Lesions of the Basolateral Amygdala Complex Block Propofol-induced Amnesia for Inhibitory Avoidance Learning in Rats

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Background: As the unitary theory of anesthesia gives way to the “multiple sites, multiple mechanisms” concept, the sites involved in mediating the components of anesthesia must be identified. In the current study, we test the hypothesis that the basolateral amygdala complex (BLAC) is a brain site involved with mediating propofol-induced amnesia.

Methods: Male Sprague-Dawley rats were divided into two groups, sham-operated control animals and rats given bilateral excitotoxic N-methyl-D-aspartate lesions of the BLAC. For each group, animals were given intraperitoneal saline or propofol (25 mg/kg) 5 min before inhibitory avoidance learning. Rats were given a foot shock (0.4 mA) upon entering the dark side of a two-sided apparatus. Rats could escape additional shock by returning to and staying in the light side. Training ended after shock avoidance for greater than 60 s. Memory was tested at 24 h. Longer latencies to enter the dark side 24 h after training imply better memory.

Results: Sham-saline–treated animals had a robust memory latency (median latency [interquartile range] = 300 [163–567] s). Sham-propofol–treated animals exhibited a significant anterograde amnesia (latency = 63 [14–111] s) (P < 0.05 r.s. sham–saline–treated animal). Both the saline–injected and propofol–injected animals with BLAC lesions showed robust memory (latency = 300 [264–485] s and 323 [143–480] s, respectively). These latencies did not differ from performance in the sham–saline–treated group and were significantly higher than the latency of the sham–propofol–treated group (both P < 0.05).

Conclusions: Discrete BLAC lesions blocked the amnestic effect of propofol. BLAC activity appears to be a requirement for propofol–induced amnesia. This finding suggests that the BLAC is a key brain site mediating anesthetic–induced amnesia.

IT has been hypothesized that two characteristics define inhaled compounds as general anesthetic agents, namely, the capacity to cause (1) immobility in response to a noxious stimulus and (2) amnesia. Given two defining characteristics for anesthetic agents and a multiple–mechanism framework for anesthetic action, it would seem equally important for an understanding of anesthesia to determine the brain sites mediating anesthetic–induced amnesia as it is to determine the neurobiology of anesthetic–induced immobility. However, identifying which brain regions mediate anesthetic–induced amnesia is a difficult proposition, especially because it is likely that memory processing involves many brain structures and anesthetics tend to globally depress brain activity. Nevertheless, a candidate site for mediating drug–induced amnesia has emerged from the learning and memory literature. The basolateral amygdala complex (BLAC), defined in the current study as the basolateral and lateral amygdala subnuclei, appears necessary for the memory–modulating effects of numerous substances. The amygdala appears to modulate the strength of a memory according to how physiologically arousing and emotionally relevant a “to-be-remembered” situation is to an organism. There has been a remarkable convergence of recent studies demonstrating the critical role of the BLAC (but not the central amygdala) in memory modulation by every class of drug or hormone tested to date. However, the response of this system to general anesthetics remains unknown.

The memory modulation effects of the amygdala occur partly through γ-aminobutyric acid–mediated (GABAergic) mechanisms. Systemically administered diazepam (a GABA agonist) fails to cause amnesia if the basolateral amygdala subnuclei are lesioned. Furthermore, intra–BLAC doses of bicuculline (a GABA antagonist) given before or just after learning block the amnestic effect of systemically administered midazolam. Because a GABAergic mechanism of action could underlie the mechanisms of anesthesia, it seems likely that part of the amnestic effects produced by anesthetics could depend on BLAC–mediated mechanisms. We tested this hypothesis by investigating the effects of propofol on the acquisition and retention of inhibitory avoidance learning in rats with N-methyl-D-aspartate (NMDA) lesions of the basolateral amygdala complex. We chose propofol as the first general anesthetic agent to examine because it is thought to have GABA agonist properties and clinically it appears to induce a level of amnesia similar to that of the benzodiazepines. To put the essence of this experiment in simple terms, if activity within the BLAC is required for propofol amnesia to...
occur, then if the BLAC is removed, propofol should no longer cause amnesia.

Materials and Methods

Animals
After obtaining Institutional Animal Care and Use Committee (University of California, Irvine, CA) approval, 85 male Sprague-Dawley rats (weight, 250–280 g on arrival) were obtained from Charles River Laboratories (Wilmington, MA). They were housed individually in a temperature-controlled (22°C) colony room with food and water available ad libitum. Animals were maintained on a 12-h light–12-h dark cycle (7:00 AM–7:00 PM, lights on). The rats were randomly assigned to one of two surgery groups: sham-operated control animals and animals with bilateral NMDA-produced lesions of the BLAC.

Surgery
Rats were maintained in the animal colony for 1 week before surgery. Rats were anesthetized with 50 mg/kg intraperitoneal sodium pentobarbital and were given 0.2 mg intraperitoneal atropine sulfate. Rats were placed into a stereotaxic frame (David Kopf Instruments, Tujunga, CA), and bilateral lesions of the BLAC were produced by NMDA, 12.5 mg/ml distilled H$_2$O (Sigma-Aldrich Corp., St. Louis, MO). The NMDA solution was back-filled into a 30-gauge needle, which was attached by a polyethylene tube to a 10-μl syringe (Hamilton Co., Reno, NV) driven by a minipump (Sage Instruments, Boston, MA). For discrete BLAC lesions, the needle was placed into the targeted basolateral amygdala subnuclei at a single injection site (coordinates: anteroposterior, −2.8 mm from bregma; mediolateral, ± 5.0 mm from midline; dorsoventral, −8.5 mm from skull surface; incisor bar, −3.3 mm from interaural line) and a volume of 0.2 μl NMDA was injected over a 25-s period. The injection needle remained in place for an additional 3 min to maximize diffusion of the solution.

Sham operations used the same general procedure except that an empty needle was lowered only to the level of the caudate. No infusion was delivered. All animals were allowed 6 or 7 days to recover before inhibitory avoidance training.

Behavioral Procedures
The rats were trained on an inhibitory avoidance apparatus,$^{20}$ which was located in a sound-shielded room. The apparatus consisted of a V-shaped alley (91 cm long, 15 cm deep, 20 cm wide at the top, and 6.4 cm wide at the floor) which was divided into two compartments separated by a manually controlled sliding door that opened by retracting into the floor. The starting compartment (31 cm long) was colored white and illuminated, whereas the shock compartment (60 cm long) was dark and not illuminated.

A continuous multiple-trial inhibitory avoidance training procedure was used. On the training day, each animal was given an intraperitoneal injection of either 25 mg/kg propofol (Diprivan; AstraZeneca Pharmaceuticals LP, Wilmington, DE) or saline 5 min before training. This dose of propofol was chosen on the basis of pilot work, which demonstrated it to be the minimal dose consistently producing anterograde amnesia in this paradigm. Each animal was placed into the light–safe compartment of the training apparatus facing away from the door. When the animal turned to face the door, the door was lowered out of the way to reveal the dark-shock compartment. The rat instinctively prefers a dark environment. As the rat stepped into the dark-shock compartment with all four paws, a foot shock (0.4 mA) was delivered until the animal escaped back into the starting light–safe compartment. The door to the dark compartment remained open, and the animals could choose to either stay in the light–safe compartment or again cross into the dark-shock compartment. Animals crossing back into the dark-shock compartment were again given a foot shock and allowed to escape back to the light-safe compartment. Learning was considered to have occurred when animals would avoid the dark-shock compartment for greater than 60 consecutive s. After the animals attained the 60-s learning criterion they were removed from the apparatus and returned to their home cages. The number of trials required for each animal to learn the task was taken as an index of how difficult the task was for a particular group of animals to learn. It is important to note, however, that even though the exposure to the anesthetic condition might be expected to make the task more difficult for some animals to learn, the use of the continuous multiple-trial inhibitory avoidance training technique ensured that all animals eventually did acquire the task information (i.e., they all learned to stay out of the dark chamber to avoid a shock).

Memory retention was tested 24 h after the training session. Each rat was placed back into the starting light–safe side of the apparatus and the time taken (maximum, 600 s) for each rat to again cross into the dark-shock side was recorded. Longer latencies to cross into the dark side were interpreted as indicating better retention of the training experience. No shock or drug was delivered during the memory testing.

Histology
The rats were anesthetized with an overdose of sodium pentobarbital (250 mg/kg) and perfused intracardially with a 0.9% saline solution followed by 10% formalin solution. Brains were removed from each animal and placed into a 10% formalin solution overnight, then transferred to a 20% sucrose–10% formalin solution for 3–5 days. Brains were sectioned into 40-μm sections using a freezing microtome and stained with thionin. Lesion extent was rated by an investigator (Dr. Vazdar-
Lesions were histologically classified into one of the following categories: (1) discrete–confined lesions of the BLAC, (2) inadequate or missing lesions, or (3) extensive lesions of the BLAC with significant collateral damage to surrounding structures. Confined lesions had to include bilateral damage to the BLAC at a minimum of 1.5 mm anteroposterior to the injection site, as well as minimal damage to surrounding structures (confined to borderline areas around the BLAC). Extensive lesions included a massive lesion of the BLAC at a minimum of 1.5 mm anteroposterior to the injection site, along with accompanying extensive damage to a number of other surrounding structures, including (1) the piriform and entorhinal cortical areas (2) the striatum, (3) the endopiriform nucleus, or (4) the central nucleus of the amygdala. Only animals with discrete–confined, approximately equivalent bilateral lesions of the BLAC were included in the behavioral analysis.

Statistical Analysis
Because the behavioral data were not normally distributed, we used a nonparametric analysis approach. The Kruskal-Wallis test was used to assess group effects, and post hoc comparisons were made using the Mann-Whitney U test. A probability level of \( P < 0.05 \) was considered significant, after Bonferroni-Dunn correction for multiple comparisons.

Results

Exclusions
After histologic examination, 28 animals were excluded from further analysis, 11 from the BLAC-saline-treated group, and 17 from the BLAC-propofol-treated group. Twenty-six of these animals had massive lateral damage in the temporal lobes, as if they had undergone temporal lobectomies. Also, the central and medial amygdala nuclei were damaged in 18 of these 26 animals. One animal showed no damage to the BLAC, and one animal had only unilateral damage to the BLAC. In addition, 15 animals were dropped from analysis for behavioral reasons: seven animals failed to learn the task secondary to an excessive sedative effect of the propofol, and eight animals apparently had inadequate intraperitoneal injections because they failed to show any sedative effect during training, with two of these animals excreting propofol per rectum immediately after injection (a clear indication of an intraintestinal rather than a proper intraperitoneal injection). All exclusions were made blind to the retention test data.

Histology of Included Animals
Figure 1 shows a schematic composite diagram of the minimum and maximum lesion extents for the animals included in the final analyses. Clearly, these lesions all centered around the basolateral amygdala subnucleus within the BLAC. The smaller lesions affected an area approximately equal in size to that of the entire basolateral amygdala subnuclei, and the larger lesions extended this area of damage to encompass most of the lateral subnuclei. Figure 2 shows two representative photomicrographs of thionin-stained rat brain sections at the level of the BLAC for both a sham-operated control animal (fig. 2A) and an animal with a BLAC lesion (fig. 2B). The normal BLAC region (fig. 2A) shows a somewhat triangular clustering of relatively large cell bodies in the area between the central amygdala nucleus medially and superior (up and to the right) and the entorhinal–piriform cortex laterally (to the left). With the lesion (fig. 2B, arrowed), damaged areas are characterized by loss of neurons and gliosis in the tissue and show a significant lack of any large cell bodies. In this figure, the majority of the BLAC is damaged, including all of the lateral and basolateral subnuclei. However, sparing of the central amygdala nucleus has occurred. This is clearly seen because the area of cellular damage has a crescent-moon shape to it, which curves around the central amygdala nucleus.

Learning
Figure 3 shows the number of trials each group of animals needed to learn the task to the 60-s acquisition criterion. There was an overall significant effect of the
drug treatment on task acquisition ability ($P < 0.005$). Saline-injected, sham-operated control animals needed approximately one trial to learn the task. The BLAC lesions, by themselves, did introduce a mild acquisition deficit because the number of trials needed for a BLAC-saline–treated animal to learn the task increased to approximately 2 ($P < 0.05$, sham-saline–treated vs. BLAC-saline–treated animals). Propofol impaired task acquisition equally for both the sham-operated control animals and the BLAC-lesioned group; this is evidenced by an increased number of trials to approximately 4 for each group. However, this effect only reached statistical significance for the sham-operated control animals ($P < 0.05$, sham-saline–treated vs. sham-propofol–treated animals). It is important that the sham-propofol–treated and BLAC-propofol–treated groups did not significantly differ in their trials-to-acquisition-criterion performance ($P = 0.47$).

**Memory**

Figure 4 shows memory performance as determined by differences in median retention latency (with interquartile ranges). There was an overall significant effect of the drug treatment on retention performance ($P < 0.005$). Sham-saline–treated control animals (n = 11) had a robust memory with a median (interquartile range) retention latency of 300 (163–567) s. Sham-propofol–treated animals (n = 12) had a significant anterograde amnesia with a median retention latency of 63 (14–111) s ($P < 0.05$ vs. sham-saline–treated controls). Thus, 25 mg/kg propofol induced a statistically significant amnesia in the sham-operated control animals. The BLAC-saline–treated animals (n = 10) had a median retention latency of 300 (264–485) s, which was nearly identical with that seen for the sham-saline–treated control animals at 300 (163–567) s ($P = 0.83$, BLAC-saline–treated vs. sham-saline–treated animals). Thus, as expected on the basis of previous studies, BLAC lesions did not, by themselves, have a significant effect on memory retention performance.

In contrast to the sham-propofol–treated animals, the BLAC-propofol–treated animals (n = 9) showed a robust memory with a median latency of 323 (143–480) s (not significantly different from sham-saline–treated or BLAC-saline–treated control animals). Thus, in the animals with confined BLAC lesions, propofol did not produce...
Discussion

Despite being a well-established clinical phenomenon, anesthetic-induced amnesia remains poorly understood in terms of its neurobiology. The present study examined the hypothesis, derived from an extensive prior animal literature, that the BLAC may be a critical brain region involved with mediating general anesthetic-induced amnesia, as assessed in the current study with propofol. Primary findings were as follows: (1) A moderate dose of propofol (25 mg/kg, intraperitoneal) administered to rats 5 min before training on an inhibitory avoidance task significantly impaired acquisition of the task; (2) this dose of propofol produced a robust amnesia in control animals at 24 h; and (3) propofol amnesia did not occur in rats with BLAC lesions. Thus, rats with discrete BLAC lesions, which had acquired the task under the influence of propofol, showed memory performance no different from rats that had acquired the task without propofol.

There is a “reverse logic” element that must be considered, to fully appreciate the findings. Because the experiment removed a part of the brain by lesioning it and the amnestic effect of propofol was eliminated, it can be concluded by reverse logic that the BLAC must be mechanistically involved with producing the amnesia of propofol-induced general anesthesia. To further clarify this main point, if the hypothesis under question had been wrong and BLAC activity was not a requirement for propofol-induced amnesia, the observed result in the BLAC-propofol-treated group would have been that of an amnestic response similar in magnitude to that found in the propofol-injected, sham-operated control group. Hence, given the results obtained, we conclude that amygdala activity is a requirement for at least one general anesthetic agent (i.e., propofol) to exert its amnestic effects on inhibitory avoidance learning in rats. Coupled with extensive prior work showing that benzodiazepine-induced amnesia also depends on the BLAC, these findings strongly suggest the possibility that the BLAC is a, and perhaps, the primary neuroanatomic site through which general anesthetic agents might exert their amnestic effects.

There are two primary opinions regarding the amygdala’s role in memory processing. One suggests that the amygdala is the structure in the brain where emotional or fearful memories are formed and stored in the brain. The other suggests that the amygdala is the site in the brain where emotional or fearful memories are formed and stored in the brain. In this experiment, because lesions of the amygdala did not prevent learning of the inhibitory avoidance task (i.e., “fearful” memories could still be formed even with a BLAC lesion) and the amygdala lesions blocked the ability of the anesthetic to modulate memory formation (i.e., by blocking its amnesia-causing ability) our data best fit with, and are best understood using, the memory modulation view of amygdala function.

The present findings will, in all likelihood, generalize to animal studies involving other paradigms. The literature on amygdala function clearly documents effects of BLAC manipulations on modulating memory in studies involving many tasks including not only one-trial and multitrial avoidance learning but also, discrimination learning, reinforcer devaluation learning, active avoidance learning, pavlovian “fear conditioning” and both spatial and cued water maze learning. In addition, it is likely that the present findings will generalize to studies of human subjects. Studies both of patients with amygdala damage and of healthy subjects with human brain imaging from several laboratories have consistently confirmed the “memory modulation” view of the amygdala derived from the animal studies. These facts make clear that, although the present conclusions must be evaluated with other species and tests, the available evidence strongly supports their general validity and the

Fig. 4. Memory retention latency at 24 h. The median values and the interquartile ranges for the number of seconds taken before animals placed into the safe/light side of the inhibitory avoidance training apparatus again crossed into the dark/shock compartment. Animals were not exposed to propofol during memory testing. Longer latencies imply better memory. An amnestic effect of propofol is clearly seen in the sham-operated control animals exposed to propofol 24 h earlier. The sham-propofol group had significantly lower memory retention performance scores than any other group (*P < 0.05). The amnestic effect of propofol is blocked in animals with basolateral amygdala complex lesions, as evidenced by a retention latency (memory) equivalent to that of the sham-operated, saline-injected control animals and the saline-injected, basolateral amygdala complex-lesioned control animals (NS = not significant; P = 0.85). IQ = interquartile range.

an amnestic response. These results are illustrated in figure 4.
general hypothesis that the amygdala may be a site that is critically involved with producing anesthetic-induced amnesia. In consideration of previous evidence indicating that anesthetic-induced immobility is mediated through anesthetic actions in the spinal cord and that anesthetic-induced unconsciousness may be mediated through anesthetic actions in the thalamus, there would now seem to be strong neuroanatomic support for the “multiple sites, multiple mechanisms” concept of anesthetic action.

For this study, an amnestic effect of propofol had to be demonstrated, to show its reversal or blockade with a BLAC lesion. It would have been preferable if the amnestic potency of propofol, relative to its sedative effects, had been strong enough to produce amnesia without also causing a significant increase in the number of trials needed to learn the inhibitory avoidance (IA) task. However, this was not the case. A lesser dose of propofol may have allowed the animals to learn the task more easily (as evidenced by fewer learning trials), but it also would not have resulted in the required anterograde amnesia. This relatively weak amnestic potency of propofol contrasts with the apparently more potent amnestic effect of diazepam. Diazepam produced anterograde amnesia without increasing the number of trials needed to learn the IA task. Midazolam, on the other hand, did cause an increase in the number of trials needed to learn the IA task. These observations suggest that interesting amnestic-versus-sedative potency differences may exist between agents, which future studies might further elucidate.

The potential effects of propofol on task acquisition cannot account for our primary findings, namely, that lesions of the BLAC prevented propofol-induced amnesia, because these potential acquisition effects were identical for the sham-treated and the BLAC-lesioned rats exposed to the same dose of propofol and there was no difference between these two groups in their acquisition performance (fig. 3). In other words, both sham-treated and BLAC-lesioned rats had the same trouble learning the task under propofol, but only the sham-treated animals seemed to “forget it,” whereas the BLAC-lesioned animals still “remembered it.” Given the influence of propofol on task acquisition, postlearning propofol administration and the use of a retrograde amnestic effect might have been a useful technique to employ to negate any drug-induced acquisition deficits. However, retrograde memory effects of propofol have not been consistently reported and we were unable to find any retrograde memory effect in pilot experiments.

In contrast to their clear effect on propofol-induced amnesia, the BLAC lesions did not appear to greatly change the sedative effect of the drug. This is evidenced by the similar increase in number of trials to criterion needed for both BLAC-treated and sham-treated rats to learn the task under the influence of the propofol. The number of trials to criterion increased from the 1–2 range for both groups trained without propofol and to the 3–5 range for both groups trained with propofol. Furthermore, there was no objective difference in the effectiveness of the propofol evident in the behavior of the rats with confined BLAC lesions compared with the sham-operated control animals. Certainly, number of trials to criterion is only a crude measure of sedative effect. More precise assessment of sedative effect in future studies, perhaps using computerized electroencephalogram or bispectral index monitoring, might be able to show whether a subtle interaction exists between BLAC lesions and levels of sedation.

Important technical differences exist between the present study and the diazepam study performed by Tomaz et al. In the study by Tomaz et al., the exact site within the amygdala mediating the amnestic effect of diazepam was unknown. That study helped establish the importance of the “basolateral” and the “lateral” rather than the “central” amygdala subnuclei for drug-induced amnestic responses. Tomaz et al. used small, ibotenic acid–induced lesions to map out regional responses within the amygdala. At their biggest, the lesions in the study of Tomaz et al. were only approximately 50% of the BLAC area. In contrast, as much intervening work established the import of the BLAC area in memory modulation responses, we used relatively large NMDA-induced lesions in an attempt to get a complete “knockout” of the basolateral amygdala subnuclei within the BLAC area. At the smallest, our lesions were approximately 50% of the BLAC area and usually did involve the entire basolateral amygdala subnuclei, with occasional sparing of the lateral amygdala subnuclei. In future studies we plan to aim for an approximate 50% BLAC area damage rate with injections centered in the basolateral subnuclei. Ibotenic acid–induced lesions, as used by Tomaz et al., can destroy cell bodies in the central amygdala nucleus. The NMDA lesions we used tend to spare cell bodies in the central amygdala nucleus (fig. 2B). This is in part why complete BLAC lesions are relatively easy to make. However, this central amygdala-sparing effect can be overpowered with too much NMDA.

Because each IA experiment involves a number of subtle variations, direct comparisons across studies can often be misleading. For example, it appears that the control rats in the study of Tomaz et al., which had a median retention latency of approximately 600 s, had better memory than our control rats, which had a median retention latency of approximately 300 s. However, a direct comparison of these numbers does not take into account the fact that Tomaz et al. used a training shock that was 38% greater than ours (i.e., 0.55 vs. 0.4 mA). It is well established that rats trained with higher foot-shock intensity acquire the IA task in fewer trials and, ultimately, show better retention performance scores, compared with rats trained with lower foot-shock inten-
sity. Therefore, given these subtle differences across studies, IA experiments are always performed with proper control groups and best interpreted for findings within a single study.

The IA technique requires that animals be sedated enough to show an amnestic effect, but not so sedated that they are unable to learn the task. It is not known whether higher doses of propofol would have overwhelmed the mechanisms involved in this BLAC blockade of amnesia effect. This would be important information to know, before one could completely conclude that activity in the BLAC is required for the amnesia of general anesthesia to occur. There may be a way to test the amnesia associated with deeper levels of anesthesia in completely anesthetized animals using some form of conditioning, but exactly how best to do this, especially in relation to the amygdala, is not entirely clear. In addition, to generalize the present findings to the realm of general anesthesia per se, volatile agents must be tested in the present paradigm.

Another issue concerns the cellular mechanisms underlying the amnestic effect of propofol. Because we have used lesions in the current study, our data do not speak directly to this issue. However, because propofol is a presumed GABA agonist, it seems logical to speculate that its GABAergic properties might underlie these results. It is known that intraamygdala infusions aimed at the BLAC, of both GABA agonists and benzodiazepines, impair IA retention in the rat, whereas intraamygdala infusions of GABA antagonists improve IA retention. Because most anesthetic agents possess some GABAergic agonist activity, it seems reasonable to suspect that most anesthetic agents might require an intact GABAergic function in the BLAC, to produce their amnestic effects.

How is it possible that propofol continued to cause sedation and yet failed to cause amnesia simply because the BLAC was removed? What could possibly be the neuroanatomic mechanism for this dissociation? The BLAC has significant connections with numerous brain areas involved in memory processing. It connects to the hippocampus, striatum, thalamus, and basal forebrain. The pathways and mechanisms mediating amygdala memory modulation are only today beginning to be worked out, so speculating about exactly why this site appears so important for drug-induced amnesia is premature. Nevertheless, based on our findings, it appears that the amnesia of propofol anesthesia is an active rather than a passive process. In other words, the drug must do something specific within the BLAC, which then changes how the BLAC interacts with other brain structures to allow amnesia to occur. Otherwise, the amnestic effect of the drug could not have been blocked with a BLAC lesion.

Given the theoretical framework for the amygdala in memory modulation, these results integrate well with the clinical phenomenon of intraoperative recall and may help explain some aspects of such cases. One aspect is that emotionally relevant material tends to be better remembered. To quote from a recent review, "... because patients are most likely to recall emotionally threatening remarks, it is prudent for the operating room team to avoid voicing negative or derogatory remarks about the patient or the prognosis." Better memory of "emotional" material is the hallmark of studies linking amygdala activity with recall performance in humans. Another aspect of recall cases is that they sometimes progress to posttraumatic stress disorder (PTSD). The amygdala memory modulation circuitry may underlie the intrusive memories that often complicate cases of PTSD. Taken together with the present experimental results, these observations expose the amygdala as a critical brain region whose functioning must be elucidated for a full understanding of anesthetic-induced amnesia and the mechanisms of anesthesia.

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