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Absence of Explicit or Implicit Memory in Patients Anesthetized with Sufentanil/Nitrous Oxide

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Verbal paired associates were presented to 25 surgical patients from initial incision to closure of the incision during general anesthesia. Sufentanil with nitrous oxide and oxygen was administered; intravenous morphine (0.05 mg/kg) was administered when the skin suturing was completed; no volatile anesthetic agents or benzodiazepines were administered. When ready for discharge from the postanesthesia care unit, and again 2 weeks later by telephone, patients were tested for free recall, cued recall, recognition, and free association. No evidence of explicit memory for the word list was demonstrated by patients on tests of free recall, cued recall, or recognition, nor did a free-association test of implicit memory demonstrate a significant priming effect, in contrast to previous results obtained with isoflurane. The precise conditions under which surgical events can be processed, and retained in the form of implicit memory outside of conscious awareness, remain to be determined. (Key words: Anesthetics, intravenous: sufentanil. Awareness. Consciousness. Memory.)

ANESTHETIZED PATIENTS rarely show any recall or recognition of surgical events. Nevertheless, the question has persisted whether surgical events might be processed to at least some degree, affecting patients after the operation and outside awareness.[1–5] For example, it has been reported that words and phrases presented during anesthesia can influence postoperative behavior on various tests of memory and perception.[6–8] Moreover, patients can respond postoperatively to cues established during surgery for simple motor behaviors.[8–10] Finally, the course of postsurgical recovery can be influenced by therapeutic suggestions administered during an operation.[11–14] Consideration of these sorts of reports must be balanced by a substantial number of negative findings,[15–20] but even so, this more recent research continues to raise the issue of whether, and to what degree, intraoperative events can be encoded in memory, and how such encodings might influence postoperative experience, thought, and action.[21]

Outside the domain of anesthesia, considerable evidence from a variety of amnesic states suggests that events can influence subsequent behavior even though they themselves are not consciously remembered.[22–24] For example, brain-damaged patients with amnesic syndrome cannot recall or recognize words that have been presented to them on a previously studied list, yet they are significantly more likely to complete word stems and fragments with list items, compared to control conditions—a phenomenon known as priming. Priming effects clearly indicate the influence of the previous exposures on subsequent performance, even though the exposures themselves are not remembered.[25,26]

Such research has led to two classifications of memory: *explicit* memory entails conscious recollection of events, as in recall or recognition; by contrast, *implicit* memory is expressed independently of conscious awareness, by changes in task performance that are attributable to past events. Experimental and clinical data indicate that these two types of memory are separate and dissociable.[25,26] Accordingly, the question about postoperative memory may be reformulated as follows: given that general anesthesia abolishes explicit memory of surgical events, what effect does it have on implicit memory? Are reports of postoperative responses to suggestions, in the absence of conscious memory for these suggestions, simply preservation of implicit memory?

An earlier experiment in our laboratory used a strict anesthetic protocol and a well-established memory paradigm to test for a dissociation between implicit and explicit memory following surgical anesthesia.[27] Anesthesia was induced in a group of 25 surgical patients by intravenous thiopental accompanied by vecuronium and was maintained by isoflurane 0.5–1.5% (average concentration at first incision 1.42% and at last suture 1.00%); no preoperative medications were given, nor were nitrous oxide or benzodiazepines used. From the first incision until the last skin suture, a tape recording consisting of one of two lists of 15 verbal paired associates was played through earphones to the patients. Postoperative testing was conducted in the recovery room and again by telephone 2 weeks later. On free-recall, cued-recall, and recognition tests, the patients showed no explicit memory for the

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words in the list that had been played to them. However, a test of free association revealed significant implicit memory for the list that had been presented during surgery. The effect was greater for patients who received the free association test before the cued-recall test: of the 13 patients in this group, 11 (85%) showed evidence of priming. The priming effect was maintained on follow-up testing 2 weeks later.

Thus, our earlier experiment[27] showed a dissociation between explicit and implicit memory obtained with isoflurane/oxygen anesthesia. Patients who had no explicit memory for the word list nevertheless showed implicit memory for the words. The purpose of the present study was to determine whether this same dissociation could be obtained with anesthesia by sufentanil, a pure μ-receptor opioid agonist, and nitrous oxide.

Materials and Methods

Subjects

After approval by the Human Subjects Committee and informed consent by each patient, a total of 36 surgical patients consented to participate in the study. Any patient undergoing a general anesthetic and assigned American Society of Anesthesiologists (ASA) physical status 1, 2, or 3 was eligible for the study. At the time of giving informed consent, the patients were told that a tape-recorded message would be played to them while they were anesthetized and that they would receive an initial test of memory in the recovery room and a follow-up by telephone 2 weeks later.

Materials

Two lists of paired associates developed by Kihlstrom were used for this experiment.[28] Each list consisted of 15 stimulus terms (cues) and the most frequent response (targets) given to each, as indicated by standard norms. The cue–target pairs in the two lists were closely matched in terms of their normal stimulus–response probabilities. The probability of the correct target in response to a given cue averaged 0.51 for each list. Different randomizations of each list, approximately 45 s in length, were recorded for presentation on auto-reverse cassette players. These materials were identical to those used in our previous study with isoflurane/oxygen, described above.[27]

Procedure

Anesthesia was induced with intravenous thiopental (4–5 mg/kg) accompanied by vecuronium (0.1 mg/kg). Anesthesia was maintained with sufentanil $0.5\text{-}\mu g \cdot kg^{-1}$ bolus followed by an infusion begun at $0.5\ \mu g \cdot kg^{-1} \cdot h^{-1}$ and controlled by an anesthesiologist not involved in the study. Nitrous oxide with oxygen was administered, and end-tidal nitrous oxide concentration was maintained at 70%. Additional vecuronium for muscle relaxation was administered to maintain one visible twitch response to a train-of-four stimulation. No preoperative medications were given; benzodiazepines were not used.

A stimulus tape was randomly selected, and the tape recorder was started at the time of skin incision and played continuously until the incision was closed. Tape recordings were not made by anyone familiar to the patient. There was a brief introduction to each tape recording. This introduction was used to adjust volume by the research assistant before the tape recorder was turned on at skin incision. Neither the anesthesiologist nor other operating room personnel could hear the tape. Each patient received several presentations of one list (critical items), whereas the other list was not presented to the patient (neutral items). Additional intravenous morphine was administered as needed in the recovery room until the patient was comfortable and ready for the postoperative interview.

The researcher who conducted the postoperative testing did not know which tape was played to the patient during surgery. The postoperative interviews consisted of the following tests. *Free recall:* the patient was reminded that he or she had been read some words during surgery and was asked to recall any remembered items. *Cued recall:* the patient was given the cue terms of both critical and neutral lists in one of three random orders and was asked if any items reminded him or her of a word that had been presented during surgery. *Free association:* the patient was read the cues, in random order, and was asked to report the first word that came to mind. *Recognition:* the cue–target pairs were read in random order, and the patient was asked to indicate those that had been read during surgery.

Testing followed one of two randomly determined orders, in which cued recall always followed free recall, and recognition was always last; the free association test preceded free and cued recall for half the subjects and followed these tests for the remainder. Approximately 2 weeks after surgery, the tests of recall, cued recall, free association, and recognition were repeated during a follow-up telephone interview. Placement of the free association test was not altered.

A $2 \times 3 \times 2$ repeated-measures analysis of variance (ANOVA) (*targets:* critical or neutral lists; *measure:* cued recall, recognition, or free association; *trial:* immediate or delayed) was applied to the responses to the various memory tests. Interactive effects were decomposed into separate repeated-measures ANOVA. Significance was $P < 0.05$.

TABLE 1. Patient and Anesthetic Variables: Sufentanil/Nitrous Oxide

Variable	Mean ± SEM (n = 25)
Patient	
Age (yr)	39.1 ± 3.0
Height (cm)	165 ± 2
Weight (kg)	73.8 ± 3.2
Anesthetic variables	
Morphine (mg) (PACU)	5.9 ± 1.5
Sufentanil dose (μg)	140 ± 12
Body temperature (° C)	
Incision (nasopharyngeal)	36.3 ± 0.1
Last stitch (nasopharyngeal)	35.8 ± 0.1
Recovery room (axillary)	36.3 ± 0.1
Cardiovascular variables	
Maximum Blood Pressure (mmHg)	
Systolic	149 ± 4
Diastolic	82 ± 3
Minimum blood pressure (mmHg)	
Systolic	109 ± 2
Diastolic	59 ± 2
Mean blood pressure (mmHg)	
Maximum	104 ± 3
Minimum	75 ± 2
Pulse (beats/min)	
Maximum	78 ± 3
Minimum	54 ± 2

PACU = postanesthesia care unit.

Results

Although 36 patients participated in the initial phase of the experiment, delayed testing could not be completed for 8 patients, such that the sample was reduced to 28 patients. Furthermore, 3 patients remembered specific items from the word list: they were excluded from the analyses that follow in order to focus on those 25 patients with no free recall of list items who received both immediate and delayed tests of memory. Although these patients showed complete lack of free recall of the list items, 9 of these patients reported vague, dreamlike recollections of other intraoperative events. None of the patients who reported recollections had any adverse feelings about those recollections.

Table 1 shows basic descriptive data on the 25 patients without recall. Of these patients, 28% were ASA physical status 1, 56% ASA physical status 2, and 16% ASA physical status 3. The mean time of anesthesia was 189.2 ± 15.9 min. The tape was played for a mean of 145.8 ± 13.6 min, or approximately 194 repetitions of the list. The mean delay in the recovery room before the immediate test trial was 277.4 ± 74.5 min. This value is inflated by one patient who was not tested until the day after surgery (median = 105.0 min). A mean of 18.0 ± 0.8 days elapsed before the retest.

The percentage of critical and neutral target items produced on the cued-recall, recognition, and free-association tests is shown in table 2. A 2 × 3 × 2 repeated-measures ANOVA yielded a significant main effect of measure, $F(2,48) = 40.80$, mean standard error = 5.70, $P < 0.001$. The main effect of trials also reached statistical significance, $F(1,24) = 11.02$, $P < 0.005$; this effect was qualified by a significant trials × targets interaction, $F(1,24) = 8.31$, MSE = 0.041, $P < 0.01$. No other main effects or interactions reached statistical significance.

Explicit Memory

None of the patients showed any evidence of explicit memory for list items on the cued-recall and recognition tests. A 2 × 2 repeated-measures ANOVA of cued-recall scores showed a significant effect of trial (immediate or delayed), $F(1,24) = 4.37$, MSE = 0.237, $P < 0.05$, indicating that subjects were more likely to produce target items on the delayed test. The main effect of targets was nonsignificant, $0.05 < P < 0.10$, as was the trials × targets interaction, $F < 2$.

A similar ANOVA of recognition scores revealed a significant main effect of trials, $F(1,24) = 6.06$, MSE = 0.212, $P < 0.05$. There was no main effect of targets, $F < 1$, and the trials × targets interaction was nonsignificant, $F(1,24) = 3.02$, MSE = 0.004.

Implicit Memory

Substantially the same results were obtained with the free-association test of implicit memory. The ANOVA showed a significant effect of delay, $F(1,24) = 5.50$,

TABLE 2. Response to Tests of Explicit and Implicit Memory: Sufentanil/Nitrous Oxide

	PERCENTAGE OF TARGETS ELICITED		
Target	Cued Recall	Recognition	Free Association
Trial: Immediate (PACU)			
Critical (list played)	10.1 ± 4.8	5.1 ± 2.7	48.0 ± 4.7
Neutral (list not played)	8.8 ± 4.8	6.4 ± 3.6	52.5 ± 4.6
Trial: delayed (2 weeks)			
Critical (list played)	21.3 ± 6.3	15.5 ± 5.8	58.9 ± 4.5
Neutral (list not played)	17.6 ± 5.6	14.4 ± 5.4	54.7 ± 5.1

Values are mean ± SEM (n = 25). PACU = postanesthesia care unit.

$P < 0.05$, indicating that subjects were more likely to produce both critical and neutral targets on the delayed test. However, there was no significant effect of targets, $F < 1$, indicating the absence of an overall priming effect. There was a marginal target × delay interaction, $F(1,24) = 3.97$, MSE = 0.048, $P = 0.06$. The patients were more likely to produce neutral targets than critical targets on the immediate trial, but this effect was reversed on the delayed trial. Overall, the patients produced 53.5% of the critical targets and 53.6% of the neutral targets. Priming, as evidenced by an advantage of at least one item for critical over neutral targets, was shown by 5 patients (25%) on the immediate trial and 11 patients (44%) on the delayed trial.

Effect of Order of Testing on Priming

In contrast to our earlier experiment,[27] there were no consistent order effects on priming. Subjects showed a small advantage for neutral over critical targets (52.5% *vs.* 48.0%) on the immediate test and a small advantage for critical over neutral targets (58.95% *vs.* 54.7%) on the delayed test.

On the initial test, only 3 of 13 (23.1%) patients who provided free associations before cued recall showed priming. Similarly, only 2 of 12 (16.7%) of patients who provided cued recall first showed priming. On the delayed test, these figures were 5 of 13 (38.5%) and 6 of 12 (50.0%), respectively.

Correlates of Priming

Table 3 shows the correlations between surgical variables and the extent of priming observed on the immediate and delayed tests. None of the correlations reached statistical significance. In particular, priming was not significantly correlated with time in surgery, interval between the immediate and delayed tests, or the duration of list presentation.

TABLE 3. Correlates of Performance on Implicit Memory Tests: Sufentanil/Nitrous Oxide

Trial	Correlation Coefficient (R) (n = 25)	
	Immediate (PACU)	Delayed (2 weeks)
Patient		
ASA physical status	−0.29	0.19
Age (yr)	0.10	−0.13
Height (cm)	−0.01	−0.13
Weight (kg)	0.02	0.11
Elapsed time (min)		
In surgery	0.05	−0.18
For tape	0.08	−0.31
To first trial (PACU)	0.14	−0.43
To second trial (2 weeks)	0.34	−0.17
Anesthetic variables		
Morphine (mg) (PACU)	−0.24	−0.09
Sufentanil dose (μg)	0.01	0.03
Body temperature (° C)		
Incision (nasopharyngeal)	0.00	0.25
Last stitch (nasopharyngeal)	−0.08	0.29
Recovery room (axillary)	−0.05	−0.10
Cardiovascular variables		
Maximum BP (mmHg)		
Systolic	−0.43	0.20
Diastolic	−0.20	0.30
Minimum BP (mmHg)		
Systolic	−0.45	0.23
Diastolic	−0.38	0.23
Mean BP (mmHg)		
Maximum	−0.32	0.28
Minimum	−0.45	0.25
Pulse (beats/min)		
Maximum	−0.36	0.31
Minimum	−0.09	0.09

PACU = postanesthesia care unit; BP = blood pressure.

Discussion

In contrast to our previous work demonstrating a dissociation between explicit and implicit memory following surgical anesthesia with isoflurane,[27] no such dissociation was obtained with sufentanil/nitrous oxide. In the isoflurane study, patients showed no explicit memory for paired associates presented during surgery, as measured by tests of free recall, cued recall, and recognition; however, a majority of these same patients displayed implicit memory for the same material, as evidenced by a priming effect on the subsequent word-association test. By contrast, patients receiving sufentanil/nitrous oxide showed more explicit memory, but impaired implicit memory.

Figure 1 illustrates the results of the present sufentanil/nitrous oxide study and the earlier isoflurane/oxygen study[27] with respect to the free-association measure of implicit memory. Because the studies were not concurrent, direct statistical comparisons between them would be weak. However, the main differences between the two studies are with respect to implicit memory: isoflurane spared implicit memory, while sufentanil/nitrous oxide did not.

Although the two experiments differed with respect to the comparison between explicit and implicit memory, both showed a consistent effect of trials on memory task performance. Regardless of the task (cued recall, recognition, or free association), the patients were more likely to produce targets from both critical and neutral lists on the delayed trial than the immediate one. This effect has nothing to do with memory for surgical events but may reflect residual effects of surgical anesthesia on general thinking processes. Although the patients were completely oriented when interviewed in the recovery room, perhaps they were not completely recovered from anesthesia at the time of initial testing, and this status may have suppressed their task performance on the immediate trial.

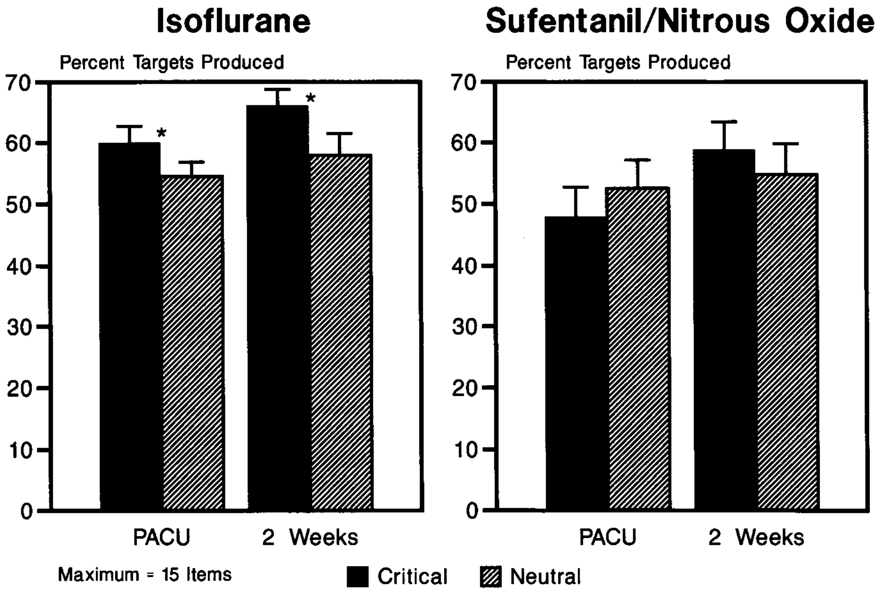

FIG. 1. Priming effect on free association performance in the present experiment with sufentanil/nitrous oxide and the previous experiment with isoflurane. *Significant difference between percent targets produced with critical *versus* neutral list ($P < 0.05$). PACU = postanesthesia care unit. (Modified after Kihlstrom *et al.*[27])

Adam[29] has shown that subanesthetic doses of anesthetic agents impair performance on a wide variety of cognitive tests. In addition, there may have been some clouding of consciousness due to the postoperative administration of morphine.

There is something of a paradox in this research, in that the findings of the earlier isoflurane study[27] lend support to other recent studies that have found that anesthesia spares implicit verbal memory,[6–8] whereas the findings of the present sufentanil/nitrous oxide study support those studies that have found neither explicit nor implicit memory after surgical anesthesia.[16,19,30] It is possible that the pattern of success and failure may be accounted for, to some degree, by the nature of the anesthetic agents used. Whereas the positive study by Bennett *et al.*[9] involved volatile anesthetic agents, the negative studies by Eich *et al.*[16] and Winograd *et al.*[19] both relied on samples of patients who received highly variable anesthetic regimes: some patients received volatile agents, and others received nitrous oxide/opioids. Therefore, it is possible that in the Eich *et al.* and Winograd *et al.* studies, positive results observed in patients who received one regime were swamped by negative results in patients who received other regimes. On the other hand, Goldman *et al.*,[10] Block *et al.*,[8] Roorda-Hrdlickova *et al.*,[6] and Jelicic *et al.*[7] obtained positive evidence of implicit memory with both volatile and opioid regimes, whereas Westmoreland *et al.*[30] obtained negative evidence with volatile agents. Future research on this matter should continue to use carefully standardized anesthetic techniques to reveal any selective effects on memory of different agents.

Differences in outcome between anesthetic techniques might be attributable to differences in anesthetic depth between patients receiving isoflurane and patients receiving sufentanil/nitrous oxide. However, light anesthesia was not clinically evident in either group. No patients in either group exhibited peripheral movement or frowning or any change in facial expression during the time that the tapes were played. In addition, no patients in either group exhibited any sweating or piloerection. Hemodynamics were not different between groups. Although there is no specific monitor with which to measure true depth of anesthesia, the clinical manifestations of these two groups of patients would indicate that they were both appropriately anesthetized for surgery.

It is known that benzodiazepines have profound effects on explicit memory, although their effects on implicit memory have not been well documented.[31–35] For this reason, we avoided the use of benzodiazepines in these studies. The use of a pure nitrous oxide/opioid technique without benzodiazepines accounts for the high incidence of explicit memory in our study.[36–38] Although Westmoreland *et al.*[30] did not find any effect of midazolam on implicit memory, future research should continue to investigate the effects of these drugs on implicit memory.

Another relevant variable may be the means by which implicit memory is assessed in terms of motor responses,[8–10] verbal behaviors,[6–8,10,16] nonverbal indices such as preference ratings,[19] and postoperative course.[11–14,17,18] Studies of both amnesic patients and normal subjects indicate that not all measures of implicit memory are equivalent,[26] and so some degree of standardization may be required of the dependent as well as the independent variables in these experiments.

Most of the positive results on implicit memory following general anesthesia published to date have involved the priming of old knowledge. Nose-touching and chin-touching,[8–10] category instances,[6,7] and free associations[27] all reflect habits or knowledge that were deeply ingrained before the patients' operations. It is not clear whether implicit memory for entirely new learning exhibits the same effects. For example, Winograd *et al.*[19] found no change in response to unfamiliar music played during surgery; however, Block *et al.*[8] did find priming-like effects on memory for nonsense words, which can be construed as evidence of new learning. Finally, Jelicic *et al.* recently obtained evidence of implicit memory for both old (statements concerning factual knowledge) and new (fictitious names) associations in surgical patients.§

The preservation of some information-processing functions during anesthesia, however limited, has some potential practical implications. For example, it has been shown that some patients respond positively to therapeutic suggestions administered during anesthesia[11–14]—an effect that obviously requires patients to encode information presented to them during surgery. If this technique could be further developed, perhaps common postoperative side effects (*e.g.*, nausea, emesis, difficulties with bowel and bladder function) could be minimized, and pain management and overall outcomes could be improved.

Although the practical and theoretical implications of implicit memory are interesting, the extent to which implicit expressions of memory are affected by general anesthesia remains uncertain. In these studies, we have attempted to organize what is known and to stimulate additional inquiry into this long-standing question. Rather than being rejected out of hand, the possibility of information-processing during general anesthesia now deserves serious consideration. While anesthesiologists tend to fear explicit memory and certainly want to minimize it, it may be possible to exploit implicit memory to achieve better postoperative outcome.

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