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EDITORIALS

Thinking, fast and slow: highlights from the 2016 BJA seminar on anaesthetic neurotoxicity and neuroplasticity

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In his best-selling 2011 book entitled "Thinking Fast and Slow", Nobel laureate Daniel Kahneman elucidates the contrast between two modes of human thought-processing: fast and slow thinking.[1] Fast thinking is characterized by rapid and automatic reaction to a simulation or problem, while slow thinking involves a measured and analytical response. This dichotomy epitomises the clash between clinicians and basic scientists on the enigma of anaesthetic neurotoxicity.[2] Based on their clinical practise that anaesthetics do not overtly produce neurocognitive deficits, the clinician's viewpoint relies on instinct and experience, while the scientist's viewpoint is based on a deliberate analysis of experimental data and its logical extrapolation to the clinical setting.

Since the initial *British Journal of Anaesthesia* sponsored 2012 Seminar on Anaesthetic Neurotoxicity and Neuroplasticity,[3] the impact of anaesthetics on the central nervous system (CNS) continues to be the focus of ardent investigation throughout the lifespan in both the laboratory and bedside. These preclinical reports have even fuelled a cautionary statement by the SmartTots collaborative and a recent United States Food and Drug Administration Drug Safety Communication on the use of anaesthetic and sedative drugs in patients aged three yr and under.[4 5] This Drug Safety Communication has disrupted the routine management of elective surgery in this age group and prompted some groups to change their preoperative discussions regarding the risks of anaesthetic and sedative drugs.[6]

A working group of laboratory and clinical investigators with expertise in neuroscience, epidemiology and clinical anaesthesia reconvened in June 2016 in London to review the current evidence on the impact of anaesthetics on the developing CNS, from the

foetus to the elderly, and discuss ongoing investigations in both the preclinical and clinical arena. A recent review by two participants of the seminar (LV and ZX) provides a comprehensive state of the art overview of this subject.[7] The following is a synopsis of the novel presentations and ensuing discussions of this two day seminar and how these ongoing investigations relate to the recent FDA drug safety communication. Nine relevant articles are included in this special issue of the *British Journal of Anaesthesia* on Anaesthetic Neurotoxicity and Neuroplasticity published this month and freely available on the web (https://academic.oup.com/bja (accessed 18 July 2017)).[8–16]

Preclinical investigations

Investigations *in vitro*

The mechanisms underlying anaesthetic neurotoxicity have not been fully elucidated, but recent evidence suggests that anaesthetic exposure during critical periods of brain development not only leads to cell death and impaired neurogenesis, but also to aberrant formation of neural circuitry. Dendrites, which receive synaptic contacts from axons and integrate signals for computational purposes, are a key component of all neural circuits which continue to develop postnatally in many brain regions. The effects of anaesthetics on epigenetic modulation of transcription clearly demonstrate a global effect on neurodevelopment and synaptogenesis.[17] This novel observation could account for the derangements caused by anaesthetic drugs on parallel signalling pathways.[7]

A key concept reiterated by several preclinical investigators is modulation of neuronal plasticity by anaesthetic drugs.[18] Evolving observations from several laboratories demonstrate aberrant growth of dendrites and axons at different developmental periods.[19–25] These morphological changes have also been observed in laboratory models of neuropsychiatric disorders such as autism, schizophrenia and Alzheimer Disease.[26]

Both sevoflurane and ketamine have been shown to activate glycogen synthase kinase-3β (GSK-3β), increasing phosphorylation of its substrates.[27 28] GSK-3β has been identified as a ubiquitous modulator of neurodevelopment, and is linked to mood disorders and Alzheimer Disease.[29] Exposure to anaesthesia and surgery worsens cognitive impairment in transgenic Alzheimer mice.[10] Ongoing work suggests that anaesthetics impair dendrite development, which has been implicated in neurodevelopmental disorders. However, the impact of these structural changes on subsequent neurocognitive deficits has been questioned and needs to be examined in other laboratory models.[9] Taken together, studies in the laboratory are identifying analogous pathological morphologies and pathways previously observed in preclinical models of various neuropsychiatric and behavioural disorders.

Investigations *in vivo*

Histopathological, anatomical and behavioural endpoints have all demonstrated utility in describing the extent of developmental anaesthetic neurotoxicity; the behavioural/cognitive effects are long-lasting if not permanent. In animal models a variety of drugs have shown promise in ameliorating the adverse effects that can accompany general anaesthesia during development.[8] Landmark investigations from the Fitzgerald laboratory have clearly demonstrated an adverse impact of unmitigated noxious stimulation on the development of nociception.[30–32] These findings clearly show that pain in early life has long-term structural and functional effects on nociceptive pathways.[33] As anaesthetic agents vary in their degree of analgesic efficacy, effects of both anaesthesia and analgesia need to be considered. These reports validate the need to provide some degree of both anaesthesia and analgesia during painful procedures. However, the impact of anaesthetic drugs on all phases of neurodevelopment and their functional consequences on cognition and behaviour need to be further interrogated in the laboratory.

Neuroglial interactions and mechanisms also play important age- and brain region-specific roles in the developing nervous system. Neuroinflammation has been identified in laboratory models of both anaesthetic and injury-induced plasticity.[34–36] Recent observations on the association of neuroinflammation induced by surgical stimuli and neurocognitive changes, clearly identify a novel therapeutic target to mitigate postoperative delirium and cognitive dysfunction in the elderly.[37 38] Importantly, changes in microglial phenotype can produce long-term alterations in response to subsequent stimuli.

Nonhuman primates provide a recognised surrogate for investigating drug effects on humans.[39 40] A striking aspect of recently published reports on the impact of volatile anaesthetics on non-human primates is that clinically relevant concentrations and exposure schedules were utilised in these studies. A single three h exposure to isoflurane significantly increases apoptosis of both neurons and oligodendrocytes in infant rhesus monkeys.[11] Repeated exposures of infant rhesus monkeys to sevoflurane resulted in increased anxiety-related behaviours after an acute stressor.[41] Furthermore, multiple exposures to isoflurane anaesthesia for five h caused motor reflex deficits and anxiety behaviours compared with naïve and single isoflurane exposure groups.[42] Repeated exposures to sevoflurane also results in visual recognition memory impairment that emerges after the first yr of life.[13]

Laboratory studies in rodents and nonhuman primates have clearly demonstrated that every anaesthetic agent rigorously tested can produce developmental neurotoxicity depending on the duration of anaesthesia and developmental stage at exposure. These effects are agent-dependent however, with some having greater effect than others. Understanding the mechanisms involved is essential for identifying: i) preventive strategies that can be administered during general anaesthesia; ii) targeting interventions to high-risk groups; and iii) modulating 'unavoidable' adverse effects (such as focused educational or behavioural interventions for children who have required anaesthesia). At this stage, multiple mechanisms have been identified with effects on neurogenesis, cell viability, synaptic function and stability, network formation and neuroglial interactions. It is not yet clear if these represent a dose-dependent continuum from plasticity to toxicity or independent mechanisms.

Clinical investigations

As most general anaesthetics are neurotoxic in young animals, there is concern that the same holds true in infant humans.[43–45] However, the clinical phenotype of anaesthesia exposure in early life has not been clearly and uniformly defined at a later age. While a wide range of outcome measures have been analysed, they vary widely across studies, and have differences in sensitivity, specificity, potential confounding by other factors at the time of anaesthesia (e.g. hypotension, concurrent illness and surgical injury), and by the extent to which persistent biological effects of anaesthetic exposure are modified by subsequent environmental, social and family factors. Age at the time of evaluation has a significant impact on the sensitivity of the outcome, with the

majority of cohort studies showing effects emerging at older ages.

Surgery in infancy is associated with increased risk of poor neuro-behavioural outcome, although the reasons for this association are unclear.[46 47] Early retrospective studies have implicated exposure to anaesthesia and surgery before two yr of age leads to measurable cognitive deficits.[46 48 49] The duration of anaesthetic exposure appears to worsen learning and cognitive function at a later time.[14 49] However, recent analyses of large databases revealed that children from two to four yr of age had statistically significant decrements in their educational assessments.[50 51] This recent finding challenges the FDA's contention that, "repeated or lengthy use of general anaesthetic and sedation drugs during surgeries or procedures in children younger than three yr or in pregnant women during their third trimester may affect the development of children's brains." It is clear from the preclinical data that anaesthetic drugs can modulate neurodevelopmental processes throughout the lifespan in an individual.[7]

Two high profile multicentre clinical trials, the GAS and PANDA trials, have recently published their findings. The GAS trial is a randomized controlled trial that provided strong evidence that one h of anaesthesia exposure in infancy does not result in neurologic deficit as measurable at two yr of age.[52] However a measure at two yr of age is insensitive, so the trial does not rule out an effect on higher executive function, cognition and memory. The five yr assessment will provide more data on cognitive outcomes. The PANDA study prospectively examined the impact of inguinal hernia surgery in infants under three yr of age on an extensive battery of neurocognitive tests.[53] When compared with a sibling cohort naïve to surgery and general anaesthesia, no significant differences in these neurocognitive domains were detected. Both negative studies only examined the impact of short exposures to general anaesthesia and surgery. This does not rule out an effect with longer exposures. These findings are consistent with the lack of toxicity and neuro-behavioural deficits after short exposures to anaesthetics in laboratory animals.

Another cognitive domain that has been examined in humans is recognition memory, which is the ability to recall specific details of an item and its context, and familiarity, which is the feeling that one has previously encountered an object or context. An ambi-directional cohort study showed that infants exposed to volatile anaesthetic for longer than two h exhibited a deficit in recognition memory compared with matched controls assessed between the ages of six and 11 yr. A comparable deficit in recollection-like memory was found in rats exposed to sevoflurane at seven days of age and tested months later.[54] A follow-up ambi-directional trial comparing late *vs* early and long *vs* short exposure to general anaesthesia with a volatile agent as the primary anaesthetic is underway.

Apart from neurotoxicity, there might be other modifiable perioperative factors that impact long-term neurocognitive outcome, among them hypotension and hypocarbia.[55] Anaesthetists are now adapting their management to mitigate iatrogenic causes of morbidity by reducing anaesthetic concentrations, avoiding hypocarbia, and treating hypotension more aggressively. Clearly, much more work must be done. Prospective studies are underway and will hopefully provide guidance. New anaesthetic regimens and drug classes need to be developed to minimize neurological morbidity for patients of *all* ages.

The role of clinical trials

The optimal design of clinical trials depends on the questions being asked. A single clinical trial cannot answer the crucial question: "does the toxicity seen in animals have clinical relevance to humans?" Such a trial would simply not be feasible as it would require large numbers of infants having long exposures to anaesthesia comparing a standard to a nontoxic anaesthetic. Future trials should be based on strong preclinical evidence that the nontoxic regimen is indeed harmless. Although the best outcome measure for these trials is debatable, it should be founded on what is expected based on preclinical studies and/or what is most important for the child.

One approach is to design a superiority trial in which an alternative anaesthetic is compared with standard care. The alternative anaesthetic must be plausibly less toxic based on preclinical data, but does not have to be proven to be definitively or completely nontoxic. The alternative also must be feasible and readily translatable into common practice. A "dexmedetomidine-based sevoflurane sparing" technique may be an alternative anaesthetic for this study design. The TREX study (Clinical Trials identification: NCT03089905) is underway at several paediatric hospitals in North America, Europe and Australasia. Other new mitigating agents are being explored in preclinical studies but are yr away from being ready for human trials.

Early recognition of the pathological processes is indispensable in mitigating the adverse consequences of anaesthetic exposure, leading to the development of minimally invasive biomarkers.[56] Imaging technology has the potential to detect and track evolving structural and metabolic derangements in the brain associated with anaesthetic drugs.[57] Micro-positron emission tomography (mPET) and computed tomography imaging in neonatal rhesus monkeys previously exposed to sevoflurane anaesthesia for eight h demonstrated increased glial activation, which was attenuated by acetyl-L-carnitine.[58] As these minimally-invasive biomarkers of anaesthetic neurotoxicity (including imaging, blood-based and behavioural) have been identified in laboratory animals,[56 59] application of these techniques should be useful in conducting studies on the ongoing effects of general anaesthesia in children and adults. Functional magnetic resonance imaging (fMRI) holds promise in assessing structural and functional changes in the brain during the perioperative period.[12] Serum levels of brain-derived neurotrophic factor have been shown to be a biomarker for postoperative delirium in elderly patients. However, these are only surrogate outcomes and their utility will depend on the confidence we have that they are indeed associated with a meaningful neurodevelopmental outcome. Although there are various candidate biomarkers, none have yet been linked to neurodevelopmental outcome in humans.

Conclusions

Accumulating evidence from preclinical studies demonstrates that general anaesthetics can modulate CNS development and function. However, recent prospective studies of the impact of prior exposure to anaesthetics on early measures of cognitive function have not been consistent with some previously published retrospective clinical reports. As evidence from ongoing clinical studies in paediatric and geriatric anaesthesia emerges, it is important for this line of research to be expanded and openly deliberated in scientific seminars such as the *British Journal of Anaesthesia* sponsored 2016 Seminar on Anaesthetic Neurotoxicity and Neuroplasticity.

Although the FDA Drug Safety Communication assertion that, "to better inform the public about this potential risk, we are requiring warnings to be added to the labels of general anaesthetic and sedation drugs" may be cause for most clinicians to react and

protest that this is too severe and a threat to their clinical practice, a "slow" and deliberate examination of this document reveals that much more work needs to be done to investigate the impact of anaesthetics on neurodevelopment. As general anaesthesia often cannot be avoided, regardless of patient age, it is important to understand the complex mechanisms and effects involved in anaesthesia-induced neurotoxicity, and to develop strategies for avoiding or limiting potential CNS injury. The Drug Safety Communication further underscores the need to pursue investigations that will permit more definitive conclusions about potential neurotoxicity in humans of all ages, and facilitate the establishment of clinically-based recommendations to guide practice.

Declaration of interest

None declared.

References

1. Kahneman D. Thinking, Fast and Slow. New York: Farrar, Straus and Giroux, 2011
2. Todd MM. Anesthetic neurotoxicity: the collision between laboratory neuroscience and clinical medicine. *Anesthesiology* 2004; **101**: 272–3
3. Jevtovic-Todorovic V, Absalom AR, Blomgren K, *et al*. Anaesthetic neurotoxicity and neuroplasticity: an expert group report and statement based on the BJA Salzburg Seminar. *Br J Anaesth* 2013; **111**: 143–51
4. Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity–clinical implications of animal models. *N Engl J Med* 2015; **372**: 796–7
5. FDA: FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women, Drug Safety Communications, 2016; **376**: 905–7
6. Andropoulos DB, Greene MF. Anesthesia and Developing Brains – Implications of the FDA Warning. *N Engl J Med* 2017; **376**: 905–907
7. Vutskits L, Xie Z. Lasting impact of general anaesthesia on the brain: mechanisms and relevance. *Nat Rev Neurosci* 2016; **17**: 705–17
8. Xu G, Lu H, Dong Y, Soriano S, Zhang Y, Xie Z. Coenzyme Q10 reduces sevoflurane-triggered cognition deficiency in young mice. *Br J Anaesth* 2017; **119**: 481–91
9. Schilling J, Kassan A, Mandyam C. *et al*. Inhibition of p75 neurotrophin receptor does not rescue cognitive impairment in adulthood after isoflurane exposure in neonatal mice. *Br J Anaesth* 2017; **119**: 465–71
10. Mardini F, Tang JX, Li JC. *et al*. Effects of propofol and surgery on neuropathology and cognition in the 3xTgAD Alzheimer transgenic mouse model. *Br J Anaesth* 2017; **119**: 472–80
11. Noguchi K, Johnson S, Dissen G, Martin L, Manzella F, Schenning K, Olney J, Brambrink A. Isoflurane exposure for three hours triggers significant apoptotic cell death in the neonatal macaque brain. *Br J Anaesth* 2017; **119**; 524–31
12. Indja B, Fanning JP, Maller JJ, *et al*. Neural network imaging to characterise brain injury in cardiac procedures. *Br J Anaesth* 2017; **118**: 680–8
13. Alvarado M, Murphy K, Baxter M. Visual recognition memory is impaired in rhesus monkeys repeatedly exposed to sevoflurane in infancy. *Br J Anaesth* 2017; **119**: 517–23
14. Ing C, Hegarty MK, Perkins AJ, Whitehouse A, DiMaggio C, Sun M, Li G, Sun LS. Duration of anaesthetic exposure in early childhood and long-term language and cognitive ability. *Br J Anaesth* 2017; **119**: 532–40
15. Lee JG, Lin E, Hofacer R, Upton B, Lee S, Ewing L, Bernadin J, Loepke AW. Alternative technique or mitigating strategy for sevoflurane-induced neurodegeneration: A randomised controlled dose-escalation study of dexmedetomidine in neonatal rats. *Br J Anaesth* 2017; **119**: 492–505
16. Perez-Zoghbi J, Zhu W, Grafe MR, Brambrink AM. Dexmedetomidine-mediated neuroprotection against sevoflurane-induced neurotoxicity extends to several brain regions in neonatal rats. *Br J Anaesth* 2017; **119**: 506–16
17. Dalla Massara L, Osuru HP, Oklopcic A, *et al*. General anesthesia causes epigenetic histone modulation of c-Fos and brain-derived neurotrophic factor, target genes important for neuronal development in the immature rat hippocampus. *Anesthesiology* 2016; **124**: 1311–27
18. Vutskits L. General anesthesia: a gateway to modulate synapse formation and neural plasticity? *Anesth Analg* 2012; **115**: 1174–82
19. Mintz CD, Barrett KM, Smith SC, Benson DL, Harrison NL. Anesthetics interfere with axon guidance in developing mouse neocortical neurons in vitro via a gamma-aminobutyric acid type A receptor mechanism. *Anesthesiology* 2013; **118**: 825–33
20. Mintz CD, Smith SC, Barrett KM, Benson DL. Anesthetics interfere with the polarization of developing cortical neurons. *J Neurosurg Anesthesiol* 2012; **24**: 368–75
21. Vutskits L, Gascon E, Potter G, Tassonyi E, Kiss JZ. Low concentrations of ketamine initiate dendritic atrophy of differentiated GABAergic neurons in culture. *Toxicology* 2007; **234**: 216–26
22. De Roo M, Klauser P, Briner A, *et al*. Anesthetics rapidly promote synaptogenesis during a critical period of brain development. *PLoS One* 2009; **4**: e7043
23. Briner A, De Roo M, Dayer A, Muller D, Habre W, Vutskits L. Volatile anesthetics rapidly increase dendritic spine density in the rat medial prefrontal cortex during synaptogenesis. *Anesthesiology* 2010; **112**: 546–56
24. Briner A, Nikonenko I, De Roo M, Dayer A, Muller D, Vutskits L. Developmental stage-dependent persistent impact of propofol anesthesia on dendritic spines in the rat medial prefrontal cortex. *Anesthesiology* 2011; **115**: 282–93
25. Platholi J, Herold KF, Hemmings HC Jr, Halpain S. Isoflurane reversibly destabilizes hippocampal dendritic spines by an actin-dependent mechanism. *PLoS One* 2014; **9**: e102978
26. Penzes P, Cahill ME, Jones KA, Vanleeuwen J-E, Woolfrey KM. Dendritic spine pathology in neuropsychiatric disorders. *Nat Neurosci* 2011; **14**: 285–93
27. Tao G, Zhang J, Zhang L, *et al*. Sevoflurane induces tau phosphorylation and glycogen synthase kinase 3beta activation in young mice. *Anesthesiology* 2014; **121**: 510–27
28. Liu JR, Baek C, Han XH, Shoureshi P, Soriano SG. Role of glycogen synthase kinase-3beta in ketamine-induced developmental neuroapoptosis in rats. *Br J Anaesth* 2013; **110(Suppl 1)**: i3–9
29. Hur E-M, Zhou F-Q. GSK3 signalling in neural development. *Nat Rev Neurosci* 2010; **11**: 539–51
30. Fitzgerald M. The development of nociceptive circuits. *Nat Rev Neurosci* 2005; **6**: 507–20
31. Schwaller F, Fitzgerald M. The consequences of pain in early life: injury-induced plasticity in developing pain pathways. *Eur J Neurosci* 2014; **39**: 344–52
32. Walker SM, Fitzgerald M, Hathway GJ. Surgical injury in the neonatal rat alters the adult pattern of descending modulation from the rostroventral medulla. *Anesthesiology* 2015; **122**: 1391–400

33. Walker SM. Translational studies identify long-term impact of prior neonatal pain experience. *Pain* 2017; **158**(Suppl 1): S29–S42
34. Shen X, Dong Y, Xu Z, *et al*. Selective anesthesia-induced neuroinflammation in developing mouse brain and cognitive impairment. *Anesthesiology* 2013; **118**: 502–15
35. Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M. Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci USA* 2010; **107**: 20518–22
36. Cibelli M, Fidalgo AR, Terrando N, *et al*. Role of interleukin-1beta in postoperative cognitive dysfunction. *Ann Neurol* 2010; **68**: 360–8
37. Zhang MD, Barde S, Yang T, *et al*. Orthopedic surgery modulates neuropeptides and BDNF expression at the spinal and hippocampal levels. *Proc Natl Acad Sci USA* 2016; **113**: E6686–95
38. Terrando N, Yang T, Wang X, *et al*. Systemic HMGB1 neutralization prevents postoperative neurocognitive dysfunction in aged rats. *Front Immunol* 2016; **7**: 441
39. Paule MG, Schulze GE, Slikker W Jr. Complex brain function in monkeys as a baseline for studying the effects of exogenous compounds. *Neurotoxicology* 1988; **9**: 463–70
40. Baxter MG, Alvarado MC. Monkey in the middle: Translational studies of pediatric anesthetic exposure. *Anesthesiology* 2017; **126**: 6–8
41. Raper J, Alvarado MC, Murphy KL, Baxter MG. Multiple anesthetic exposure in infant monkeys alters emotional reactivity to an acute stressor. *Anesthesiology* 2015; **123**: 1084–92
42. Coleman K, Robertson ND, Dissen GA, *et al*. Isoflurane anesthesia has long-term consequences on motor and behavioral development in infant rhesus macaques. *Anesthesiology* 2017; **126**: 74–84
43. Jevtovic-Todorovic V, Hartman RE, Izumi Y, *et al*. Early exposure to common anesthetic agents causes widespread neurodegeneration in the developing rat brain and persistent learning deficits. *J Neurosci* 2003; **23**: 876–82
44. Stratmann G, Sall JW, May LD, *et al*. Isoflurane differentially affects neurogenesis and long-term neurocognitive function in 60-day-old and 7-day-old rats. *Anesthesiology* 2009; **110**: 834–48
45. Yon JH, Daniel-Johnson J, Carter LB, Jevtovic-Todorovic V. Anesthesia induces neuronal cell death in the developing rat brain via the intrinsic and extrinsic apoptotic pathways. *Neuroscience* 2005; **135**: 815–27
46. Wilder RT, Flick RP, Sprung J, *et al*. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology* 2009; **110**: 796–804
47. DiMaggio C, Sun LS, Li G. Early childhood exposure to anesthesia and risk of developmental and behavioral disorders in a sibling birth cohort. *Anesth Analg* 2011; **113**: 1143–51
48. Ing C, DiMaggio C, Whitehouse A, *et al*. Long-term differences in language and cognitive function after childhood exposure to anesthesia. *Pediatrics* 2012; **130**: e476–85
49. Block RI, Thomas JJ, Bayman EO, Choi JY, Kimble KK, Todd MM. Are anesthesia and surgery during infancy associated with altered academic performance during childhood? *Anesthesiology* 2012; **117**: 494–503
50. O'Leary JD, Janus M, Duku E, *et al*. A population-based study evaluating the association between surgery in early life and child development at primary school entry. *Anesthesiology* 2016; **125**: 272–9
51. Glazt P, Sandin RH, Pedersen NL, Bonamy AK, Eriksson LI, Granath F. Association of anesthesia and surgery during childhood with long-term academic performance. *JAMA Pediatr* 2016; **171**: e163470
52. Davidson AJ, Disma N, de Graaff JC, *et al*. consortium GAS: Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. *Lancet* 2015; **387**: 239–50
53. Sun LS, Li G, Miller TL, *et al*. Association between a single general anesthesia exposure before age 36 months and neurocognitive outcomes in later childhood. *JAMA* 2016; **315**: 2312–20
54. Stratmann G, Lee J, Sall JW, *et al*. Effect of general anesthesia in infancy on long-term recognition memory in humans and rats. *Neuropsychopharmacology* 2014; **39**: 2275–87
55. Englehart MS, Allison CE, Tieu BH, *et al*. Ketamine-based total intravenous anesthesia versus isoflurane anesthesia in a swine model of hemorrhagic shock. *J Trauma* 2008; **65**: 901–8; discussion 908–9
56. Zhang X, Liu F, Slikker W Jr, Wang C, Paule MG. Minimally invasive biomarkers of general anesthetic-induced developmental neurotoxicity. *Neurotoxicol Teratol* 2017; **60**: 95–101
57. Vutskits L, Soriano SG. Imaging the progression of anesthetic-induced neurotoxicity: a leap toward translational relevance. *Anesthesiology* 2015; **123**: 497–8
58. Zhang X, Liu S, Newport GD, *et al*. In vivo monitoring of sevoflurane-induced adverse effects in neonatal nonhuman primates using small-animal positron emission tomography. *Anesthesiology* 2016; **125**: 133–46
59. Paule MG, Li M, Allen RR, *et al*. Ketamine anesthesia during the first week of life can cause long-lasting cognitive deficits in rhesus monkeys. *Neurotoxicol Teratol* 2011; **33**: 220–30

Appendix

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