

Repeated anesthesia in infancy increases anxiety-linked behavior in nonhuman primates

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Rhesus macaques repeatedly exposed to anesthesia during infancy display persistent anxiety-linked behaviors later in life in response to social stress, a study from Yerkes National Primate Research Center at Emory University and Icahn School of Medicine at Mount Sinai shows.

The results were published online on March 1 by the *British Journal of Anaesthesia*.

Epidemiological studies of human children have detected an association between multiple exposures to anesthesia and learning problems. The cause-and-effect relationship is unclear because children who need surgery may have underlying medical issues. Also, research in other animal models, such as rodents, has shown anesthesia <u>exposure</u> early in life can lead to cell death in the brain and cognitive impairments.

In the Yerkes and Mount Sinai study, the research team sought to determine whether non-surgical exposure to sevoflurane, an inhaled anesthetic commonly used with children, could lead to cognitive and behavioral alterations in a nonhuman primate (NHP) model. A translational animal model for this type of study provides information for consideration in the human clinical population.

Researchers exposed <u>rhesus macaques</u> three times during the first six weeks of life to sevoflurane for four hours each time. Animals' behavioral responses to a mild stress (an unfamiliar human) were recorded at one and two years of age. In these situations, animals exposed to anesthesia displayed increased behaviors such as scratching,



self-touching and self-grooming, which could be interpreted as fidgeting.

"These are subtle behavioral changes that we are seeing," says first author Jessica Raper, PhD, research associate at Yerkes National Primate Research Center. "There is no evidence that the exposed animals are treated differently in a normal social setting, but express increased displacement behavior under an acute stressor. In humans, displacement (self-touching) behaviors are a coping strategy for anxiety, thus one could interpret our results as a coping mechanism for increased anxiety in the monkeys"

Raper, other Yerkes researchers and Mark Baxter, PhD, at Mount Sinai School of Medicine in New York, previously assessed the behavioral effects of anesthesia exposure at an earlier age, as well as effects on visual recognition memory. The team is continuing to assess the effects of early anesthesia exposure on behavior at older ages.

In human children, alterations in anxiety levels could impact learning in school or test scores, although existing evidence is not so fine-grained. Epidemiological studies find increased incidence of learning disabilities and ADHD in kids with more than one exposure before the age of 3-4 years. The monkey studies are consistent with these reports and provide an opportunity to understand the mechanisms of anesthesia-induced cognitive changes, as well as show that the effects in humans may at least be partially due to anesthesia itself rather than surgery or an underlying condition that requires surgery, Raper says.

"If our current studies continue to add to the mounting evidence for neurocognitive effects after early anesthesia exposure, then our next steps will include studies to determine how to best protect the developing brain when <u>anesthesia</u> is required," she adds.

More information: J. Raper et al, Persistent alteration in behavioural



reactivity to a mild social stressor in rhesus monkeys repeatedly exposed to sevoflurane in infancy, *British Journal of Anaesthesia* (2018). DOI: 10.1016/j.bja.2018.01.014

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