address the issue of identifying objective brain-based biomarkers for pain in the newborn brain. Initially, the authors examined the NPS and SIIPS1 in ten adults who were administered varying intensities of noxious stimuli during fMRI. The adults rated the intensity of the stimuli. The activation patterns in adults were evaluated in relation to predefined signatures for the NPS, SIIPS1, and four control signatures (the vicarious pain signature, the picture-induced negative emotion signature, the social rejection signature, and a global signal signature).

Subsequently, in two prospective cohorts of healthy newborn babies, a similar stimulation protocol to that used in the adults, but consisting of milder intensities of noxious stimuli, was administered to elicit pain-related activation during fMRI. The resulting neonatal statistical parametric maps for the stimulus intensities were transformed into adult-template space to enable a direct quantitative analysis with the adult signatures. Infants had high concordance with the NPS observed in adults, reflecting core pain-processing brain regions. These findings suggest that newborn babies process nociceptive input in a similar way to adults. By contrast, divergent associations were observed between the neonatal pain-evoked activation signatures and the SIIPS1 signature in the adult brain. Findings were interpreted by the authors to indicate a similarity in nociceptive processing between newborns and adults, whereas developing pain modulatory systems diverge between newborns and adults.

This study provides evidence for brain-derived biomarkers of pain-evoked activation in the neonatal brain. A unique signature for the experience of neonatal pain might offer opportunities to assess pharmaceutical therapies and non-pharmacological interventions that might be more clinically efficacious than the currently available options for neonatal pain. Furthermore, the findings might be used to corroborate in-hospital monitoring methods such as electroencephalography and functional near infrared spectroscopy to monitor discomfort when infants are unable to reliably express this non-verbally. Novel functional imaging methods might be used to complement observable indicators of pain to improve pain management and ultimately brain health in neonates.

The study by Duff and colleagues is important for understanding pain in the neonatal brain. Considering

the importance of pain as a predictor of brain health in preterm neonates, a key next step will be to understand the developmental emergence of the fMRI signature identified in this study. Similarly, since most critically-ill neonates, such as those born preterm, with congenital heart disease, or with hypoxic–ischaemic encephalopathy, are repeatedly exposed to painful stimuli of varying intensities as part of intensive care practices (eg, surgeries, chest intubations, heel lances), identifying how the pain signature evolves over time will inform more optimal pain management strategies. Application of this new imaging signature might enable understanding of how available pain management strategies mitigate the cerebral response to pain. Improving the experience of pain will improve the trajectory of brain development of neonates who require life-saving care. Until these issues are addressed, neonatal health-care providers are reminded by Duff and colleagues to do all they can to minimise the exposure of babies to pain.

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