BJA

British Journal of Anaesthesia, 0 (0): 1–7 (2017)

doi: 10.1093/bja/aew473
Special Issue

SPECIAL ISSUE

Visual recognition memory is impaired in rhesus monkeys repeatedly exposed to sevoflurane in infancy

M. C. Alvarado[1,*], K. L. Murphy[2] and M. G. Baxter[3]

[1]Division of Developmental and Cognitive Neuroscience, Yerkes National Primate Research Centre, Emory University, Atlanta, Georgia, USA, [2]Comparative Biology Centre, Newcastle University, Newcastle, UK and [3]Department of Neuroscience and Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA

*Corresponding author. E-mail: malvara@emory.edu

Abstract

Background. Experimental studies in animals have shown that exposure to general anaesthesia in infancy can cause loss of cells in the central nervous system and long-term impairments in neurocognitive function. Some human epidemiological studies have shown increased risk of learning disability after repeated anaesthesia exposure in early childhood. Thus, we investigated in a highly translational rhesus monkey model, whether repeated exposure in infancy to the inhalation anaesthetic sevoflurane is associated with impaired visual recognition memory during the first two yr of life.
Methods. Rhesus monkeys of both sexes were exposed to sevoflurane inhalation anaesthesia on approximately postnatal day 7 and then again 14 and 28 days later, for four h each time. Visual recognition memory was tested using the visual paired comparison task, which measures memory by assessing preference for looking at a new image over a previously-viewed image. Monkeys were tested at 6–10 months of age, again at 12–18 months of age, and again at 24–30 months of age.
Results. No memory impairment was detected at 6–10 months old, but significant impairment (reduced time looking at the novel image) was observed at 12–18 and 24–30 months old.
Conclusions. Repeated exposure of infant rhesus monkeys to sevoflurane results in visual recognition memory impairment that emerges after the first yr of life. This is consistent with epidemiological studies that show increased risk of learning disability after repeated exposure to anaesthesia in infancy/early childhood. Moreover, these deficits may emerge at later developmental stages, even when memory performance is unaffected earlier in development.

Key words: general anaesthesia; neurotoxicity syndromes; cognitive disorder; sevoflurane; macaque, rhesus

The possibility that exposure to general anaesthesia in infancy or early childhood may have long-term adverse effects on neurocognitive function is of concern to anaesthetists. Anaesthetic neurotoxicity has been demonstrated in newborns of a number of species,[1–6 44–45] although never directly observed in humans. Neurocognitive impairment after anaesthesia exposure early in life is also common in animal studies. Some human epidemiological studies have found that repeated exposure to anaesthesia early in childhood (before the age of four), is associated with increased risk of learning disability and attention deficit/hyperactivity disorder,[7–9] although this observation is not universal.[10 11] Moreover, single, relatively brief exposures to general anaesthesia early in childhood seem to be safe in terms of neurocognitive outcome in prospective studies, at least in terms of the endpoints and developmental stages that have been studied to date.[12 13]

Editorial decision: December 20, 2016; **Accepted:** Month 0, 0000

Editor's key points

- Exposure to general anaesthesia in infant animals can cause long-term neurocognitive deficits, especially after repeated or prolonged exposures.
- The effects of repeated exposure to sevoflurane anaesthesia in infancy on visual recognition memory were evaluated in a nonhuman primate model.
- Three four hour exposures to sevoflurane anaesthesia in infant rhesus monkeys led to neurocognitive deficits that appeared over a year later.

Because repeated exposure to general anaesthesia early in development seems to be associated with greater risk of later neurocognitive difficulties, we have developed a rhesus monkey model of repeated anaesthesia exposure in infancy. This model has a number of advantages, including the ability to monitor and support physiological homeostasis during anaesthesia to a much greater degree possible than with rodents, and allows assessment of the complex cognitive behaviours that nonhuman primates can display. In this model, we exposed infant macaques to sevoflurane anaesthesia for four h on postnatal day seven, and again on days 21 and 35. We then followed the animals that live with their mothers in large social groups at the Yerkes National Primate Research Centre for two yr of socioemotional and cognitive testing starting at six months of age, five months after their last anaesthetic exposure.[14]

The present report describes the development of recognition memory in these subjects, which were tested at six, 12 and 24 months of age using the visual paired comparison task (VPC)[15–18] (Fig. 1). This task, developed to study human memory,[15 16] measures incidental visual recognition memory and takes advantage of the spontaneous preference to look at novel stimuli. It requires no training, thus it is an ideal task for the study of memory in preverbal humans or non-verbal monkeys. Monkeys as young as 1 month of age will reliably spend more time looking at a novel image than the familiarized image.[19] Memory is further taxed by increasing the delay between initial viewing of the familiarized object and presentation of the novel stimulus. In adult humans and monkeys, damage to structures in the medial temporal lobe yields a recognition memory impairment at long delays and may vary in the type of memory impacted (e.g. object *vs* spatial).[20 21] Because this task is also sensitive to disruptions in memory during development as a consequence of neonatal damage to medial temporal lobe structures,[17 18 22 23] our second aim was to determine whether impairment patterns followed those produced by selective damage to those structures.

Methods

All animal procedures were approved by the Yerkes National Primate Research Centre and the Emory University Institutional Animal Care and Use Committee, and were conducted in full compliance with PHS Policy on Humane Care and Use of Laboratory Animals. Subject descriptions and anaesthetic procedures have been published elsewhere.[14] Briefly, twenty newborn rhesus macaques of Indian origin (*Macaca mulatta*) were born in two cohorts, in the breeding colony at the Yerkes National Primate Research Centre field station. The first, six female and four male, were born in the 2012 birth season. The second cohort (four female, six male) were born the following yr. All infants were delivered vaginally without veterinary intervention in their natal group compounds. Infants were born to middle-ranking dams and were housed in large social groups of 50-100 individuals and comprising several family groups. Infants were assigned as they were born and with consideration to balancing for sex and weight to either the control group or the anaesthesia group.

Monkeys received either three anaesthetic exposures to sevoflurane (anaesthesia group), or three brief maternal separations (Control group) on or about postnatal day seven (range from day six-10), that was repeated at two-week intervals for a total of three exposure/separations between postnatal days ~seven-35. After removal from the dam, all infants received a brief neurological exam (see[14]). At this point, monkeys in the anaesthetic group were mask-induced with sevoflurane (from 2 vol % to effect, maximum 8 vol % in 100% O_2), intubated and catheterized for i.v. fluids. Sevoflurane was administered for 4 h, with monitoring of vital signs, depth of anaesthesia and blood gases (see Table 1 in[14]). After complete recovery, the infant was returned to its dam. The recovery period lasted on average 20-30 min. Subjects in the control group experienced maternal separation at the same ages, that comprised the neurological exam and a period of handling that matched in total duration the separation consciously experienced by the experimental group. Thus, on average, control infants experienced 30-40 min of maternal separation and were returned to the dam. Details of the mother-infant interactions after these separations have been published[24] and did not differ between groups, indicating that the separations involved in anaesthesia exposures did not cause alterations in mother-infant bonding that might have impacted later cognitive or socioemotional behavior.

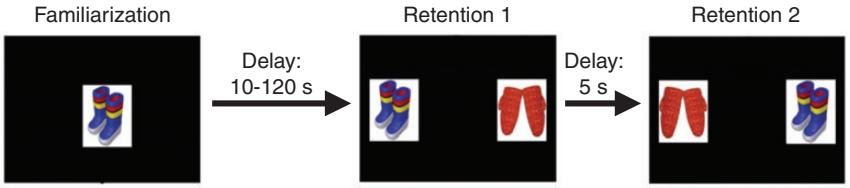

Fig 1 Illustration of a single trial of the visual paired comparison task.