Long-Term Effects of Neonatal Sevoflurane on Recognition Memory in Rats

Kyle Barbour

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University of California, Berkeley
Department of Molecular and Cell Biology, Neurobiology Emphasis
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Abstract

1 Introduction

2 Methods

3 Results

4 Discussion

List of Tables

1 Anesthesia protocol. .............................................................. 6
2 Odor recognition testing bias levels. ........................................... 8
3 Odor detection dilution levels. ................................................... 10

List of Figures

1 ROC curve and indices for Cohort 1. ........................................... 12
2 ROC curve and indices for Cohort 1 and Cohort 2 combined. ........ 14
3 Odor detection results. ............................................................ 16
Abstract

Sevoflurane, a popular pediatric and veterinary general anesthetic, is thought to cause deficits in learning and memory when administered to neonatal rodents [1, 2]. However, the precise nature of sevoflurane-mediated memory deficits remain unclear. Based on prior findings of sevoflurane-induced impairment in hippocampus-dependent tests [1, 2], we hypothesized that neonatal sevoflurane anesthesia impairs recollection, which is mediated by the hippocampus, but not familiarity, which is mediated by other areas [3, 4]. To test this, we compared performance in an odor recognition task of rats anesthetized as neonates with sevoflurane to performance of an unanesthetized control group using receiver operating characteristics, which statistically separate recollection and familiarity type memory. While our study is still in progress, results thus far indicate that recollection but not familiarity may be impaired by neonatal sevoflurane exposure.
Acknowledgements

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To Crima Pogge of the Biology Department of CCSF, thank you so much for believing in me and supporting both myself and my research from the absolute beginning of my scientific career and through to the present. My gratitude for your wisdom, help, and faith in me is impossible to put into words.

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1 Introduction

All general anesthetics in current use are known to damage neuronal structure or to increase the likelihood of neurocognitive deficits when administered to neonatal rats [5]. Sevoflurane is one such general anesthetic in widespread human and veterinary use, albeit one which appears to produce less neurotoxicity compared to isoflurane [6], propofol [7], and desflurane [8]. Despite this, other studies still show a neurotoxic profile [1, 2, 9] which can potentially lead to cognitive dysfunction. Given this lack of clarity, it is critical to determine whether sevoflurane leads to cognitive impairment, and if so, further determine the causal mechanisms.

Recognition memory is believed to be separable into two distinct processes, recollection and familiarity. Recollection involves active recall of specific prior encounters, whereas in familiarity, only a general feeling of prior interaction is experienced. To distinguish between the two, dual-process signal detection (DPSD) receiver operating characteristic (ROC) curves can be used [10, 11, 12]. In this model, recollection is assumed to be a threshold process, only being engaged when sufficient information is encountered, whereas familiarity is considered to be an equal-variance process, engaged with all previously-encountered items [11]. Consequently, in a delayed non-match to sample task, recollected items will have a response profile different from items which were solely familiar. In the DPSD ROC model, familiarity is reflected in the curvilinearity ($d'$) of the curve, whereas recollection is reflected in the y-intercept ($R$) of the curve [10, 11, 12].

No study to date has examined the effect of sevoflurane on the individual components of recognition memory. However, recent research has used the DPSD ROC model to show that recollection is mediated by the hippocampus, while familiarity is mediated by other areas [3, 4]. This gives credence to the possibility that sevoflurane could selectively cause a deficit either recollection or familiarity, as the processes are mediated by separate brain regions.
rather than being unified. As such, we tested the hypothesis that sevoflurane anesthesia impacts recollection but not familiarity.

2 Methods

Responsibilities and project status

In the present study, I was one of several experimenters. Recognition memory experiments were executed in two cohorts of rats. While experimental protocols were identical between the two cohorts, results are separated here to make clear my role, which was primarily with Cohort 1.

Animals, materials, and experimental design

With Institutional Animal Care and Use Committee approval, 23 male Sprague-Dawley rats (Charles River, Wilmington, MA) were split into two cohorts, with 13 in Cohort 1 and 10 in Cohort 2. Animals were singly housed and kept on a 12 hour light-dark cycle, with lights coming on at 7 AM and turning off at 7 PM. All experiments were conducted during light hours. Animals had *ad libitum* access to water and food until the start of odor recognition testing on post-natal day (P) 67, with the day of birth set as P0. After this point, rats were fed three times 5% of their body weight in grams and maintained at a minimum of 85% their *ad libitum* body weight (382.5 g). Following conclusion of odor recognition testing, all animals were returned to *ad libitum* feeding.

In both Cohort 1 and Cohort 2, rats were randomly selected to be in either control or anesthesia groups (Cohort 1: control, n = 6; anesthesia, n = 7; Cohort 2: control, n = 5; anesthesia, n = 5; combined: control, n = 11; anesthesia, n = 12). Pups were cross-fostered and initially housed in groups of 3, then separated into individual housing on P63.

Anesthesia or sham anesthesia was delivered to animals on P7. As odor recognition
testing relies on rats digging in cups of sand, which is not a native behavior, the rats were first trained to dig in cups for a reward and then in the ROC odor recognition task. Training for the odor recognition task began on P32, and odors were added on P67. Testing started around five months after birth and concluded 10 – 11 months after birth. Rats were trained or tested from the start of dig training until the conclusion of testing.

Training and testing for ROC analysis was performed in the home cage of each animal (25 cm × 45 cm × 20 cm). Training and testing were both performed using translucent plastic cups in three sizes, small (4 cm), regular (6 cm), and large (8 cm). Each cup was filled with 100 g of playground sand (Natural Play Sand, Sakrete, Dixon, CA) scented with one of 43 spices. Concentration of scent for each cup was 0.5 g spice per 100 g sand, modulated within ±0.5 g for five particularly pungent or non-aromatic spices to maintain a roughly consistent strength of scent. Cups were attached to a black plastic platform via Velcro which could be lowered into the cage with a metal rod which was glued to the base of the platform. For food reward, Froot Loops cereal (Kellogg’s, Battle Creek, MI) were used.

Anesthesia

Rats assigned to the anesthesia group were administered 4 hours of 1 minimum alveolar concentration (MAC) sevoflurane on P7, where 1 MAC is the concentration of inspired anesthetic at which 50% of animals do not respond to a painful stimulus. Cohort 1 and Cohort 2 were treated separately. Sevoflurane was administered in an O₂/air mixture with the fraction of inspired oxygen (FiO₂) being 40 – 60%. FiO₂ and CO₂ were monitored using an anesthesia monitor (Capnomac Ultima, Datex, Chalfont St Giles, UK). Anesthesia administration occurred in a custom-built glovebox.

The inspired anesthetic concentration of sevoflurane was initially set to be 6% and was assessed and readjusted every 15 minutes to maintain administration at 1 MAC. To assess MAC, a pain stimulus was applied to ten randomly selected rats every 15 minutes after
the start of anesthesia via an alligator clamp to the tail. Motion was considered to be any movement other than breathing. Then, inspired sevoflurane was adjusted according to the algorithm in Table 1. This algorithm is empirically derived, accounts for the diminishment of anesthetic requirements over time in P7 rats, and aims for 50% of all animals to respond to tail clamping.

Rats were placed on copper Peltier warming plates built into the floor of the anesthesia chamber and their temperature monitored using probes subcutaneously inserted into the masseter muscle. Rat body temperature was maintained at 36.5 ± 1°C throughout anesthesia using a custom-made computer program which directly set the temperature of the Peltier warming plates based on the monitored body temperature.

<table>
<thead>
<tr>
<th>Percent of rats moving in response to tail clamping</th>
<th>Subsequent percent adjustment of inspired sevoflurane concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>-1.4%</td>
</tr>
<tr>
<td>10%</td>
<td>-1.15%</td>
</tr>
<tr>
<td>20%</td>
<td>-0.9%</td>
</tr>
<tr>
<td>30%</td>
<td>-0.6%</td>
</tr>
<tr>
<td>40%</td>
<td>-0.3%</td>
</tr>
<tr>
<td>50%</td>
<td>no change</td>
</tr>
<tr>
<td>60%</td>
<td>no change</td>
</tr>
<tr>
<td>70%</td>
<td>+0.15%</td>
</tr>
<tr>
<td>80%</td>
<td>+0.3%</td>
</tr>
<tr>
<td>90%</td>
<td>+0.5%</td>
</tr>
<tr>
<td>100%</td>
<td>+0.7%</td>
</tr>
</tbody>
</table>

Table 1: Anesthesia protocol. Initial anesthesia concentration set to 6% sevoflurane. Tail clamping performed every 15 minutes after the start of anesthesia until anesthesia administration ceased.

**Sham anesthesia**

Rats assigned to the control group were isolated from their mothers for 4 hours without exposure to any anesthetic on P7. As with the anesthesia group, Cohort 1 and Cohort 2
were treated separately, but all animals within a cohort were treated simultaneously. This differs from the anesthesia treatment in that no temperature probes were inserted, instead, temperature was monitored using a laser infrared thermometer to ensure the rats remained normothermic. No temperature control interventions were needed or provided, as the rats were able to huddle together, unlike under anesthesia. While the rats were not placed in the anesthesia chamber glovebox, they breathed a similar air composition. As MAC did not need to be measured, tail clamping also did not occur.

**Odor recognition training**

Rats were trained to dig into unscented cups of sand using $\frac{1}{4}$ of a Froot Loop buried as a reward, starting with small cups on P32 and regular cups when sufficiently large. Rats were considered to have learned this task when they successfully found the buried reward on three successive training sessions. This occurred for all rats by P67, at which point the odor recognition component was added.

Cups were scented as described in the materials section. Rats were trained in a non-matching to sample odor recognition task wherein an odor with a $\frac{1}{4}$ buried Froot Loop reward was presented, then, following a delay, two odors were presented sequentially. The rat then received a reward by digging in the presented cup if the odor was new (non-match) or by instead heading to an alternative tray placed in the back right of the cage if the odor was old (match). The experimenter pretended to put a reward in the old odor cup to ensure that the rat was not making decisions based on the experimenter’s movements. When this task was learned (determined by 80% correct responses over 3 consecutive sessions), the number of new and old odors gradually increased to 5 and then to 10 each and the delay increased to 5 minutes, then 10, then 20, and then finally 30 minutes. Rats were then overtrained on the task 10 more times and then entered odor recognition testing.
Odor recognition testing

Odor recognition testing followed the same protocol as the final stage of odor recognition training, except in the following ways: rats were no longer rewarded for incorrect answers, 11 old and 11 new odors were used, and during testing, rewards and cup size varied according to the bias level (Table 2). Each session, the bias level was randomly chosen. As it is necessary for the rat to be alerted to the rules of the task specific to the bias level for their behavior to change, the first two odors tested were always a new and old odor pair. For these two odors, the experimenter would wait for a correct response to ensure that the rat sampled both possible rewards. For all other odors, the presented cup was promptly removed following an incorrect answer. While cup size and reward varied during testing according to the bias level, presentation of odors during sampling always used regular-sized cups and a \( \frac{1}{4} \) Froot Loop reward.

<table>
<thead>
<tr>
<th>Cup size</th>
<th>B5</th>
<th>B4</th>
<th>B3</th>
<th>B2</th>
<th>B1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old reward</td>
<td>( \frac{1}{4} )</td>
<td>( \frac{1}{4} )</td>
<td>( \frac{1}{4} )</td>
<td>( \frac{1}{4} )</td>
<td>( \frac{1}{4} )</td>
</tr>
<tr>
<td>New reward</td>
<td>( \frac{1}{2} )</td>
<td>( \frac{1}{2} )</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 2: Odor recognition testing bias levels. *Cup size*, the height of the cup presented during testing; *Old reward*, the fraction of Froot Loop placed into cup when an old odor is presented as a reward for a correct answer; *New reward*, the number of Froot Loops or fraction thereof dropped into the tray in the back of the cage for a correct answer when a new odor is presented.

After a complete trial, two scores were generated: False Alarm (FA) and Hit. Before calculating these scores, the responses to the first two presented odors were discarded as they were not randomly presented, correct answers were required, and they existed solely to alert the rat to the bias level prior to actual testing. FA was calculated by dividing the number of incorrect responses to new odors by 10, Hit by dividing the number of correct responses to old odors by 10. After a rat scored the same FA score ±0.2 on 3 consecutive
tests of that bias level, the learning curve was considered to have leveled off. After leveling off, a rat was tested only twice more within that bias level. Once the learning curve leveled off in all bias levels, testing was completed. The mean of the last 5 calculated FA and Hit scores were taken from each bias level and used as inputs to generate ROC curves as described in the statistical methods section.

**Odor detection**

To test the possibility that sevoflurane impairs olfaction, we performed a logarithmic stepwise dilution of the odors we used in odor recognition testing. Rats were tested under the same protocol as for the final stage of odor recognition training. However, after each day of testing, the cups of scented sand were diluted on a scale from the experimental concentration of spice down to $1.00 \times 10^{-9}$ times the experimental concentration. The dilutions used are shown in table 3. To ensure that the rats were not smelling residual scent on the sides of the cups, a final cup was tested which had been thoroughly cleaned with soap and water and whose sand had no scent whatsoever. Rats were scored on percent total correct answers rather than by FA or Hit.

**Statistical methods**

ROC curves were generated using a least squares dual process signal detection (DPSD) method [3, 11, 12, 13] to analyze the respective contributions of recollection and familiarity to recognition memory. As inputs, the mean of the last five recorded False Alarm and Hit scores from each bias level were used rather than the means from the entire dataset to ensure that the animals had learned the task and were performing at a consistent level. In the DPSD model, the value of the $y$-intercept ($R$) indicates the contribution of recollection and is referred to here as the recollection index, while the curvilinearity of the ROC curve ($d'$) indicates the contribution of familiarity and is here termed the familiarity index [11, 13].
<table>
<thead>
<tr>
<th>Spice concentration as percentage of experimental concentration</th>
<th>Negative logarithmic equivalent ($-\log_{10}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>0</td>
</tr>
<tr>
<td>10%</td>
<td>1.0</td>
</tr>
<tr>
<td>5%</td>
<td>1.3</td>
</tr>
<tr>
<td>1%</td>
<td>2.0</td>
</tr>
<tr>
<td>0.1%</td>
<td>3.0</td>
</tr>
<tr>
<td>0.01%</td>
<td>4.0</td>
</tr>
<tr>
<td>0.001%</td>
<td>5.0</td>
</tr>
<tr>
<td>0.0001%</td>
<td>6.0</td>
</tr>
<tr>
<td>0.00001%</td>
<td>7.0</td>
</tr>
<tr>
<td>0.0000001%</td>
<td>9.0</td>
</tr>
</tbody>
</table>

Table 3: Odor detection dilution levels. Experimental concentration is 5 g spice per 100 g sand, ± 0.5 g for five particularly pungent or non-aromatic spices to maintain a roughly consistent strength of scent. Negative logarithmic values provided for graphical purposes.

ROC curves were generated by plotting the mean FA score against the mean Hit score in each bias level. Following this, a best-fit curve was calculated according to the equation $P(\text{Hit}) = P(\text{FA}) + R_o + (1 - R_o)\Phi(d'/2 - c_i)$, where $P(\text{Hit})$ is the probability of a Hit, $P(\text{FA})$ is the probability of a False Alarm, $R_o$ is the probability the item was recollected, $\Phi$ is the cumulative normal response function, and $c_i$ is the proportion of items which exceed the response criterion [10]. ROC curves of both types, $R$, and $d'$ indices were all calculated using a ROC curve generation program written in Microsoft Excel generously provided by the Eichenbaum laboratory at Boston University. GraphPad Prism (GraphPad Software, La Jolla, CA) was used for all other statistical analyses.

Familiarity and recollection are analyzed here in two ways: by generating ROC curves for each rat individually and by generating a ROC curve for all rats in a group. These analyses will be referred to as individual and aggregate ROC analyses, respectively. As individual ROC analysis provides one $R$ and $d'$ index per rat, and therefore multiple values for each group, the groups can be compared using the Mann Whitney U test. Parametric median comparison tests were not used as we could not guarantee normality: Cohort 1 datasets
were too small to test using the D’Agostino and Pearson omnibus normality test, and while when combined with Cohort 2, both $R$ and $d'$ groups pass the normality test in control and anesthesia ($R$, control: $K^2 = 3.65$, $p = 0.16$; $R$, anesthesia: $K^2 = 5.75$, $p = 0.06$; $d'$, control: $K^2 = 2.45$, $p = 0.29$; $d'$, anesthesia: $K^2 = 0.36$, $p = 0.11$), this does not guarantee normality. Due to the non-Gaussian appearance of our data, especially in recollection, we assumed that our data was non-Gaussian.

To analyze the trends in our odor detection data, least squares linear regression was applied to each group after transforming the percent correct score to the negative base-10 logarithmic equivalent. Scores for the clean cup were not included in the regression as it was not expected to fit the trend for decreasing concentration and was intended primarily as a negative control.

3 Results

Both individual and aggregate ROC analyses are in Fig. 1 for Cohort 1 and in Fig. 2 for Cohort 1 and Cohort 2 combined.

With Cohort 1, neither median recollection indices nor median familiarity indices appear different between control and anesthesia groups in the aggregate ROC curve ($R$: control, 0.32; anesthesia, 0.25; $d'$: control, 0.70; anesthesia, 0.78, Fig. 1A). Similarly, median individual recollection indices show no significant difference between groups (control, 0.24; anesthesia, 0.07; $p = 1$; $U = 21.00$; Mann Whitney U test; Fig. 1B). Median individual familiarity indices also show no significant difference between groups (control, 0.52; anesthesia, 0.86; $p = 0.95$; $U = 20.00$; Mann Whitney U test; Fig. 1C).

When Cohort 1 and Cohort 2 data are combined, the recollection index of the aggregate ROC curve shows a substantial decrease in the anesthesia group (control, 0.26; anesthesia, 0.00; Fig. 2A). The aggregate familiarity indices remain similar between groups (control, 0.81; anesthesia, 0.93, Fig. 2A). However, in the individual data, the median recollection
Figure 1: Results for Cohort 1. (A) ROC curve. Control, gray; anesthesia, black. Familiarity indices ($d'$): control, 0.70; anesthesia, 0.78. Recollection indices ($R$): control, 0.32; anesthesia, 0.25. Error bars depict ± standard error. Points represent bias levels 5 through 1 from left to right. $p(FA)$, probability of a False Alarm, responding to a new odor as if it were old; $p(Hit)$, probability of a Hit, correctly responding to an old odor.
Figure 1: Results for Cohort 1 (continued).  (B) Recollection indices ($R$) from individual rat ROC curves: control, 0.24; anesthesia, 0.07.  (C) Familiarity indices ($d'$) from individual rat ROC curves: control, 0.52; anesthesia, 0.86.  ROC, receiver operating characteristic.
Figure 2: Results for Cohort 1 and Cohort 2 combined. (A) ROC curve. Control, gray; anesthesia, black. Familiarity indices ($d'$): control, 0.81; anesthesia, 0.93. Recollection indices ($R$): control, 0.26; anesthesia, 0.00. Error bars depict ± standard error. Points represent bias levels 5 through 1 from left to right. $p(FA)$, probability of a False Alarm, responding to a new odor as if it were old; $p(Hit)$, probability of a Hit, correctly responding to an old odor.
Figure 2: Results for Cohort 1 and Cohort 2 combined (continued). (B) Recollection indices ($R$) from individual rat ROC curves: control, 0.32; anesthesia, 0.000090. (C) Familiarity indices ($d'$) from individual rat ROC curves: control, 0.70; anesthesia, 0.71. ROC, receiver operating characteristic.
indices are not significantly different between groups despite a median index in the anesthesia group of close to zero due to the presence of 3 large values in this group (control, 0.32; anesthesia, 0.000090; p = 0.37; U = 51.00; Mann Whitney U test; Fig. 2B). Again, median familiarity indices are not significantly different between groups (control, 0.70; anesthesia, 0.71; p = 0.98; U = 65.00; Mann Whitney U test; Fig. 2C).

Figure 3: Odor detection results. Control, light, R^2 = 0.33; anesthesia, dark, R^2 = 0.44. Regression lines generated by least squares linear regression. Percent correct generated from the mean of all correct answers of animals in a group. Clean, cup thoroughly cleaned and filled with unscented sand.

Since the odor recognition test used in this study critically depends on the rats’ ability to smell, we sought to rule out the possibility that sevoflurane impairs olfaction. We did this by a logarithmic stepwise dilution of the odors used in the odor recognition test. The results are shown in Fig. 3. As shown, linear regression reveals no difference between groups (control, R^2 = 0.33; anesthesia, R^2 = 0.44) and visual inspection reveals no non-linear trends. Up until a dilution of 1 × 10^{-9} times the experimental spice concentration, rats
were able to successfully perform the odor recognition task. However, once all spice was completely removed from the cups and the cups were thoroughly cleaned, the performance of rats in both groups dropped to random chance. This indicates that rats smell extremely well, that sevoflurane does not impair olfaction, and that olfaction is the mechanism used by rats in both groups to complete the odor recognition task.

4 Discussion

It remains controversial whether neonatal sevoflurane anesthesia does [1, 2, 8] or does not [6, 7, 8] lead to deficits in memory, or whether it does [6, 9, 14, 15] or does not [7, 16] lead to morphologic changes in the brain. Group ROC analysis shows a marked deficit in recollection memory when Cohort 1 and Cohort 2 data are combined, however, individual ROC analysis of the same group shows no deficit (Fig. 2). Previously, these two types of analysis have always been in concordance [3, 4, 10, 11, 17]. Our data therefore shows for the first time that results obtained from comparing ROC distributions using p-values generated from individual data do not necessarily reflect the ROC distribution generated from the group. This brings the DPSD ROC recognition memory model into question, as it now appears to be capable of generating internally inconsistent results. More data is needed to determine whether this is an issue only of differing statistical power between group and individual ROC analyses or if this demonstrates that the DPSD ROC model does not accurately reflect the underlying processes of recognition memory.

Due to this discrepancy, we do not as yet make any conclusions as to the effect of sevoflurane on recollection memory. Since the difference may result only from a difference in statistical power between the two analyses, we considered whether our sample size was sufficient to come to a conclusion given the distribution of our data. A power analysis with the larger of the standard deviations of the recollection groups (anesthesia, 0.26), our desired power (0.9), and the difference in medians between groups (0.32) indicates that to test our
hypothesis that sevoflurane anesthesia negatively impacts recollection memory would require 30 subjects, slightly more than we tested [18]. Accordingly, we are running this experiment again with a third cohort, having 6 rats in control and anesthesia groups. This provides 35 total rats, enough to surpass 30 total subjects with a margin of error in case some rats cannot participate in the experiment due to sickness or other reasons. This cohort additionally has an isoflurane-treated group as a positive control (n = 6), as both our laboratory and others have been able to show deficits resulting from isoflurane anesthesia [6, 16, 19, 20].

We were unable to show a statistically significant impact on recollection memory due to 3 large values in Cohort 1. Investigation of the rats who had these recollection indices showed that they also had middle to very low familiarity indices, inversely proportional to their recollection index ($d'$: 0.10, 0.43, 1.05; $R$: 0.75, 0.58, 0.39). These three animals include the lowest and third lowest familiarity indices recorded. This is also consistent with the dual-process signal detection ROC recognition memory model which requires that recollection and familiarity describe discrete processes [10, 21]. Further, it supports recent research which suggests that recollection and familiarity are mediated by separate brain regions, and when one is impacted, the other compensates [4].

As the data regarding familiarity memory is consistent between individual and group ROC analyses, we conclude that sevoflurane anesthesia does not impact familiarity memory. As previous research shows that hippocampal lesions lead to an increase in familiarity memory [4], this suggests that sevoflurane anesthesia does not significantly impact the hippocampus. This corresponds to prior work, both in our laboratory and elsewhere, which show that the hippocampus suffers no apoptosis following sevoflurane anesthesia [1, 7]. While it is possible that sevoflurane anesthesia causes non-apoptotic injuries to the hippocampus, other mechanisms of damage have not been investigated in this brain region.

We have previously shown that sevoflurane anesthesia leads to increased thalamic apoptosis [1]. The thalamus has substantial connections to the hippocampus and is implicated in
recollection but not familiarity [22], thus, sevoflurane-induced thalamic damage could potentially explain the appearance of deficits in the former but not the latter. A previous study in mice similarly showed that sevoflurane anesthesia led to the greatest apoptosis in the thalamus, although other brain regions were also impacted [2]. The appearance in this study of apoptosis in non-thalamic brain regions, which was only minor in our previous study, may be due to our lower dosage of sevoflurane [1], or differences between rat and mouse responses to sevoflurane. Isoflurane similarly causes cell death in the thalamus and cortex [19], which may indicate that thalamic damage is a shared detrimental impact of both anesthetics. However, neither the present study nor prior research currently indicate any causal relationship between cell death and cognitive or memory deficits.

The odor recognition test used in this study is unable to differentiate between deficits in memory and deficits in other systems necessary for the task, such as olfaction, cognitive processing, and others. This study demonstrates that the sensory system most critical for odor recognition, olfaction, is not impacted by sevoflurane administration. Consequently, it is more probable that if sevoflurane anesthesia does lead to deficits detected by an odor recognition task, the deficits are caused by damage to a cognitive or memory system rather than a sensory one.

Limitations

The primary limitation of the present study is the differing results between group and individual DPSD ROC analyses with respect to recollection memory, as discussed above. The present study shows for the first time that the DPSD ROC model can lead to internal contradictions. It is at present unclear what impact this has on studies relying on the DPSD ROC model with respect to recognition memory. More data is needed to address this issue and to affirm or reject the validity of this model in describing recollection and familiarity memory processes. Specific to the present study, this issue prevents us from making a con-
clusion regarding the impact of sevoﬂurane on recollection despite an apparently signiﬁcant result in the group ROC analysis due to the lack of a signiﬁcant result in the individual ROC analysis.

A further limitation is the lack of data describing a causal mechanism by which sevoﬂurane anesthesia could lead to deﬁcits in recollection. While several are proposed above, no conclusions can yet be made.

Extrapolating results from animal tests to human clinical practice is fraught with difﬁculties. Any deﬁcits observed in this study cannot necessarily be said to exist in humans due to differences in anatomy, physiology, environment, and many other characteristics. Even if human and rat ROC studies showed identical deﬁcits, the origin of such deﬁcits could be different between species. No changes in clinical practice are thus encouraged by the ﬁndings in this or other related studies until research speciﬁc to clinical practice can be done on this topic.

Conclusion

We have shown that sevoﬂurane anesthesia does not affect familiarity or olfaction in rats. The affect of sevoﬂurane anesthesia on recollection remains unclear, with group ROC analysis showing a deﬁcit and individual ROC analysis not. This is being addressed with the addition of an appropriately-sized cohort to the experiment, however, it could also reﬂect deeper ﬂaws in the DPSD ROC model. Should sevoﬂurane ultimately be shown to cause a deﬁcit in recollection after the addition of the third cohort, the underlying mechanism would remain unclear.
References


