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Is there implicit memory after propofol sedation?

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Summary

Recent evidence indicates that implicit memory may be preserved during general anaesthesia. We tested for the presence of explicit and implicit memory in patients undergoing surgical procedures with local or regional anaesthesia and sedation with propofol. Initial i.v. boluses of propofol 0.5 mg kg^{-1} and fentanyl 1 μg kg^{-1} were administered, followed by an infusion of propofol 50 μg kg^{-1} min^{-1}. Administration of one or more doses of propofol 30 mg i.v. during operation was controlled either by the patient or the anaesthetist. At the start of the last skin stitch, patients were presented with a list of 15 stimulus words and the most frequently associated response. The infusion was then discontinued. After 1 h in the recovery area, all patients were tested for free recall, free association, cued recall and recognition on the list presented during surgery (critical list) and a matched list not presented (neutral list). Data of all patients without free recall (explicit memory) were analysed with repeated-measures analysis of variance. Of 36 patients, five demonstrated free recall. For the remaining 31 patients, cued recall and recognition showed no evidence of explicit memory. However, the free association tests demonstrated significant priming. The mean number of critical free associations was 6.6 (SEM 0.4) compared with 5.5 (0.4) neutral free association ($P < 0.05$). In the absence of explicit memory, implicit memory persists after intraoperative sedation with propofol. (*Br. J. Anaesth.* 1996; **76**: 492–498)

Key words

Anaesthetics i.v., propofol. Memory. Anaesthesia, depth.

Memory during anaesthesia has been classified into two different types: explicit and implicit [1]. Explicit memory involves conscious recollection of some previous episode and is what most of us understand as recall during anaesthesia. Implicit memory, however, refers to any effect on a person's experience, thought or action that is attributable to a past event, even if that person does not remember the event. Evidence for implicit memory during general anaesthesia has been controversial [2–4]. Although there is some concern that implicit memory may be spared despite profound impairment in explicit memory, different investigations have yielded different results, even in the same laboratory. For example, we have found that in surgical patients, implicit memory can be preserved during general anaesthesia with a pure oxygen–isoflurane technique [5]. However, using the same programme, we have found that implicit memory is not preserved during nitrous oxide–sufentanil anaesthesia [6]. It is difficult to draw conclusions from other available evidence, however, because of the heterogeneity in the anaesthetic programmes and memory tasks used. The difficulties of research in this area are compounded by the fact that we lack reliable, accurate measures of depth of anaesthesia. Recent investigations of non-patient volunteers found implicit memory preserved only at subanaesthetic concentrations of isoflurane [7] or nitrous oxide [8]. In our study involving anaesthetic concentrations of isoflurane, explicit memory did not occur in any of the patients [5].

Sedative drugs, such as the benzodiazepines, produce profound impairment of explicit memory, but they may spare implicit memory [9–11]. For example, in studies of non-patient volunteers, midazolam impaired recognition memory (a test of explicit memory), but spared priming effects in perceptual identification (a test of implicit memory) [12]. In a study using the same programme, it was found that propofol, a non-benzodiazepine sedative, also dissociated explicit and implicit memory; however, explicit memory was relatively unimpaired compared with midazolam [13]. Because the two drugs produced the same level of sedation, it appears that sedation *per se* does not necessarily impair memory. With the exception of this study, and some anecdotal evidence [14], the amnesic effects of propofol, as distinguished from its sedative effects, are unknown. In this study we tested for the presence of explicit and implicit memory in patients undergoing surgical procedures and sedation with propofol.

Patients and methods

After obtaining approval from the Louisiana State University Institutional Review Board and written informed consent, we studied patients undergoing

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Table 1 Sedation score

Responsiveness	
0	Asleep
1	No response to mild prodding or shaking
2	Response only after mild prodding or shaking
3	Response to name spoken loudly
4	Lethargic response to name spoken in normal tone
5	Immediate response to name spoken in normal tone
Speech	
0	Asleep
1	Few recognizable words
2	Slurring or prominent slowing
3	Mild slowing or thickening
4	Normal
Facial expression	
0	Asleep
1	Marked relaxation (slack jaw)
2	Mild relaxation
3	Normal
Ptosis	
0	Closed
1	Marked ptosis (half of the eye or more)
2	Mild ptosis (less than half of the eye)
3	No ptosis
Pain	
0	None
1	Mild
2	Moderate
3	Severe

ambulatory procedures involving local or regional anaesthesia with sedation. Exclusion criteria were ASA III or greater, allergy to propofol or soybeans, intellectual impairment or hearing difficulty. All patients were trained to "finger tap" as rapidly as possible on a counting device designed specifically for this study (by Joseph M. Moerschbaecher II, PhD, Professor and Head, Department of Pharmacology, LSU Medical Center).

No premedication was administered. Arterial systolic and diastolic pressures, heart rate, pulse oximetry, end-tidal P_{CO_2} ($P_{E'_{CO_2}}$), and temperature were measured throughout the procedure. Before surgery, each patient was given a bolus dose of propofol 0.5 $\mu g\,kg^{-1}$ i.v. and fentanyl 1 $\mu g\,kg^{-1}$ i.v. The time taken for administration of each bolus was 5 s, and the second drug was given 5 min after the first. The order of administration of the two drugs was determined randomly. A constant infusion of propofol 50 $\mu g\,kg^{-1}\,min^{-1}$ was given via a Bard InfusO.R. (C. R. Bard, Inc., North Reading, MA, USA) for all patients after the initial boluses of fentanyl and propofol. Patients were allocated randomly to receive supplementary boluses of propofol 30 mg during the procedure by one of two techniques: patient-controlled sedation (PCS) or anaesthetist-controlled sedation (ACS). PCS was carried out by the patient pushing a button attached to a demand pump (Bard Ambulatory PCA, C. R. Bard, Inc., North Reading, MA, USA). The patients were told to push the button whenever they wished to be "sleepier". ACS was carried out by the anaesthetist who was given instructions to sedate the patient to a responsiveness score of 4 and a speech score of 3 (see table 1). Clinical variables were recorded at the following events: (1) Baseline, before any drugs were given; (2) 2 min after the initial fentanyl bolus; (3) 2 min after the initial propofol bolus (the order of (2) and (3) were determined randomly); (4) 2 min after surgical incision; (5) at the last skin stitch; (6) on admission to the recovery room; and (7) 1 h after admission to the recovery room. Clinical variables included heart rate, arterial systolic and diastolic pressures, ventilatory frequency, $P_{E'_{CO_2}}$ and haemoglobin saturation by pulse oximetry. $P_{E'_{CO_2}}$ was not measured in the recovery room. At the same times, ordinal scores of pain reported by the patient, pain perceived by the anaesthetist, and sedation, as measured by scoring responsiveness, speech, facial expression and eye ptosis were allocated from the scale shown in table 1. In addition, the number of finger taps over a 10-s period were recorded. At the end of the procedure, total amounts of propofol, fentanyl and fluids administered were noted.

MEMORY TESTS

Four lists of paired associates developed by Kihlstrom were used for this experiment [15]. Each list consisted of 15 stimulus terms and the most frequent response given to each, as indicated by standard norms. For example, "boy—girl, man—woman, hammer—nail". The word pairs in the four lists were matched in terms of their normal stimulus–response probabilities. The probability of the correct response to a given cue averaged 0.51 for each list. Patients were allocated randomly to listen to one presentation of either lists 1 and 2 (tape A) or lists 3 and 4 (tape B) at the start of the last skin stitch. Both words of each word pair were presented. There was a brief identical introduction to each tape recording: "Please listen to the following word pairs." This introduction was used to adjust volume by the research assistant. Neither the anaesthetist nor other operating room personnel could hear the tape which lasted 90 s. When the word lists had been presented, the infusion of propofol was discontinued and no further administration was permitted.

Postoperative interviews were conducted 1 h after admission to recovery. By this time all patients were awake and responsive. The researcher who conducted the postoperative testing was not the same person who recorded the tape. In addition, this researcher did not know which paired associates had been played to the patient during surgery. The postoperative interviews comprised tests of free recall, cued recall and recognition for explicit memory, and free association for implicit memory. Patients were allocated randomly to receive one of two test sequences during the postoperative interview. Both test sequences included identical questions for free recall and recognition. However, in order to provide for adequate counterbalancing, patients who were given test 1 were tested only on lists 1 and 3 for cued recall and lists 2 and 4 for free association, while those given test 2 were tested on lists 2 and 4 for cued recall and lists 1 and 3 for free association. In each case, the list presented during surgery was the *critical list*, while the list not presented was the *neutral list*. The order of testing was as follows:

Free recall. Patients were asked if they remembered hearing words during surgery. If not they were

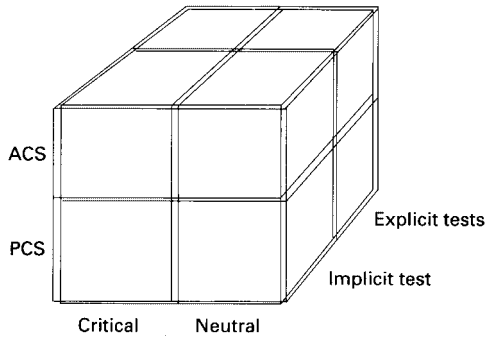

Figure 1 Experimental design. Independent variables are anaesthetist-controlled sedation (ACS) *vs* patient-controlled sedation (PCS), critical *vs* neutral list and implicit *vs* explicit tests. Analysis is with repeated-measures analysis of variance.

reminded that they had been read some words during surgery and were asked to recall any remembered items. A positive response was when patients remembered any of the words presented.

Free association. The cues were read to the patients in random order, and patients were asked to report the first word that came to mind. If no word came to mind, "none" was the accepted response. Patients were not forced to offer a word.

Cued recall. The patients were read the cues in random order and asked if any items reminded them of a word that had been presented during surgery. Again, "no" and/or "none" were acceptable responses. Guessing was discouraged.

Recognition. All 30 word pairs were read in random order and patients were asked to indicate those that had been read during surgery. "None" was an acceptable response and patients were discouraged from guessing.

The experimental design for tape and test is shown in figure 1. Key dependent variables were number of critical and neutral associates as measures of implicit memory (free association) and explicit memory (cued recall and recognition). The critical list of word pairs was played to the patient; the neutral list was not. Data were analysed with repeated measures analysis of variance. Within-subject effects examined were number of correct associations (critical *vs* neutral lists) and measure (free association, cued recall or recognition). The between-subject effect examined was sedation technique (PCS *vs* ACS). In addition, counterbalancing variables tested for potentially confounding effects were tape (A or B), test (1 or 2) and first drug bolus (fentanyl *vs* propofol). Comparison of clinical variables between those patients who demonstrated priming and those who did not was with Student's *t* test for grouped data. We accepted a result as significant if $P < 0.05$. All results for continuous variables are given as mean (SEM).

Results

Of the 36 patients studied, five (14 %) demonstrated free recall (explicit memory) of words played on the tape. The analysis that follows focuses on those 31 patients with no free recall of any words on the tape. There were no differences in the results between tapes A and B or between tests 1 and 2. However, these comparisons were only for the complete group of 31 patients. Subgroups were not analysed because of the small number of patients. Table 2 lists the basic descriptive data for the 31 patients without recall, and table 3 the values of different variables collected during operation.

Table 2 Patient characteristics ($n = 1$) (mean (SEM) [range] or number (% of total))

Age (yr)	48 [20–83]
Sex (M/F)	9 (29 %)/22 (71 %)
Height (cm)	169 (2) [152–188]
Weight (kg)	79 (3) [40–110]
ASA	
I	7 (22.6 %)
II	24 (77.6 %)
Ethnic background	
Black	26 (83.9 %)
White	3 (9.7 %)
Hispanic	2 (6.5 %)
Surgical procedure	
General surgery	17 (54.8 %)
Orthopaedics	7 (22.6 %)
Vascular	3 (9.7 %)
Urology	4 (12.9 %)
Regional anaesthesia	
Infiltration	23 (74.2 %)
Spinal	6 (19.4 %)
Bier block	2 (6.5 %)

Table 3 Intraoperative variables ($n = 31$) (mean (SEM) [range]). SAP = Systolic arterial pressure, HR = heart rate

Duration of surgery (min)	49 (6) [8–175]
Duration of anesthesia (min)	106 (9) [50–300]
Total propofol (mg)	279 (18) [75–525]
Fluids (ml)	913 (74) [200–1700]
Highest SAP (mm Hg)	164 (5) [120–212]
Highest HR (beat min^{-1})	83 (2) [60–118]
Lowest SAP (mm Hg)	113 (3) [80–142]
Lowest HR (beat min^{-1})	67 (2) [42–90]

CLINICAL, PAIN AND SEDATION VARIABLES

Clinical variables, including arterial systolic and diastolic pressures, ventilatory frequency, $P_{E'CO_2}$ and haemoglobin saturation by pulse oximetry, are shown in table 4 for the events studied, including baseline, fentanyl bolus, propofol bolus, incision, last stitch, recovery admission and recovery discharge. There was no difference between patients receiving ACS or PCS in clinical variables or in the amount of propofol used (250 (30) mg for ACS *vs* 300 (30) mg for PCS). Heart rate, arterial systolic and diastolic pressures, ventilatory frequency and saturations exhibited significant time effects ($P < 0.05$), but $P_{E'CO_2}$ did not change significantly throughout the procedure. Heart rate was greater, and arterial systolic and diastolic pressures and ventilatory frequency less at the last stitch, when the tape was played, compared with recovery at 1 h, when the interview was conducted ($P < 0.05$). Heart rate, arterial pressures and ventilatory frequency were all less when the tape was played compared with baseline ($P < 0.05$).

Ordinal scores of pain and consciousness are

Table 4 Clinical variables (mean (SEM)). HR = Heart rate, SAP = systolic arterial pressure, DAP = diastolic arterial pressure, f = ventilatory frequency. Order of initial fentanyl and propofol was determined randomly. Fentanyl and propofol results include all patients, irrespective of which drug was given first. *$P < 0.05$ compared with baseline and recovery (1 h)

	Baseline	Fentanyl (2 min)	Propofol (2 min)	Incision (2 min)	Last stitch (tape)	Recovery admission	Recovery (1 h)
HR (beat min^{-1})	78 (3)	76 (2)	76 (2)	72 (3)	73 (2)*	71 (2)	67 (2)
SAP (mm Hg)	153 (5)	150 (5)	138 (5)	139 (5)	124 (3)*	126 (3)	131 (3)
DAP (mm Hg)	82 (3)	79 (3)	74 (3)	74 (3)	69 (2)*	70 (2)	73 (2)
f (bpm)	17 (1)	15 (1)	15 (1)	17 (1)	15 (1)*	18 (1)	18 (1)
$P_{E'CO_2}$ (kPa)	5.2 (0.2)	5.2 (0.2)	5.2 (0.2)	5.3 (0.2)	5.1 (0.2)	—	—
Saturation (%)	98.8 (0.2)	98.0 (0.4)	95.9 (0.7)	97.8 (0.3)	98.8 (0.3)	98.7 (0.2)	98.7 (0.2)

Table 5 Pain and consciousness variables (mean (SEM)). Finger tapping = number of taps/10 s; other scores based on ordinal scales in table 1. Order of administration of fentanyl and propofol was determined randomly. Fentanyl and propofol results include all patients, irrespective of which drug was given first

	Baseline	Fentanyl (2 min)	Propofol (2 min)	Incision (2 min)	Last stitch	Recovery admission	Recovery (1 h)
Pain reported (Patient)	0.03 (0.03)	0.03 (0.03)	0.00 (0.00)	0.26 (0.12)	0.06 (0.04)	0.13 (0.06)	0.29 (0.12)
Pain observed (Anaesthetist)	0.03 (0.03)	0.03 (0.03)	0.00 (0.00)	0.23 (0.10)	0.13 (0.06)	0.03 (0.03)	0.13 (0.08)
Finger tapping	37.4 (1.6)	28.9 (1.5)	21.8 (2.1)	25.0 (2.1)	23.3 (2.1)	35.1 (1.7)	38.1 (2.0)
Responsiveness	5.0 (0.0)	4.7 (0.1)	3.7 (0.2)	4.0 (0.2)	3.9 (0.2)	4.8 (0.1)	5.0 (0.0)
Speech	4.0 (0.0)	3.7 (0.1)	2.6 (0.2)	3.1 (0.1)	2.9 (0.2)	3.8 (0.1)	4.0 (0.0)
Facial expression	3.0 (0.0)	2.7 (0.1)	1.8 (0.2)	2.1 (0.1)	2.1 (0.1)	2.8 (0.1)	3.0 (0.0)
Ptosis	3.0 (0.0)	2.7 (0.1)	1.8 (0.2)	1.9 (0.2)	2.0 (0.2)	2.8 (0.1)	3.0 (0.0)

summarized in table 5 for the intraoperative and recovery periods. There was no difference between patients receiving ACS and PCS in pain or level of consciousness. Both pain reported by the patient and pain observed by the anaesthetist exhibited a time effect ($P < 0.05$), but neither pain score was significantly different from the other at any time. Finger tapping, responsiveness, speech, facial expression and eye ptosis revealed time effects ($P < 0.05$). As indices of sedation, these variables indicated an awake baseline, sedation after the initial dose of fentanyl and propofol, sedation at the last stitch and return to baseline by admission to the recovery area. These variables were significantly different between the last stitch, when the tape was played, and recovery at 1 h, when the tests for memory were performed ($P < 0.05$).

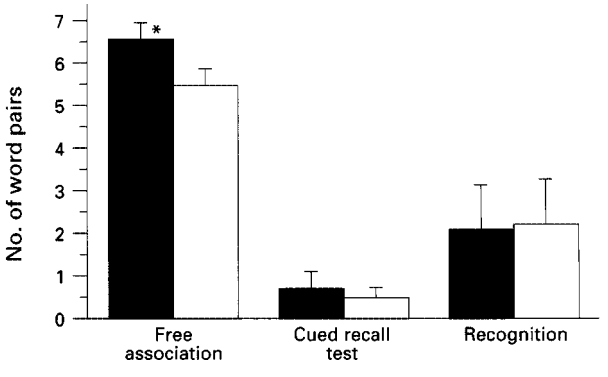

Figure 2 Critical (on tape) (■) and neutral (not on tape) (□) responses provided by the patient at the time of the postoperative interview. Critical responses were greater than neutral responses in the free association test ($P < 0.05$). Numbers of cued recall responses and word pair recognitions were not significantly different between the critical and neutral lists.

MEMORY

The results of five patients who demonstrated free recall were excluded from subsequent analysis, and the cued recall and recognition tests of the remaining 31 revealed no evidence of explicit memory. However, the results from the free association tests performed on the remaining 31 patients suggested implicit memory. Figure 2 shows the number of critical and neutral word pairs provided for each test at the time of the postoperative interview. Cued recall and recognition tests exhibited no difference between the number of critical and neutral word pairs provided as responses during the interview. In contrast, the number of critical free associations was 6.58 (0.36) compared with 5.48 (0.40) neutral free associations ($P < 0.05$). Figure 3 shows the distribution of the number of critical and neutral word pair free associations by number of patients. This shows that the difference detected was attributable to a small consistent difference in a number of patients, rather than extreme differences in a few patients. There were no effects attributable to the counterbalancing variables of tape (A *vs* B) or test (1 *vs* 2). There were also no effects from the initial drug (fentanyl *vs* propofol) or sedation technique (PCS *vs* ACS).

If we define priming as one or more critical responses than neutral responses, 20 of the 31 patients (64.5 %) demonstrated priming. A number of clinical and sedation variables, most related to the response of the patient to the initial bolus of propofol,

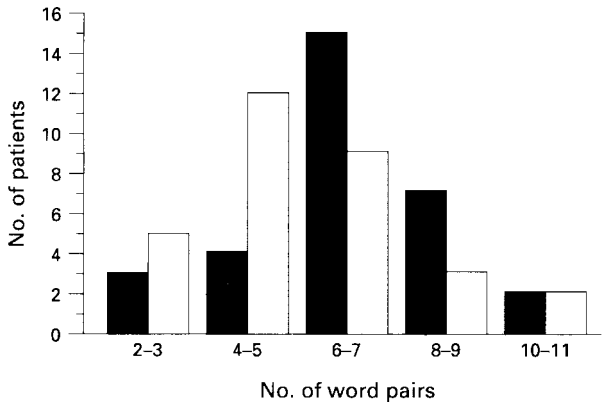

Figure 3 Distribution of the number of critical (■) and neutral (□) word pair free associations by number of patients. This shows that the difference detected was attributable to a small consistent difference between critical and neutral responses in a number of patients, rather than extreme differences in a few patients.

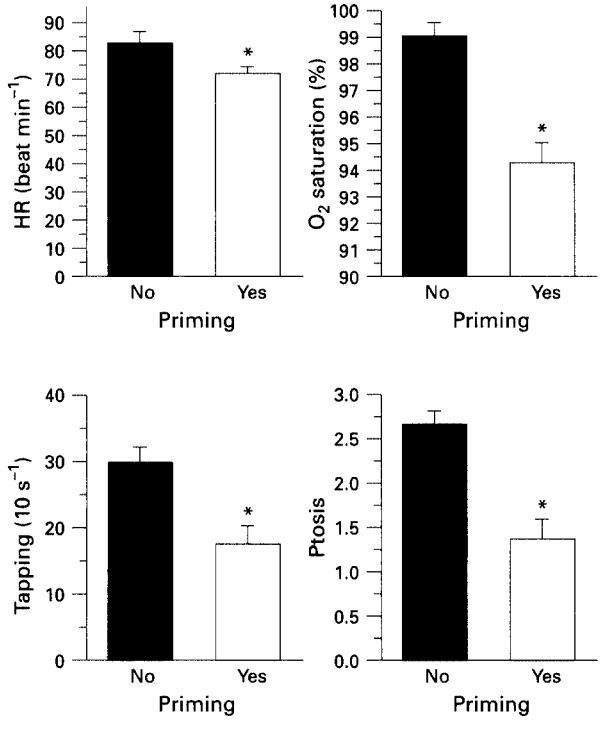

Figure 4 Variables after bolus administration of propofol which were different between those patients who subsequently demonstrated priming and those who did not. Priming was associated with lower heart rate (HR), decreased oxygen (O_2) saturation, slower finger tapping and lower ptosis scores (more ptosis) after the initial bolus of propofol 0.5 mg kg^{-1} ($P < 0.05$).

were associated with priming. Figure 4 shows the four variables which were significantly different between those patients who demonstrated priming and those who did not. Priming was associated with lower heart rate, decreased oxygen saturation, slower finger tapping and lower ptosis scores (more ptosis) after the initial bolus of propofol ($P < 0.05$). In addition to the difference in heart rate after propofol, mean heart rate was 72 (2) beat min^{-1} after the initial bolus of fentanyl for those patients who demonstrated priming, compared with 83 (4) beat min^{-1} for those who did not ($P < 0.05$).

Key variables not associated with priming were total propofol dose, time from the start of infusion and number of propofol boluses. There was no association between the dose of propofol administered and the priming response.

Discussion

This study has shown that patients who received sedation with propofol during surgery showed clear impairments in explicit memory. This was measured by free recall, cued recall and recognition of a list of paired associates presented during surgery. However, these patients also showed a priming effect on free association, which indicates that implicit memory was spared to some degree. This is the first study of ambulatory patients sedated with propofol to show preserved implicit memory, and it corroborates earlier results in non-patient volunteers [14].

For ACS *vs* PCS, our results differed from those of Osborne and colleagues [16] who studied the use of propofol with patient-controlled sedation in subjects undergoing bilateral extraction of third molar teeth during local anaesthesia. They found that patients controlling their own sedation (PCS) were less sedated than those receiving a propofol infusion by an anaesthetist. We found no difference in the level of sedation between ACS and PCS.

Our first two studies of implicit memory during general anaesthesia involved repeatedly playing the word lists to the patients from the first skin incision until the last skin stitch [5, 6]. We reasoned that the more repetitions played, the higher the likelihood of detecting implicit memory. However, a significant problem with this approach is that depth of general anaesthesia during surgery is variable and as yet unmeasurable, varying with both the amount of anaesthetic administered and surgical stimulation. It is possible that depth of anaesthesia during isoflurane-oxygen general anaesthesia (where preservation of implicit memory was demonstrated) varies more with surgical stimulation than depth of anaesthesia during nitrous oxide–sufentanil general anaesthesia (where preservation of implicit memory was not demonstrated).

To overcome this problem, first we used sedation, rather than general anaesthesia, so that we could measure depth by patient response. Second, we provided the patient with only one reading of the critical word pair list at exactly the same point in the procedure for each patient. These steps minimized the effect of varying anaesthetic depths, but neither solves the experimental problem. The solution, of course, is to develop a method of measuring depth of anaesthesia.

Our concerns about repetition enabling us to detect implicit memory are diminished by recent findings showing that repetition and duration of exposure to the stimulus seem to affect explicit but not implicit memory [17, 18]. Our results indicate that a single exposure is sufficient to alter post-operative behaviour. In addition, behaviour is altered in the absence of memory for the source of the suggested alteration in behaviour.

This is the first study of implicit memory that has

found significant associations between the way in which patients respond to a drug and the degree of implicit memory. The responses noted, however, seem paradoxical. As shown in figure 3, those patients who later demonstrated implicit memory at the end of the procedure showed increased sensitivity to the initial bolus of propofol at the beginning of the procedure. Ptosis was more evident, and heart rate, oxygen saturation and number of finger taps in 10 s were more depressed by propofol in those patients who exhibited priming. Thus those patients who appeared to be more sedated after the initial bolus of propofol exhibited more implicit memory. There were no differences noted at the last skin stitch when the word pair tapes were played. This observation indicates that patient variability in response to sedation may also play a role in the variability of demonstrated implicit memory. In this case, a more sensitive CNS response to the initial dose of propofol was associated with subsequently increased implicit memory at a later time in the procedure.

Serum concentrations of propofol and dose–response examinations of the effect of different rates of propofol infusion on memory were not performed and EEG was not measured in this study. Our aim was to test for the presence of explicit and implicit memory in patients undergoing surgical procedures and sedation with propofol. Dose–response pharmacodynamic studies of implicit memory in a clinical situation are difficult. Under-sedating and over-sedating patients for a surgical procedure carry unwanted risks and repercussions.

EEG is neither a consistent nor precise measure of depth of anaesthesia. The EEG effects of propofol have been measured with a similar sedation programme by Veselis and colleagues [19]. EEG changes with increased power in the beta and delta frequency ranges were associated with propofol serum concentrations of 0.86 (0.04) $\mu g\ ml^{-1}$. A verbal learning task (Rey auditory–verbal learning task) administered before, during and after infusion demonstrated a marked reduction in short-term memory capacity and dramatically impaired free recall and recognition during infusion. This agrees with our results of inhibition of free recall, cued recall and recognition during infusion of propofol.

Chortkoff, Bennett and Eger observed significant implicit memory at 0.15 minimum alveolar concentration (MAC) of isoflurane in 10 volunteers [7]. At 0.28 MAC, statistical variance in response was greater than at 0.15 MAC, and with 10 observations, the power to detect a difference (if one existed) was compromised. This study and an earlier one by the same group [8] attempted to describe the pharmacodynamics of implicit memory by examining the degree of impairment as a function of drug dose. They found complete suppression of learning (both implicit and explicit) at less than 0.45 MAC of isoflurane in healthy volunteers not undergoing surgery. However, implicit memory may not be "well-behaved" pharmacodynamically because of the number of factors which may contribute to its existence. These include the physiological and psychological state of the patient, timing and degree of surgical stress, and timing and degree of sedation provided by the anaesthetist. Our study revealed no association between the dose of propofol administered and priming evidence of implicit memory.

There is some evidence that the degree of stress may play a role in the preservation of information. Exogenous catecholamines improve learning in anaesthetized rats [20]. Propofol-induced amnesia is impeded by amphetamine administration in mice [21]. Also several studies demonstrating learning during anaesthesia have used nitrous oxide [22–25], which has sympathetic stimulating properties. Our previous study with nitrous oxide also used a large dose of opioid which blunts the stress response. In contrast, our study with isoflurane–oxygen without nitrous oxide was probably a more stressful anaesthetic, because no opioids were given.

Why should propofol spare implicit memory in the absence of explicit memory? In common with the benzodiazepines, propofol interferes with normal hippocampal functioning [26]. Damage to hippocampal structures produces a profound anterograde amnesia affecting explicit memory, while leaving implicit memory intact [27]. Recent neuropsychological studies have provided evidence for a perceptual memory system which stores information about the form and structure, but not the meaning and function, of perceptual objects [28, 29]. Hippocampal damage apparently leaves this system intact, permitting priming to occur in the absence of explicit memory. However, not all forms of implicit memory may be spared equally. For example, the literature on implicit memory distinguishes between repetition priming, which can be mediated by a perceptual representation system, and semantic priming, which requires that the meaning and the structure of the stimulus be analysed.

Repetition priming appears to be preserved during sedation for surgery (and, we believe, in certain cases of general anaesthesia for surgery also), but this sparing may not be extended to semantic priming, and other forms of implicit memory. Future studies of implicit memory during both general anaesthesia and sedation should use multiple measures of implicit memory, whose underlying cognitive mechanisms are known.

In theoretical terms, it is possible that propofol, in common with the benzodiazepines, may be used to create a pharmacological model for the study of the role of the hippocampus and other brain structures on memory [10]. But the sparing of implicit memory also has practical implications. Because propofol spares implicit memory, it is possible that surgical patients receiving sedation may be affected after operation by surgical events (such as untoward remarks made by medical personnel), even though they have no conscious recollection of these remarks. Anaesthetists and surgeons should not rely on sedation with propofol to abolish all traces of memory.

References

1. Schacter DL. Implicit memory: history and current status. *Journal of Experimental Psychology* (*Learning, Memory and Cognition*) 1987; **13**: 501–518.
2. Kihlstrom JF, Schacter DL. Anaesthesia, amnesia, and the

cognitive unconscious. In: Bonke B, Fitch W, Millar K, eds. *Memory and Awareness in Anaesthesia*. Amsterdam: Lisse, Swets & Zeitlinger, 1990; 21–44.
3. Kihlstrom JF. Implicit memory function during anesthesia. In: Sebel PS, Bonke B, Winograd E, eds. *Memory and Awareness in Anesthesia*. Englewood Cliffs: Prentice Hall, 1993; 10–30.
4. Ghoneim MM, Block RI. Learning and consciousness during general anesthesia. *Anesthesiology* 1992; **76**: 279–305.
5. Kihlstrom JF, Schacter DL, Cork RC, Hurt CA, Behr SE. Implicit and explicit memory following surgical anesthesia. *Psychological Science* 1990; **1**: 303–306.
6. Cork RC, Kihlstrom JF, Schacter DL. Absence of explicit or implicit memory in patients anesthetized with sufentanil/nitrous oxide. *Anesthesiology* 1992; **76**: 892–898.
7. Chortkoff B, Bennett H, Eger E. Subanesthetic concentrations of isoflurane suppress learning as defined by the category-example task. *Anesthesiology* 1993; **79**: 16–22.
8. Dwyer R, Bennett H, Eger E, Heilbron D. Effects of isoflurane and nitrous oxide in subanesthetic concentrations on memory and responsiveness in volunteers. *Anesthesiology* 1992; **77**: 888–898.
9. Ghoneim MM, Mewaldt SP. Benzodiazepines and human memory: a review. *Anesthesiology* 1990; **72**: 926–938.
10. Polster MR. Drug-induced amnesia: Implications for cognitive neuropsychological investigations of memory. *Psychological Bulletin* 1993; **114**: 477–493.
11. Bethune DW, Ghosh S, Gray B, Kerr L, Walker IA, Doolan LA, Sharples LD. Learning during general anaesthesia: Implicit recall after methohexitone or propofol infusion. *British Journal of Anaesthesia* 1992; **69**: 197–199.
12. Polster MR, McCarthy RA, O'Sullivan G, Gray PA, Park GR. Midazolam-induced amnesia: Implications for the implicit/explicit memory distinction. *Brain and Cognition* 1993; **22**: 244–265.
13. Polster MR, Gray PA, O'Sullivan G, McCarthy RA, Park GR. Comparison of the sedative and amnesic effects of midazolam and propofol. *British Journal of Anaesthesia* 1993; **70**: 612–616.
14. Wilson E, Mackenzie N, Grant IS. A comparison of propofol and midazolam by infusion to provide sedation in patients who receive spinal anaesthesia. *Anaesthesia* 1988; **43** (Suppl): 91–94.
15. Kihlstrom JF. Posthypnotic amnesia for recently learned material: Interactions with "episodic" and "semantic" memory. *Cognitive Psychology* 1980; **12**, 227–251.
16. Osborne GA, Rudkin GE, Jarvis DA, Young IG, Barlow J, Leppard PI. Intraoperative patient-controlled sedation and patient attitude to control. *Anaesthesia* 1994; **49**: 287–292.
17. Challis BH, Sidhu R. Dissociative effect of massed repetition on implicit and explicit measures of memory. *Journal of Experimental Psychology* (*Learning, Memory and Cognition*) 1993; **19**: 115–127.
18. Musen G. Effects of verbal labeling and exposure duration on implicit memory for visual patterns. *Journal of Experimental Psychology* (*Learning, Memory and Cognition*) 1991; **17**: 954–962.
19. Veselis RA, Reinsel RA, Wronski M, Marino P, Tong WP, Bedford RF. EEG and memory effects of low-dose infusions of propofol. *British Journal of Anaesthesia* 1992; **69**: 246–254.
20. Weinberger N, Gold P, Sternberg D. Epinephrine enables Pavlovian fear conditioning under anesthesia. *Science* 1984; **223**: 605–607.
21. Pang R, Quartermain D, Rosman E, Turndorf H. Effect of propofol on memory in mice. *Pharmacology, Biochemistry and Behavior* 1993; **44**: 145–151.
22. Levinson B. States of awareness during general anaesthesia. *British Journal of Anaesthesia* 1965; **37**: 544–546.
23. Bennett H, Davis H. Nonverbal response to intraoperative conversation. *British Journal of Anaesthesia* 1985; **57**: 174–179.
24. Evans C, Richardson P. Improved recovery and reduced post-operative stay after therapeutic suggestions during general anaesthesia. *Lancet* 1988; **2**: 491–493.
25. McLintock T, Aitken H, Downie C, Kenny G. Postoperative analgesic requirements in patients exposed to positive intraoperative suggestions. *British Medical Journal* 1990; **301**: 788–790.
26. Peduta VA, Concas A, Santoro G, Biggio G, Gessa GL. Biochemical and electrophysiologic evidence that propofol enhances GABAergic transmission in the rat brain. *Anesthesiology* 1991; **75**: 1000–1009.
27. Squire LR, Zola-Morgan S. The medial temporal lobe memory system. *Science* 1991; **253**: 1380–1386.
28. Schacter DL. Perceptual representation systems and implicit memory: Toward a resolution of the multiple memory systems debate. In: Diamond A, ed. The Development and Neural Bases of Higher Cognitive Functions. *Annals of the New York Academy of Sciences* 1990; **608**: 543–571.
29. Tulving E, Schacter DL. Priming and human memory systems. *Science* 1990; **247**: 301–306.