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Corresponding author:
Valery Likhvantsev

lik0704@gmail.com

Author Affiliation:
Department of Clinical Trials and intelligent IT, Federal Research and Clinical Centre of Intensive Care Medicine and Rehabilitology, Moscow, Russia.

Effects of repeated anesthesia on neurocognitive function: a systematic review and meta-analysis of experimental studies

Kuznetsov, IV; Berikashvili, LB; Tkachenko, AA; Ponomarenko, AV; Orlova, VA; Yadgarov, MYa; Likhvantsev, VV.

ADMINISTRATIVE INFORMATION

Support - No support.

Review stage at the time of initial registration - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 16 November 2026 and was last updated on 16 November 2026.

INTRODUCTION

Review question / Objective The objective of this systematic review and meta-analysis was to assess the effects of repeated general anesthesia on neurocognitive function and behavioral outcomes in rats compared with a single exposure to general anesthesia. Additionally, we aimed to evaluate whether the magnitude of these effects varied according to anesthetic type, the timing of outcome assessment, and the number of anesthetic exposures.
PICOS framework:
(i) Population: Rats used in experimental studies.
(ii) Intervention: Repeated exposure to general anesthesia (two or more anesthetic procedures) using anesthetic agents employed in clinical practice.
(iii) Comparator: A single exposure to general anesthesia.
(iv) Outcomes: Quantitative measures of cognitive function and behavior.
(v) Study design: Prospective interventional experimental studies.

Rationale The potential neurocognitive effects of repeated general anesthesia remain insufficiently understood. In clinical studies, the independent contribution of anesthesia is difficult to distinguish from the effects of surgery, underlying disease, and other perioperative factors.
Experimental animal models allow repeated anesthetic exposure to be investigated under controlled conditions while minimizing these confounding factors. However, existing studies differ in anesthetic agents, exposure frequency, timing of assessment, and behavioral testing methods, complicating the interpretation of their findings.
Therefore, this systematic review and meta-analysis aimed to evaluate the effects of repeated versus single general anesthesia on neurocognitive function in rats, with particular attention to anesthetic type, timing of outcome assessment, and the number of anesthetic exposures.

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Condition being studied The review investigated potential neurocognitive and behavioral alterations associated with repeated general anesthesia in rats. The primary focus was on changes in spatial learning, memory, and other behavioral functions following multiple anesthetic exposures. This experimental model allows the effects of repeated anesthesia to be evaluated independently of surgical interventions.

METHODS

Search strategy A systematic literature search was conducted in PubMed (MEDLINE) and the Cochrane Library, covering publications from 2001 onward. The final search was performed on January 12, 2026, by two independent investigators.
The search focused on experimental studies involving repeated general anesthesia in rats and subsequent assessment of cognitive or behavioral outcomes. Search concepts included general anesthesia, repeated or multiple anesthetic exposures, rats, learning, memory, cognition, and behavior.
No language restrictions were applied. Study selection involved independent screening of titles and abstracts, followed by full-text assessment against predefined eligibility criteria.

Participant or population Rats included in prospective experimental studies evaluating the effects of general anesthesia on cognitive function and behavioral outcomes.

Intervention Repeated exposure to general anesthesia, defined as two or more anesthetic procedures, using anesthetic agents employed in clinical practice. Eligible interventions included inhalational anesthetics (sevoflurane, desflurane, and isoflurane) and intravenous anesthetics (propofol and ketamine). Studies involving surgical interventions in the analyzed groups were excluded.

Comparator A single exposure to general anesthesia in rats.

Study designs to be included Prospective interventional experimental studies in rats comparing repeated (≥2 exposures) versus single general anesthesia, with quantitative assessment of cognitive function or behavioral outcomes.

Eligibility criteria Studies were eligible if they met the following criteria:
1. Original prospective interventional experimental studies published in 2001 or later.
2. Experimental models involving rats.
3. Inclusion of both repeated (≥2 exposures) and single general anesthesia groups within the same study.
4. Use of anesthetic agents employed in clinical practice.
5. Assessment of cognitive function or behavioral outcomes using quantitative tests.
6. Availability of the full text and sufficient numerical data for analysis.
Studies or individual experimental groups were excluded if quantitative outcome data were unavailable for either comparison group, sample sizes were not reported, or surgical procedures were performed in the analyzed groups.

Information sources PubMed (Medline), Cochrane Library.

Main outcome(s) The principal neurocognitive outcomes were measures of spatial learning and memory assessed using the Morris water maze:
• Escape latency (seconds).
• Number of crossings over the former platform location.
• Time spent in the target quadrant (seconds).
Outcomes were assessed after anesthetic exposure. For temporal subgroup analyses, assessment periods were classified as short-term (1–7 days), intermediate-term (8–36 days), and long-term (≥37 days).
Effect sizes were expressed as mean differences (MDs) between repeated- and single-anesthesia groups, with corresponding 95% confidence intervals (CIs).

Additional outcome(s) • Distance traveled in the Morris water maze (meters).
• Time spent in the central zone of the open-field test (seconds).
• Total distance traveled in the open-field test (meters).
• Sucrose preference index (%).

Quality assessment / Risk of bias analysis A formal risk-of-bias assessment using a standardized assessment tool was not performed in the current review.

Strategy of data synthesis Data were extracted from the full texts of eligible studies using Microsoft Excel. The extracted variables included study identification details, sample sizes, anesthetic agents and concentrations, number of anesthetic exposures, timing of outcome assessment, behavioral testing methods, outcome metrics, measurement units, and quantitative results in repeated- and single-anesthesia groups.

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When numerical outcome data were available only in figures, they were extracted using WebPlotDigitizer. Where necessary, reported medians and interquartile ranges were converted into means and standard deviations using established statistical methods. Standard errors were converted into standard deviations.

For quantitative synthesis, data from comparable experimental conditions within individual studies were combined as described in the review methodology. When multiple comparisons shared a common group, its sample size was divided by the number of comparisons to reduce double-counting.

Meta-analysis was performed using STATA 18.0 (StataCorp LLC, College Station, USA). The effect measure was the mean difference (MD) between repeated- and single-anesthesia groups, calculated with corresponding 95% confidence intervals (CIs).

Individual effect estimates were pooled using inverse-variance weighting. Statistical heterogeneity was assessed using the I^2 statistic and Cochran's Q test. A random-effects model was applied when I^2 was ≥50% and/or the Cochran Q test yielded $p < 0.05$; otherwise, a fixed-effect model was used. Between-study variance in random-effects models was estimated using restricted maximum likelihood (REML).

Subgroup analyses were conducted according to anesthetic type and timing of outcome assessment. Univariate random-effects meta-regression was used to investigate the association between the number of anesthetic exposures and the magnitude of observed effects. Regression coefficients were reported with 95% CIs, and statistical significance was assessed using the Wald test.

All statistical tests were two-sided, with statistical significance set at $p < 0.05$.

Subgroup analysis Subgroup analyses considered:

1. Anesthetic type: inhalational anesthetics (sevoflurane, desflurane, and isoflurane) versus intravenous anesthetics (propofol and ketamine).
2. Timing of outcome assessment: short-term (1–7 days), intermediate-term (8–36 days), and long-term (≥37 days) assessment after anesthetic exposure.

Subgroup analyses were performed for outcomes with sufficient comparable data. Differences between subgroups were examined to explore potential variations in the magnitude and persistence of the effects associated with repeated anesthesia.

Sensitivity analysis No separate sensitivity analysis was reported in the current review.

Language restriction No language limitations.

Country(ies) involved Russian Federation.

Keywords Repeated anesthesia; Cognitive function; Spatial memory; Morris water maze.

Contributions of each author

Author 1 - Ivan Kuznetsov - data curation, investigation, writing – original draft
Email: ikuznecov@fnkcrr.ru
Author 2 - Levan Berikashvili - conceptualization, methodology, supervision, writing – review & editing
Email: levan.berikashvili@mail.ru
Author 3 - Alla Tkachenko - investigation, data curation, writing – review & editing
Email: solovyova.dr@mail.ru
Author 4 - Artur Ponomarenko - investigation, data curation, writing – review & editing
Email: artur.v.ponomarenko@gmail.com
Author 5 - Valeriya Orlova - formal analysis, writing – review & editing
Email: vorlova@fnkcrr.ru
Author 6 - Mikhail Yadgarov - methodology, supervision, writing – review & editing
Email: myadgarov@fnkcrr.ru
Author 7 - Valery Likhvantsev - conceptualization, methodology, project administration, writing – review & editing
Email: lik0704@gmail.com

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