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Developmental exposure to general anaesthesia: missed connections?

Mark G. Baxter* and Tristan Fehr

Nash Family Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

*Corresponding author. E-mail: mark.baxter@mssm.edu

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Since the discovery in 2003 of neurodegeneration and persistent cognitive impairments after exposure of infant rats to a cocktail of common general anaesthetics,[1] the implications of early life exposure to general anaesthesia for brain structure and function later in life have been an intense area of research and debate in anaesthesiology. As in many areas of biomedical research, translation between basic research in animal models and clinical research in humans remains challenging. This reflects a balance between the ability to perform experimental treatments in animals that cannot be done in humans, for example developmental anaesthetic exposure for research rather than therapeutic purposes, and the biological differences between animals and humans.

Considerable animal research has shown that early-life exposure to general anaesthesia is linked to neuronal and glial death, and to persistent impairments in behaviour and cognition.[2] Clinical studies have also found associations between prolonged or repeated exposure to anaesthesia during early development and neurobehavioural impairments. However, the presence of illness that requires surgery is a confound that weakens causal inferences.[3] Importantly, and reassuringly, brief and singular exposure to general anaesthesia during development in humans appears to present little risk for later disturbances in behaviour and cognition.[3]

Part of the tension between preclinical research in animal models and clinical studies with humans has been attributed to differences in anaesthetic duration and frequency of exposure. Animal studies often use prolonged exposures that are not common in paediatrics. In part, this is to mirror durations of exposure shown to cause loss of neurones and glia in animal studies. Nonetheless, long exposures can limit potential applications of this work to paediatric anaesthesia practice. However, significant advantages in research on animal models are the abilities to study the effects of anaesthesia without concomitant surgery or illness, and to minimise environmental variability that may obscure more subtle effects in humans.[4,5] Work in monkeys is especially important in this context because it is possible to monitor and support infant monkey physiology, for example by tracheal intubation and capnography, in ways that are not possible in rodents.

In this issue of *British Journal of Anaesthesia*, a new study by Young and colleagues[6] in rhesus monkeys promises to fill in another piece of this puzzle. This study evaluated the effects of briefer developmental general anaesthesia exposures on neuroimaging measurements related to white matter integrity. The data for the study were obtained by a secondary, opportunistic analysis of rhesus monkey neuroimaging data from neurodevelopmental studies performed at two non-human primate research centres. Rhesus monkeys require anaesthesia for neuroimaging, both for the safety of the monkey and for the safety of the researchers. As it was not possible to compare imaging data between monkeys exposed to anaesthesia *vs* non-exposed controls, the researchers instead calculated a 'total normalised exposure' index to ketamine and isoflurane. These anaesthetics were used in monkeys at both centres, thereby allowing correlation of the total normalised exposure to two anaesthetic drugs, one injectable and one inhaled, with measures from diffusion MRI scans. Monkeys at both centres received between zero and four MRI sessions under anaesthesia before the acquisition of diffusion MRI scans at 12 or 18 months of age, with each session requiring ~2 h of anaesthesia. Cumulative exposure to anaesthetic drugs in the course of these scans was associated with the final diffusion scans acquired at 12 or 18 months of age. This study provides an advantage by examining the effect of multiple, shorter exposures on a relevant imaging measure of white matter integrity, albeit without a behavioural endpoint.

The researchers used diffusion MRI to assess white matter micro-organisation *in vivo*. This approach infers the integrity

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of white matter, tissue that carries axonal connections between neurones, via the movement of water molecules in brain tissue.[7,8] Anisotropic diffusion means that the diffusion of water molecules is constrained in three-dimensional space in some way. In diffusion MRI, fractional anisotropy (FA) measures the degree of coherent directional water movement along fibre tracts. A higher measure of FA indicates greater directional coherence, whereas a lower value indicates greater disorganisation. Greater diffusivity is thought to reflect poorer organisation of white matter structure. Clinically, lower FA and greater diffusivity are associated with white matter damage, as in the case of traumatic brain injury,[9] Alzheimer's disease,[10] and multiple sclerosis.[11]

Because general anaesthesia was used for neuroimaging, exposures were relatively briefer than those that have been used in studies explicitly focused on anaesthesia – on the order of 2 h per exposure in this study compared with 4–24 h per exposure in other developmental studies in monkeys. Surgery and anaesthesia during infancy in humans have been associated with decreased white matter integrity and volume later in life.[12] Yet, as with other studies in humans, this association is obscured by confounding conditions, including illness that predicates the need for surgery. Analysing white matter microstructure in healthy monkeys without surgery illuminates the effects of anaesthesia on white matter in more clinically relevant anaesthetic conditions.

Young and colleagues[6] found substantial and widespread disruptions to white matter integrity that correlated with total normalised exposure to isoflurane and ketamine. Specifically, reductions in FA and increases in diffusivity were seen throughout the brain in data from both primate centres. These effects were enhanced with greater total normalised exposure. The magnitude of the changes in diffusion measures was substantial in some cases, with decreases in FA up to 40%. This vastly exceeds the magnitude of changes seen in clinical conditions, for example in traumatic brain injury.[13] This suggests that anaesthetic toxicity to oligodendrocytes, as has been shown in infant monkeys after longer single exposures to general anaesthesia,[14] may also occur with shorter exposures throughout development. These results also suggest that changes in white matter structure associated with oligodendrocyte loss can be detected *in vivo* via diffusion imaging.

An important confounding factor is that the two centres used different drugs in addition to ketamine and isoflurane. One used Telazol (tiletamine and zolazepam) for induction of anaesthesia, and the other used dexmedetomidine for maintenance of sedation during scanning. Because each of these drugs was only used in one of the two facilities, it was not possible to compute normalised exposure indices. Likewise, because total exposure to each drug within a facility was highly correlated with exposure to ketamine and isoflurane, it was not possible to separate effects of these drugs by including them as covariates in statistical analyses. Telazol is common in veterinary medicine with non-human primates because it provides safe, rapid, and effective sedation, but tiletamine has similar pharmacology to ketamine and may also have similar neurotoxic properties. Dexmedetomidine, by contrast, is an alpha-2 adrenergic agonist that may have neuroprotective properties in early development.[15,16] Indeed, the authors suggest that this may have contributed to some of the differences between data from the two primate centres, as the relationship between diffusion measures and total normalised exposure to ketamine and isoflurane was stronger in data from the facility that used Telazol than from the facility that used dexmedetomidine. Although tantalising, additional study is required to exclude the possibility that the difference is related to other factors.

Practically, the need for anaesthesia during neuroimaging may be a substantial confound that can complicate efforts to study developmental changes in brain structure, especially in the context of animal models of psychiatric and neurological disease. In the context of developmental anaesthesia research, future studies might investigate shorter exposures spread throughout the first year of life in monkeys, based on the evidence from this study that changes in white matter integrity are associated with anaesthesia exposure outside the first month or two postnatally. These data also bolster findings in humans of an association between general anaesthesia in infancy and reduced white matter volume and integrity later in life.[12] Finally, these findings point to the need for greater exploration of the potential implications of diminished white matter integrity in the context of anaesthesia early in development, to the extent that compromised brain connections may exacerbate risk after brain injury or with the development of neurological diseases.

Authors' contributions

Both authors contributed to the drafting of the article, revisions, and final approval of the submitted article.

Declarations of interest

The authors declare that they have no conflicts of interest.

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Normalising good communication in hospital teams

Jennifer M. Weller[1,2,*] and Craig S. Webster[1]

[1]Centre for Medical and Health Sciences Education, School of Medicine, University of Auckland, Auckland, New Zealand and [2]Department of Anaesthesia, Auckland City Hospital, Auckland, New Zealand

*Corresponding author. E-mail: j.weller@auckland.ac.nz

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Poor communication is widely acknowledged as a causal factor in healthcare failures and adverse events.[1] Modern healthcare is a complex sociotechnical system, in which effective communication between clinical personnel and patients is critical to the delivery of safe and appropriate healthcare. At the negative extreme, dysfunctional communication, including bullying, harassment, explicit bias, and discriminatory behaviours, is known to have powerful deleterious effects on individual and team performance.[2]

Many researchers have considered the structural elements of communication, often focusing on communication deficits, including missing, unclear, misdirected, mistimed, or unresolved utterances.[3] Efforts to improve communication based on such deficit models frequently involve strategies to promote competencies in clear, concise, and directed communication, using structured handovers and recaps, and graded assertiveness. Other researchers have considered the relational components of communication: the social and cultural influences of interactions between team members, and the extent to which team members respect each other and value the contributions and perspectives of all members of the team.

Consistent with the relational approach to communication, in this issue of the *British Journal of Anaesthesia*, Bertrand and colleagues[4] consider how the way we talk to each other in the clinical environment has knock-on effects in terms of subsequent clinical performance. In particular, they position their

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