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Detrimental effects of general anaesthesia on young primates: are we closer to understanding the link?

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This editorial accompanies the following articles: Infant isoflurane exposure affects social behaviours, but does not impair specific cognitive domains in juvenile non-human primates by Neudecker et al., *Br J Anaesth* 2021:126: 486–99, doi: 10.1016/j.bja.2020.10.015
Prospectively assessed neurodevelopmental outcomes in studies of anaesthetic neurotoxicity in children: a systematic review and meta-analysis by Ing et al., *Br J Anaesth* 2021:126: 433–44, doi: 10.1016/j.bja.2020.10.022

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'There must be no barriers to freedom of inquiry. There is no place for dogma in science. The scientist is free, and must be free to ask any question, to doubt any assertion, to seek any evidence, to correct any errors.'

- J. Robert Oppenheimer

The complexity of investigating a phenomenon where a direct cause-and-effect relationship may not be possible to establish cannot be overestimated. How can one with absolute certainty make a causal connection between an event in the distant past with the currently observed outcome?

This is a dilemma that has been plaguing investigators for more than two decades in the field of anaesthesia-induced developmental neurotoxicity, a dilemma not caused by a lack of animal evidence. To the contrary, hundreds of published studies from around the world using a variety of animal species, experimental models, and clinically-used general anaesthetics have shown over and again the link between early exposure to general anaesthesia and long-lasting effects on behavioural and cognitive development. The complexity of this dilemma becomes evident when the translational value of these observations is queried. How could it be confirmed beyond a reasonable doubt that a similar phenomenon exists in humans? How can we establish a link between exposure to general anaesthesia during a very young age and cognitive/behavioural impairment years later?

In this issue of the *British Journal of Anaesthesia*, we have a unique opportunity to examine two scientific investigations focused on anaesthesia-induced developmental neurotoxicity in primates; one focused on rhesus macaque monkeys and the other focused on humans. These studies confirm the notion that non-human primates are a useful model of anaesthesia-induced developmental neurotoxicity when it comes to the subtle, but unique impact of general anaesthesia on higher socio-emotional aspects of primate behaviours.

In an elegant non-human primate study published in this issue, Neudecker and colleagues[1] examined spontaneous social behaviours in juvenile monkeys exposed in infancy to the volatile anaesthetic isoflurane. Using multiple behavioural assessment tools and two experimental paradigms consisting of a single exposure or multiple (total of three) exposures, they report significant, although different, behavioural outcomes during juvenile development.

Specifically, a single 5-h exposure to isoflurane promoted anxiety-related behaviour and increased behavioural inhibition. Multiple exposures, by contrast, led to decreased close social behaviour. Interestingly, neither of the experimental paradigms suggested impairment in cognitive domains when the focus was on object permanence, executive function, spatial working memory, and stimulus-response learning and testing that occurred by the age of 2 yr.

Based on previous reports in which histomorphological changes were assessed using this anaesthesia regimen, it appears that significant apoptosis in both neurones and oligodendrocytes was detected in the amygdala and the cortical (prefrontal and cingulate) brain regions of infant monkeys.[2,3] This is of interest since these brain regions are critical for the development of socio-emotional behaviours[4,5] which suggests that neuronal and oligodendroglial morphological damage leading to faulty neuronal circuitry development may be responsible for functional impairments observed later in life. Although it is difficult to discern with certainty what the reported behavioural changes may represent in the long term, the authors bring to our attention the fact that 'anxious temperament' early in development has been linked to anxiety and depressive disorders later in life.[6] This suggests that

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early onset of anxiety and behavioural inhibition could be detrimental to normal socio-emotional development.[7]

The authors reminded us that their non-human primate study may not be relevant to human anaesthesia considering that there are '… only a few human neonatal procedures requiring anesthesia to extend to 5 hours and even fewer would involve three episodes of such length.' Although this is possibly correct, it is interesting that a second study published in this issue (a meta-analysis of prospectively examined neurodevelopmental outcomes in children exposed to general anaesthesia early in childhood) highlights the possibility that prolonged, repeated, or both exposures may not be necessary for impairments to arise. This meta-analysis suggests what has been known for a long time in the animal literature: the key to vulnerability is the timing of exposure and whether the exposure occurs during the critical stages of brain development.[8]

Using a well-designed and comprehensive meta-analysis, Ing and colleagues[9] examined long-term neurodevelopmental outcomes in children exposed to a single general anaesthetic procedure. They focused on RCTs and non-randomised studies to examine five outcome measures: full-scale intelligence quotient; parentally reported Child Behavior Checklist total, externalizing and internalizing problem scores; and Behavioral Inventory of Executive Function. They report that a single general anaesthetic procedure causes a 47% increased risk of an internalising behavioural deficit and a 68% increased risk of impaired executive function, and a significant increase in externalising problems in exposed children compared with unexposed ones (although no differences were noted in full-scale intelligence quotient). When one considers that up to one million very young children are exposed to general anaesthesia each year in the USA alone,[10,11] it is reasonable to suggest that observed impairments on an individual level may have substantial implications at the population level over the course of many years.

The authors go on to note that parental reports on behavioural function of their children suggest a higher incidence of behavioural problems leading to attention deficit and hyperactivity, and note that these impairments in socio-emotional development are consistent with the reports in non-human primates.[12] Parental reports are an invaluable tool for the assessment of children's behavioural development, because many aspects of socio-emotional development cannot be examined in 'the structured setting of neurophysiological assessment but are evident in other settings such as home or school.' Hence, I find it particularly illuminating that the authors took the time to address the issue of parental bias. They report that even when the parents were blinded to the type of anaesthesia their child received (regional *vs* general), the outcomes reported by blinded and unblinded parents were comparable: parents who knew that their child was exposed to general anaesthesia did not report a higher incidence in behavioural problems compared with parents who were not aware of the type of anaesthesia their child received.[13] This would suggest that parent reporting was less likely to be biased but rather represents a valuable assessment of socio-emotional behavioural development of their children.

Based on the two notable studies discussed herein and numerous others previously published, it is becoming increasingly clear that an early exposure to general anaesthesia during critical stages of young brain development is not innocuous, as suggested by previous studies. Although we found solace in believing that prolonged, multiple, or both exposures were necessary to cause significant issues in behavioural development later in life, thus perhaps affecting only a subgroup of vulnerable children, we are now learning that even a single exposure of common duration could pose a risk. We are also learning that focusing only on cognitive development may provide a limited approach to what seems to be a need for comprehensive assessment of long-term outcomes of early exposure to general anaesthesia, with socio-emotional behavioural development being crucially important and perhaps a more sensitive signal of anaesthesia-induced developmental impairment. Indeed, as Neudecker and colleagues[1] bring up in their closing remarks, although there are perhaps no effects on general intelligence, the alteration in social behaviour in children exposed to anaesthesia during infancy mimics the observed impairments in non-human primates, thus advising us to keep an open mind and to broaden our quest for understanding all aspects of anaesthesia-induced impairment in human behavioural development.

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