

## Neuroscience Forefront Review

### Title

Preventing the long-term effects of general anesthesia on the developing brain: how translational research can contribute.

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## Preventing the Long-term Effects of General Anesthesia on the Developing Brain: How Translational Research can Contribute

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**Abstract**—In 2017, the Food and Drug Administration published a safety recommendation to limit the exposure of children to general anesthesia as much as possible below the age of three. Indeed, several preclinical and clinical studies have questioned the possible toxicity of general anesthesia on the developing brain. Since then, recent studies have tried to mitigate this alarming issue. While preliminary data suggest that, contrary to some perceptions, the possible toxicity of general anesthesia on the developing brain is not over yet, only stronger translational research will allow scientists to provide concrete answers to this public health issue. In this review, we will provide an overview of the current data in this field, including the view of preclinical researchers, neuropsychologists and pediatric anesthesiologists. Through translational research, preclinical researchers have more than ever a role to play to better understand and identify long-term effects of general anesthesia for pediatric surgery on brain development in order to minimize it. © 2021 IBRO. Published by Elsevier.

Version publiée  
Published version

**Key words:** children, developing brain, general anesthesia, translational research, neurotoxicity.

### INTRODUCTION

Each year, millions of children require surgery. One out of seven children is subjected to general anesthesia before three years old in western countries (Shi et al., 2018). General anesthesia for pediatric surgery is a safe procedure with a low risk of immediate complications (Habre et al., 2017). However, preclinical studies have shown that exposure to general anesthesia during the early stages of the developing brain- *in utero* or in the early infancy- could lead to structural and functional brain

abnormalities, as well as cognitive and behavioral disorders (Jevlovic-Todorovic, 2018). From a neurochemical aspect, cerebral consequences are conceptually possible, as most anesthetic agents exert their hypnotic effect through their agonist activity on GABA receptors or their antagonist activity on NMDA receptors, which are critical in neurodevelopmental processes. These preclinical considerations rightfully opened the debate on the possible neurotoxicity of general anesthesia in children and have been the driving force behind several retrospective clinical studies. In this context, in 2017 the Food And Drug Administration (FDA) issued a warning that repeated or prolonged general anesthesia in children younger than 3 years old should be performed with caution (Andropoulos and Greene, 2017). Following this recommendation, recent clinical studies have provided reassuring evidence of the safety of anesthesia in children. Yet, the debate is not over.

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Abbreviations: EDI, Early Development Index; FDA, Food and Drug Administration; TNF, tumor necrosis factor.