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# Investigation of Implicit Memory during Isoflurane Anesthesia for Elective Surgery Using the Process Dissociation Procedure

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*Background:* **This prospective study evaluated memory function during general anesthesia for elective surgery and its relation to depth of hypnotic state. The authors also compared memory function in anesthetized and nonanesthetized subjects.**

*Methods:* **Words were played for 70 min *via* headphones to 48 patients (aged 18–70 yr) after induction of general anesthesia for elective surgery. Patients were unpremedicated, and the anesthetic regimen was free. The Bispectral Index (BIS) was recorded throughout the study. Within 36 h after the word presentation, memory was assessed using an auditory word stem completion test with inclusion and exclusion instructions. Memory performance and the contribution of explicit and implicit memory were calculated using the process dissociation procedure. The authors applied the same memory task to a control group of nonanesthetized subjects.**

*Results:* **Forty-seven patients received isoflurane, and one patient received propofol for anesthesia. The mean (± SD) BIS was 49 ± 9. There was evidence of memory for words presented during light (BIS 61–80) and adequate anesthesia (BIS 41–60) but not during deep anesthesia (BIS 21–40). The process dissociation procedure showed a significant implicit memory contribution but not reliable explicit memory contribution (mean explicit memory scores 0.05 ± 0.14, 0.04 ± 0.09, and 0.05 ± 0.14; mean automatic influence scores 0.14 ± 0.12, 0.17 ± 0.17, and 0.18 ± 0.21 at BIS 21–40, 41–60, and 61–80, respectively). Compared with anesthetized patients, the memory performance of nonanesthetized subjects was better, with a higher contribution by explicit memory and a comparable contribution by implicit memory.**

*Conclusion:* **During general anesthesia for elective surgery, implicit memory persists even in adequate hypnotic states, to a comparable degree as in nonanesthetized subjects.**

MANY studies have demonstrated that events occurring during general anesthesia can be remembered.[1] Some have observed that a conscious retrieval of information can occur during general anesthesia (explicit memory or awareness),[2–4] *e.g.*, patients report having heard conversations or noises or having felt discomfort such as being operated on or paralyzed. This phenomenon is rare (0.1–0.2%).[2–4] It often reveals an inadequate level of anesthesia, and its psychological consequences can be severe.[5] Other studies suggest that an automatic or unconscious retrieval of information presented during general anesthesia can also occur (implicit or automatic memory).[6,7] They evidenced an immediate postanesthetic change in behavior or in performance on a memory test without conscious recall of the information presented during anesthesia. The importance and the psychological consequences of this kind of implicit memory process during general anesthesia are not known. Moreover, whether this phenomenon actually occurs remains controversial in the literature.[6,7] This controversy may be explained either by the lack of standardization of the type and depth of anesthesia or by the fact that implicit and explicit memory tests do not measure one type of information retrieval exclusively, because both types of memory processes often operate in concert during different memory tasks. Performances on implicit memory tests may thus be contaminated by conscious memory processes, and the results of explicit memory tests may be enhanced by implicit memory processes. The process dissociation procedure proposed by Jacoby[8] is an elegant method of solving this contamination problem, because it allows one to separate the degree to which explicit and implicit memory processes contribute to the performance of a single memory task such as the completion of a word stem by a word presented previously during general anesthesia.

The process dissociation procedure has been used in many studies to evaluate the occurrence of memory during general anesthesia and to distinguish between explicit and implicit memory retrieval processes.[9–12] Lubke *et al.*[9] have demonstrated that the chance of memory formation decreases with the depth of anesthesia, as measured by the electroencephalogram-based Bispectral Index (BIS),[13] in the context of emergency surgery for trauma. Using the process dissociation procedure, they observed that during adequate anesthesia (BIS between 40 and 60), implicit memory occurred without the presence of explicit memory. In the case of

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deeper states of anesthesia (BIS $<$ 40), the chance of memory formation was no longer statistically significant.

Anesthetized trauma patients are known to be at risk for awareness.[9] Major traumatic injury frequently causes hemodynamic instability, which may require a reduction in the usual dose of anesthetics. In addition, the stress and pain experienced in such situations may affect memory, because it is accepted that high concentrations of catecholamines can enhance memory performance.[12,14–16]

However, in the study by Lubke *et al.*,[9] BIS explained a relatively small proportion of the variance in patients' memory scores, suggesting that depth of anesthesia is not the only determinant of learning. Deeprose *et al.*[15] showed that learning was more likely to take place during surgical stimulation, which triggers a major increase in catecholamines.

The purpose of this study was to evaluate the occurrence of memory during general anesthesia and to distinguish between explicit and implicit memory retrieval processes by using the process dissociation procedure in patients scheduled to undergo elective surgery, where there is less variation in the depth of the hypnotic state. We also wanted to evaluate whether the likelihood of memory formation was related to the depth of anesthesia, as measured by the BIS, and to the stimulus of surgery. Finally, we wanted to compare the likelihood of memory formation in anesthetized patients and nonanesthetized volunteers.

## Materials and Methods

### *Subjects*

After approval by the local institutional ethics committee (Geneva University Hospital, Geneva, Switzerland) and written informed consent from each participant, 48 patients aged 18–70 yr, with American Society of Anesthesiologists physical status of I or III, undergoing elective surgery during general anesthesia lasting more than 70 min were included in the study.

Patients who had a known hearing deficit, did not speak French fluently, were affected by a pathology or a preoperative treatment that could affect cognitive functions (*e.g.*, sleeping pills, benzodiazepines, antipsychotics, antidepressants, long-term antiepileptics), had chronic alcoholism or other drug abuse, or were undergoing cardiac or brain surgery were excluded.

Patients older than 60 yr were tested with the Mattis Dementia Rating Scale[17] and were only included if their score was higher than the cutoff score of 130.

In addition, we recruited 24 control volunteers who were matched with 24 patients for age, sex, and education level and fulfilled the same inclusion criteria. These subjects were noninstitutionalized and were given the same memory test as the anesthetized patients.

### *Anesthetic Procedure*

All patients were unpremedicated. The anesthesia procedure was left up to the responsible anesthesiologist, based on his experience and good clinical practice. At the time of arrival in the operating room, patients were monitored with an electrocardiogram, a pulse oximeter, a noninvasive blood pressure monitor (AS/3Datex Engström, Finland), and a BIS A-2000® monitor (Aspect Medical Systems Inc., Newton, MA). Single-use silver–silver chloride electrodes (Zipprep; Aspect Medical Systems) were attached to the head through a single channel, according to a left or right frontotemporal referential montage: referential electrode in the middle of the forehead (Fpz), left or right temporal active electrode (At1 or At2), ground electrode 2 cm to the left or to the right of the reference electrode (Fp1 or Fp2). Impedance was kept below 5 k$\Omega$. BIS was recorded every 15 s on a portable computer and then averaged for each presented word.

After administering a lactated Ringer's solution hydric charge of 10–20 ml/kg, the anesthesia induction consisted of the association of an opiate with a hypnotic. Succinylcholine or nondepolarizing agents were used to facilitate tracheal intubation. Anesthesia was maintained with an opiate, a mixture of $O_2$–air or $N_2O$, a nondepolarizing agent if necessary, and a hypnotic (halogenated agent or propofol). A regional anesthesia might be associated with the general anesthesia. Induction and maintenance of anesthesia were at the discretion of the responsible anesthesiologist, who was aware of the goal of the study but not of the nature of the auditory stimuli. Anesthesia was titrated using classic clinical signs (blood pressure and heart rate variation, sudation, movements, eyes opening, grimacing, cough, and pupil diameter). The BIS® monitor screen was not visible to the anesthesiologist responsible for the anesthesia.

### *Cognitive Task*

This task consisted of auditorily presenting six-letter words after the induction of general anesthesia and of testing the memory for these words during a postoperative evaluation within 36 h after the stimulus presentation, using a word stem completion test based on the process dissociation procedure.

This procedure includes two conditions: the inclusion condition, in which explicit and implicit memory processes act in concert and influence performance of memory in the same way, and the exclusion condition, in which explicit and implicit processes have opposing effects, with one process acting to produce the correct answer, while the other acts to produce an error. A combination of the two parts of the test makes it possible to evaluate the contribution of implicit and explicit memory processes to task performance.

*Materials*

The stimuli included 60 six-letter French words. This list of words was created such that each word stem (*i.e.*, the first three letters of each word) was unique within the experiment but not within the language. Each word stem could be completed by at least five six-letter French words (*e.g.*, *cha*: *chaque*, *chacun*, *chaton*, *chacal*, *chatte*, *charte*, and so on), but only one of the completions appeared in the experiment.

These 60 words were divided into three sets of 20 words. The words in each set were selected to have an equal distribution of frequency of occurrence in the French language,[18] an equal mean probability that each stem might be completed by its target word without previous presentation (a base rate probability of completion was tested with 20 pilot subjects), and an equal mean number of possibilities for completing stems with other six-letter French words.

*Procedure*

In the first part (presentation phase), two lists of 20 words were played to the patients *via* closed headphones placed on the ear, connected to a Toshiba personal portable computer (Satellite Pro 4300; Toshiba America Inc., New York, NY), interfaced with E-Prime software version 1.0 (Psychology Software Tools Inc., Pittsburgh, PA).[19]

On arrival in the operating room, patients could hear two practice words, giving them the opportunity to adjust the volume of the tape. The presentation then started immediately after the patient lost consciousness, determined by a lack of response to the verbal command "open your eyes." The 40 words were presented in a random order that was different for each patient. Each word was repeated 25 times consecutively, with a 2-s delay between repetitions. Because the words were pronounced slowly, we allotted a period of 2 s to each word presentation, even though some word presentations did not last 2 s. Consequently, the standardized duration of presentation was 4 s for each word. The total duration of the presentation of each word, which was repeated 25 times, was 100 s. New word presentation started 5 s after the end of the previous presentation. The entire auditory stimulation process lasted 70 min. There was always at least one investigator present during the entire word presentation, to ensure that it was performed in a uniform fashion, without any interruptions. This person was not responsible for or involved in the anesthesia.

By connecting the computer to the BIS® monitor and by using a common clock, it was possible to relate the mean value of BIS to the presentation phase for each word, which lasted 1.5 min.

This same task was administered to the 24 control volunteers in a quiet room. They were told that they would listen to a series of repeated words that would be included in a later (unspecified) test. Subjects were not asked to perform any specific encoding task but only to listen carefully to the words.

The second part (evaluation phase) was performed for the control volunteers between 12 and 36 h after the stimulus presentation. For patients, this took place within 36 h after the stimulus presentation, when they felt comfortable enough to answer appropriately. They were first asked whether they explicitly remembered any words or any intraoperative events. The memory test included two conditions.

In one condition, *inclusion*, three-letter stems corresponding to previously presented words were presented auditorily *via* headphones connected to the computer. These stems were audible only to the testee, not to the investigator. Subjects were asked to use the stems as a clue to recall the previously heard words (*e.g.*, *mot* for *motard*). If subjects could not retrieve the target word, they had to complete the stem with the first six-letter word that came to mind.

In this condition, subjects completed the stem with a target word either because they recalled it consciously (probability designated as C) or because the word came automatically to mind by implicit recovery or by chance (probability designated as A), when conscious recollection was not possible $(1 - C)$. Assuming that these two processes are independent, the following equation presented by Jacoby[8] makes it possible to describe the subject's performance during the inclusion test: $\text{Inclusion} = C + A\,(1 - C)$.

In the condition *exclusion*, the procedure was identical, except that according to the recall instruction, subjects had to use the stem as a clue to recall a word presented previously, and then exclude the recalled word and find another word. In this condition, subjects would complete the stem with a word from the recorded list only if it came automatically to their mind without being aware of the previous presentation. An explicit memory effect in this condition results in a less frequent response with the word presented during anesthesia.

The subject's performance in the exclusion condition may be described as follows: $\text{Exclusion} = A\,(1 - C)$. On the basis of these two equations, it is easy to quantify the contribution of the explicit memory (C: conscious) and of automatic influences (A: implicit memory and chance). Thus, the difference between the inclusion and exclusion scores makes it possible to assess the contribution of conscious information retrieval processes: $C = \text{Inclusion} - \text{Exclusion}$.

Based on this assessment of C, it is then possible to measure the probability of a word's being automatically recalled: $A = \text{Exclusion}/(1 - C)$.

The control volunteers were given the same memory test within the same period after presentation as the matched patients.

In the memory evaluation phase, each subject was presented with the three lists of equivalent word stems. Thirty word stems were presented in each condition, 20 of which corresponded to the first three letters of the words that had been presented during anesthesia (target words) and 10 of which were for words that had never been presented to the patient during anesthesia (distractor words). Therefore, for each subject, one list of 20 words was presented in inclusion, one list of 20 words was presented in exclusion, and one list of 20 words was used as distractors and was shared between the two conditions, with 10 word stems for each condition. Each subject was presented with a different combination of the three lists to achieve counterbalancing of items. There were 24 different versions of the task, according to the way in which the three lists of words were distributed between the various conditions (one list for the inclusion condition, one list for the exclusion condition, and one list for the distractors) or according to the order of presentation of the inclusion and exclusion conditions (inclusion, then exclusion, or exclusion, then inclusion).

The distractor words made it possible to assess the completion rate due to chance (base rate), *i.e.*, the probability that the patient would complete the stem with a target word at random without ever having heard it. The aim of this distractor list is twofold: (1) to find out whether subjects use the same criterion for responding in the inclusion and exclusion conditions by comparing the base rate level for each of these conditions and (2) to verify that implicit memory processes actually correspond to the unconscious influence of memory by showing that scores of implicit memory processes are significantly above the base rate or chance level.

In all conditions, subjects had to complete stems according to the following rules: six-letter words, no plurals, no proper nouns, and no conjugated verbs (except past participles). If the subject came up with a solution that met these criteria, the experimenter pressed the space bar, and the next stem was presented automatically. Otherwise, the experimenter informed the subject of the error and the subject was encouraged to generate a more appropriate solution or was allowed to listen a second time. Subjects had a maximum of 30 s to complete each stem. If the stem had not been completed with an appropriate six-letter word when the allotted time was over, the stem was replaced automatically by the next item.

The evaluation phase lasted a maximum of 35 min: 5 min of explanation, then 15 min for the inclusion condition, and 15 min for the exclusion condition.

Before the inclusion and exclusion conditions, the investigator gave instructions to the subjects in a standard fashion, with the help of written guidelines visible on the computer screen.

*Data Analysis*

**Number of Subjects and Randomization.** Patients were randomized into 24 groups, corresponding to the 24 versions of the cognitive task, each group having the same number of patients. We started the study with two patients in each group. When a patient could not complete the two phases of the study (presentation and evaluation), his or her version was repeated for the next patient recruited. There was one control volunteer for each version of the cognitive task, matching a patient with the same version of the task.

**Method of Analysis.** For each subject, we calculated the scores for word stem completion in the inclusion and the exclusion conditions by the target words (hit rate) and the distractor words (base rate).

One-tailed related-samples $t$ tests were used to compare the proportion of hits for target words with the base rate in the inclusion (general memory indication without distinction between implicit and explicit memory) and exclusion conditions.

Memory scores (C and A) were calculated for each subject using Jacoby's[8] equation as described previously.

One-tailed one-sample $t$ tests were used to test whether the derived mean explicit memory score differed from zero. Because the automatic influence score is not a measure of implicit memory alone but includes other automatic influences on performance, such as the tendency to respond with a particular word even without previous exposure to that word, a related-samples one-tailed $t$ test was used to compare the derived mean automatic influence score with the base rate.

To investigate the impact of depth of anesthesia, BIS values were categorized as follows: BIS 21–40, 41–60, and 61–80. The same analyses were performed for these different BIS categories. In addition, the memory scores for the different BIS categories were compared using a two-tailed $t$ test. We also used Pearson correlations to test the relation between global mean BIS scores and memory scores.

To investigate the influence of surgical stimulation on the likelihood of memory formation during general anesthesia, we calculated for each patient the hit rates in the inclusion and exclusion conditions for the words presented before and after incision.

We studied the impact of different uncontrolled factors. Pearson correlations were used to test the relation between the memory scores and the time interval between the word presentation and the memory test. The memory scores were subjected to an analysis of variance with type of surgery (visceral, urologic, and orthopedic surgery) and type of anesthesia (general anesthesia alone *vs.* general anesthesia combined with regional anesthesia) as between-subjects variables.

Two-tailed $t$ tests for independent samples were used to compare demographic variables and memory scores between anesthetized and nonanesthetized subjects.

**Table 1. Patient Characteristics**

| | |
|---|---|
| n | 48 |
| Age, yr | 44.7 ± 13.9 |
| Patients older than 60 yr, n | 6 |
| Mattis DRS of patients older than 60 yr | 141.7 ± 1.4 |
| Sex, M/F, n | 31/17 |
| Education level, yr | 12.7 ± 2.6 |
| Duration of anesthesia, h | 3.83 ± 0.98 |
| Duration of surgery, h | 2.63 ± 0.76 |
| Interval between word presentation and memory test, h | 28.58 ± 3.42 |

Values are presented as mean ± SD.
Mattis DRS = Mattis Dementia Rating Score.

$P < 0.05$ was considered statistically significant. Data are presented as mean ± SD.

## Results

*Anesthetized Patients*

Fifty-five patients were initially included and underwent a word presentation process during general anesthesia. Seven did not complete the evaluation phase for the following reasons: one patient left the institution before the memory test, three patients were too sedated and in pain at the time of memory testing, two patients had to be eliminated because of a preoperatively undetected exclusion criterion (hearing deficit and insufficient knowledge of French, respectively), and one patient had surgery that ended before completion of the word presentation. Therefore, 48 patients completed the study, with two patients in each of the 24 versions of the cognitive task.

Table 1 shows patient characteristics, durations of anesthesia and surgery, and the interval between the time of word presentation and the time of evaluation of memory.

The patients had mainly visceral (n = 15), urologic (n = 12), and orthopedic surgery (n = 21). Forty-seven patients received isoflurane, and 1 patient received propofol as a hypnotic during word presentation. Thirty patients received nitrous oxide, and all patients received opioids, (20 patients received a mean of 33 ± 9.3 μg sufentanil and 28 patients received a mean of 260 ± 83.2 μg fentanyl during the word presentation). Twenty-eight patients had general anesthesia alone, and 20 patients had general anesthesia combined with regional anesthesia (epidural or spinal anesthesia, upper or lower extremity blocks). Thirty-six percent of the total words were presented during regional anesthesia.

No patients manifested awareness or spontaneous recall of intraoperative events or of the presented words. The mean BIS was 49 ± 9.

The results of the memory tests are presented in table 2. Mean base rates were comparable in the inclusion (0.13 ± 0.08) and exclusion (0.10 ± 0.07) conditions,

**Table 2. Mean Hit Rates in the Two Test Conditions and Mean Scores of Memory for Words Presented during General Anesthesia and for Distractor Words (Base Rate)**

| Mean Hit Rate | | Mean Memory Score | | |
|---|---|---|---|---|
| Inclusion | Exclusion | Explicit Memory | Implicit Memory | Base Rate |
| 0.15 ± 0.08* | 0.15 ± 0.09* | 0.04 ± 0.06 | 0.16 ± 0.09* | 0.12 ± 0.06 |

Values are presented as mean ± SD.
* $P < 0.01$ (> base rate).

indicating that patients responded consistently during both parts of the test. We present in this table the average value for both conditions.

Scores for words correctly completed in the inclusion and exclusion conditions were significantly higher than the base rate ($P < 0.01$), indicating that patients had memory for the target word list. These scores in inclusion and exclusion were then used to calculate the contribution of explicit memory and automatic influence to the memory performance, using the Jacoby[8] equation. There was no evidence of an explicit memory contribution, because the explicit memory score was not statistically greater than zero. On the contrary, the contribution of implicit memory to memory performance during anesthesia was significant, because the automatic influence score was significantly higher than the base rate ($P < 0.01$). Moreover, the implicit memory effect size was 0.47.

The memory performance for different levels of anesthesia is shown in figure 1, which represents explicit and automatic influence scores for different BIS categories. In this regard, 18.5% of the words were presented at BIS 61–80, 51% of the words were presented at BIS 41–60, 28.5% of the words were presented at BIS 21–40, and 2% of the words were presented at BIS 0–20. We found no evidence of memory during deep anesthesia (BIS 21–40, C = 0.05 ± 0.14 and A = 0.14 ± 0.12). However, memory for words was significant during adequate (BIS 41–60) and light (BIS 61–80) anesthesia, with a significant contribution by implicit memory, because the au-

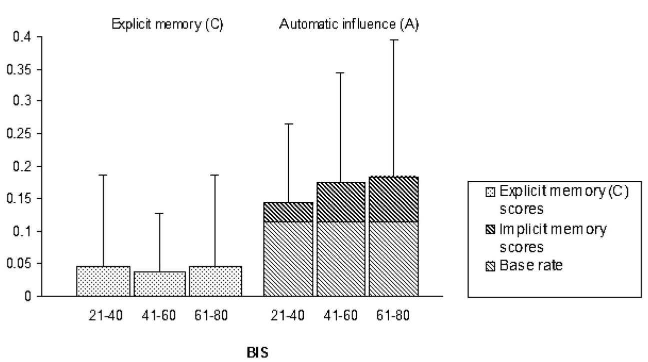


**Fig. 1. Explicit and automatic memory (implicit memory and base rate performance) scores for words presented during general anesthesia at three categorized Bispectral Index (BIS) levels for the 48 anesthetized patients.**

**Table 3. Anesthetized and Nonanesthetized Matching Subject Characteristics**

| | Anesthetized Subjects | Nonanesthetized Matching Subjects |
|---|---|---|
| n | 24 | 24 |
| Age, yr | 37.9 ± 12 | 37.6 ± 12.1 |
| Sex, M/F, n | 15/9 | 15/9 |
| Education level, yr | 13 ± 2.2 | 13.6 ± 2 |
| Interval between word presentation and memory test, h | 27.7 ± 3.3 | 32.7 ± 3.17 |

Values are presented as mean ± SD.

**Table 4. Mean Hit Rates in the Two Test Conditions and Mean Scores of Memory for Target Words and Distractor Words (Base Rate) for the Anesthetized and Nonanesthetized Subjects**

| | Anesthetized Subjects | Nonanesthetized Matched Subjects |
|---|---|---|
| Hit rate in inclusion | 0.17 ± 0.08 | 0.49 ± 0.22* |
| Hit rate in exclusion | 0.17 ± 0.08 | 0.15 ± 0.08 |
| Explicit memory scores | 0.03 ± 0.06 | 0.35 ± 0.24† |
| Implicit memory scores | 0.17 ± 0.07‡ | 0.22 ± 0.12‡ |
| Base rate | 0.12 ± 0.05 | 0.14 ± 0.08 |

Values are presented as mean ± SD.

* $P < 0.001$ (> hit rate in inclusion in anesthetized patients). † $P < 0.001$ (> zero and than explicit memory in patients). ‡ $P < 0.05$ (> base rate).

tomatic influence score was significantly greater than the base rate ($P < 0.05$ (A = 0.17 ± 0.17 at BIS 41–60 and A = 0.18 ± 0.21 at BIS 61–80). We found no evidence of explicit memory contribution regardless of the level of anesthesia (C = 0.04 ± 0.09 at BIS 41–60 and C = 0.05 ± 0.14 at BIS 61–80). Memory scores for BIS 41–60 and BIS 61–80 were comparable. There was no correlation between global mean BIS and memory scores.

For 16 patients, the word presentation was completed before incision, because of the time taken for patient positioning, preparation, and disinfection for surgery. Ninety-one percent of the words were presented before surgical stimulation. Because a mean of only 3.7 words/subjects were presented after incision, we could calculate the scores for inclusion and exclusion but not the memory scores. Mean scores in inclusion were 0.16 ± 0.07 before incision and 0.12 ± 0.12 after incision. Mean scores in exclusion were 0.15 ± 0.06 before incision and 0.17 ± 0.15 after incision. We did not observe any difference between mean scores for words presented before and after incision, in either the inclusion or the exclusion condition.

Type of anesthesia (general anesthesia alone or general anesthesia combined with regional anesthesia), type of surgery (visceral, urologic, or orthopedic surgery), and type of analgesia did not influence the explicit and implicit memory scores. The time between word presentation and memory testing did not correlate with the explicit or implicit memory scores for target words ($r$ = 0.01).

### *Nonanesthetized Volunteers*

Twenty-four nonanesthetized volunteers underwent the word presentation and memory testing processes. These nonanesthetized subjects did not differ from the matching anesthetized patients in terms of sex, age (t(46) = 0.071, $P > 0.05$), or education level (t(46) = 0.887, $P > 0.05$) (table 3). Table 4 shows the results of the memory test for the 24 nonanesthetized subjects and the 24 matching anesthetized patients. Base rates were comparable for the 24 patients in inclusion (0.13 ± 0.06) and exclusion (0.10 ± 0.07) and for the 24 control subjects in inclusion (0.13 ± 0.0) and exclusion (0.14 ± 0.09). We present the average value for both conditions in this table.

Compared with anesthetized patients, the memory performance of nonanesthetized volunteers was better, with significantly higher hit rates in inclusion. Explicit memory contributed significantly to memory performance in nonanesthetized volunteers (explicit memory score > 0; $P < 0.001$) and was significantly higher in the nonanesthetized volunteers than in anesthetized patients ($P < 0.001$). There was also an implicit memory contribution (> base rate; $P < 0.05$), which was comparable in anesthetized and nonanesthetized subjects.

## Discussion

This study was designed to assess memory of words presented during general anesthesia in patients undergoing elective surgery, where the level of anesthesia is expected to be stable, and to relate the memory performance to the level of anesthesia measured by the BIS. Using a word stem completion test combined with the process dissociation procedure, we found evidence of memory for words presented during light (BIS 61–80) and adequate (BIS 41–60) anesthesia but not during deep anesthesia (BIS 21–40), with a contribution by implicit memory but not explicit memory. There was no relation between memory performance and surgical stimulation. Finally, to discover the impact of general anesthesia on memory performance, we compared the memory performance of anesthetized patients and nonanesthetized volunteers. Nonanesthetized subjects performed better than anesthetized patients, with a higher contribution by explicit memory and a comparable contribution by implicit memory.

### *Base Rate*

Hit rates for our distractor list (base rate) were lower (12%) than in other studies[9–12] (20–30%). Our patients had to complete word stems according to strict rules (six-letter words, no plurals, no proper nouns, and no conjugated verbs), compared with the English, Dutch, and German subjects in previous studies,[9–12] who did not have to comply with the same demand. Moreover, our list of 60 six-letter French words was created such that each word stem (*i.e.*, the first three letters of each word) was unique within the experiment but not within the language. Each word stem could be completed by at least 5 six-letter French words (*e.g.*, *bal*: *ballot*, *ballet*, *ballon*, *balcon*, *baleze*, *balise*, and so on), but only one of the completions appeared in the experiment. An average of 8 other words could complete each word stem. Among these 8 words, the words selected for our study were never the most frequently used in the French language (*e.g.*, *ballot* is less frequent than *ballon*, *balcon*, or *ballet*). The mean frequency position for the completion possibilities was 4. Thus, there was an average of 3 other more frequent completion possibilities than the word selected for our study. Consequently, there was less opportunity for the subject to complete the stem with a study word by chance, because other, more frequently used words were available to complete our stems.

*Explicit Memory*

In the inclusion condition, subjects are instructed to complete stems with a word presented previously during general anesthesia or with the first word that came to mind. In this condition, explicit and implicit memory lead to the same response rate, which will be higher than the rate due to chance. The exclusion condition allows one to separate explicit from implicit memory processes. In this condition, the subjects are told not to use the presented words for stem completion but to use another word instead. If the subjects use an explicit memory process, they will complete the stem by the word presented during anesthesia less frequently, and the score for exclusion will be lower than chance. Our subjects had comparable scores in inclusion and exclusion conditions, and these scores were both higher than the base rate, meaning that their memory performance was not dictated by an explicit memory process. Moreover, no patient had any conscious recall of intraoperative events or of the presented words. Using the Jacoby equation, we found a low explicit memory score ($C = 0.04$). The low probability we obtained for explicit memory is comparable to the results of Lubke *et al.*[9] in the trauma surgery study. Their patients had general anesthesia with isoflurane like the majority of our subjects at the time of word presentation. Their level of hypnotic state was lighter and more variable (BIS of $49 \pm 9$ [range, 22–73] in our study and of $53 \pm 14$ [range, 21–96] in the trauma study). We would have expected a higher level of explicit memory in the trauma surgery patients because the level of their anesthesia was lighter. Moreover, this type of surgery is associated with variations in the depth of anesthesia and increased concentrations of circulating catecholamines, which are known to enable learning.[14–16,20]

Other studies using word presentation during anesthesia and the process dissociation procedure to dissociate explicit and implicit memory processes showed different results.[10–12] Patients anesthetized for emergency cesarean delivery with a superficial anesthesia ($BIS > 70$)[10] and patients with near adequate titrated anesthesia (BIS 60–70)[11] before the start of surgery made correct inclusion and exclusion decisions, with scores in inclusion higher than chance and scores in exclusion lower than chance. However, because none of the words were consciously recalled or recognized, decisions to either include or exclude a word were made without conscious awareness. Because decision making involves some control over memorized information, the authors[10,11] call this explicit memory in the absence of conscious recall "unconscious controlled memory" and suggest that it is a weak form of explicit memory. Like Stapleton and Andrade,[12] we are not convinced of the existence of this unconscious controlled memory: It is possible that these subjects were too cautious in the exclusion condition and may have rejected words that were too familiar, or those that came to mind too easily by an automatic process. Such behavior could have been induced by instructions different from those that were used in our study. Further, at the beginning of the memory test in our study, we simply asked whether the subjects had any recall of intraoperative events or of the presented words, whereas Lubke *et al.*[10] and Kerssens *et al.*[11] also asked patients to report any of the words they consciously recalled when the word stems were presented. In such tasks, instructions can strongly influence the subject's choice.

*Implicit Memory*

We showed the persistence of implicit memory during light and adequate anesthesia but not during deep anesthesia. Implicit memory did not differ between light and adequate anesthesia. The implicit memory effect size of 0.47 is a relatively good in this field and is comparable to the effect size observed in other studies of learning during anesthesia.[15,21]

In the trauma patient study, Lubke *et al.*[9] demonstrated a statistically significant but weak relation between depth of anesthesia and implicit memory. This difference may be the consequence of an insufficient number of patients in our study (48 *vs.* 96 patients in the trauma study). Other studies tried to demonstrate the persistence of an implicit memory during general anesthesia for elective surgery, with mixed results. They differed by many experimental variables, *e.g.*, type of stimuli and memory test, time of intraanesthetic presentation, interval before postoperative testing, anesthetic regimen and depth of anesthesia, type of surgery. The influence of these factors on positive outcomes of such studies is still unclear. If implicit memory is demonstrated, it is important to know whether it persists during adequate anesthesia or whether it occurs only during periods of light anesthesia. For this reason, we focused only on studies where implicit memory was related to the depth of anesthesia monitoring. Kerssens *et al.*[22] and Struys *et al.*[23] failed to show the persistence of an implicit memory in patients during general anesthesia with propofol for elective surgery titrated using the BIS at an adequate level (BIS 40–60). These studies used different memory tests that were not based on the process dissociation procedure but on category exemplar generation[22] and on intraoperative suggestions.[23] We found three differences between our study and their methodology: First, differences in the anesthetic regimen may explain controversial findings, because we used mainly isoflurane, and both the Kerssens and Struys studies used propofol. These two hypnotics have different sites and mechanism of action, as demonstrated by Alkire and Haier.[24] The second difference between our study and the negative findings of Struys and Kerssens is that we recorded BIS every 15 s, compared with more frequent (every 4 s) recording in the study of Struys *et al.*[23] (unknown in Kerssens *et al.*[22]). Consequently, our positive results, even with adequate anesthesia, may be related to learning during a period of lighter anesthesia that was "missed" by our BIS recording. Third, in these two studies, anesthesia was titrated to adequate BIS between 40 and 60, whereas our patients had non–BIS-titrated anesthesia. Therefore, titrating anesthesia using BIS could prevent explicit and implicit memory. This must be demonstrated in a controlled study.

Using a recognition test for words presented before the start of surgery, Renna *et al.*[25] showed the persistence of implicit memory for patients receiving a low concentration of sevoflurane (1.2% end-tidal concentration) but not for those receiving deeper anesthesia (1.5% and 2% sevoflurane end-tidal concentrations). BIS correlated poorly with the different sevoflurane concentrations and did not significantly predict susceptibility to priming.

Münte *et al.*[26] found implicit memory evidenced by an increased postoperative reading speed for stories presented during light to moderate but not for deep propofol–remifentanil anesthesia monitored and titrated by the automatic Narcotrend electroencephalogram classification system (MonitorTechnik, Bad Bramstedt, Germany). This new depth of anesthesia monitor is based on a visual classification of 14 electroencephalographic anesthesia stages and has been shown to correlate to the BIS® monitor.[27]

Finally, Schwender *et al.*,[28] Ghoneim *et al.*,[29] and Aceto *et al.*,[30] using midlatency auditory evoked potentials, showed preserved implicit memory for stories presented during anesthesia with various anesthetic regimes only for those patients who had preserved midlatency components, which indicates light anesthesia. They found that automatic memory was absent in deeper anesthesia. In these studies, depth of anesthesia measured by midlatency auditory evoked potentials was not categorized in different levels (deep, adequate, or light) as in our study or in the trauma patient study.[9] Therefore, we cannot conclude from their studies whether implicit memory occurred only during light anesthesia or also during adequate anesthesia.

An important factor contributing to learning during general anesthesia is surgical stimulation. Deeprose *et al.*[15] reported implicit memory for words played during but not before surgical stimulation, with a constant and adequate depth of anesthesia during these two tested periods. The influence of surgical stimulation is supported by other studies[16,31] that show no learning during propofol anesthesia before surgery. Surgery triggers an increase in catecholamines and cortisol, which have been shown to exert an influence *via* the amygdala on learning and memory.[14,20] Moreover, the stress of surgery may enhance memory consolidation even for neutral word lists, because it has been demonstrated that administering epinephrine to animals and humans mimics the effect of emotion and thus improves memory for neutral stimuli.[15,20,32] However, in our study, hit rates for the words presented before and after the incision were comparable in both inclusion and exclusion conditions.

*Effect of Anesthesia on Memory*

In this study, we also wanted to measure to what extent general anesthesia could affect memory in anesthetized patients compared with nonanesthetized volunteers who were given the same list of words and the same word stem completion test combined with the process dissociation procedure. Memory performance was better in nonanesthetized than in anesthetized subjects, with a higher contribution by explicit memory and a comparable contribution by implicit memory. By its effect on consciousness, a moderate or light general anesthesia suppresses a significant contribution by explicit memory processes but does not affect implicit memory processes any more than in the nonanesthetized situation.

To be comparable to the stressful condition of surgery, a control group that was experiencing some stress would have been preferable, *e.g.*, dental patients receiving local anesthesia without sedation or volunteers subjected to some type of experimental stressor.

In conclusion, patients who underwent elective surgery during general anesthesia demonstrated evidence of an implicit memory for words presented during light and adequate anesthesia, but not during deep anesthesia. There was no evidence of explicit memory. Nonanesthetized subjects showed similar implicit memory performance compared with anesthetized subjects, but much more explicit memory. We know that memory formation occurs at various sites of the brain, with some areas being more involved in explicit memory and others in implicit memory. Anesthetics may affect any or all of these sites, but the specific sites where these different actions occur are not known and should be the subject of more research using uncontaminated memory tests. Finally, the consequence of the persistence of implicit memory during general anesthesia is unknown. This kind of memory cannot be verbalized by the patient, who is unconscious at the time of stimulation. More research is necessary to find out whether it may be the cause of unspecific postanesthesia symptoms (anxiety, sleep disturbance, tiredness). The persistence of implicit memory during general anesthesia raises an ethical question: Can it be used for the benefit of the patient, or should we avoid it by administering deeper anesthesia?

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