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No Evidence of Memory Function during Anesthesia with Propofol or Isoflurane with Close Control of Hypnotic State

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Background: **The authors previously demonstrated memory function during apparently adequate general anesthesia in trauma patients. Hypnotic state fluctuations, stress, and variable amnesic qualities of commonly used anesthetics could account for this effect.**

Methods: **The authors replicated the trauma investigation in 90 elective surgical patients to enable anesthetic titration to a bispectral index value of 50–55 during auditory presentation of word stimuli. Patients were randomly assigned to maintenance with propofol (n = 48) or isoflurane (n = 42). Before surgery, state anxiety and trait anxiety were assessed using self-report measures. Postoperative memory assessment relied on the process dissociation procedure using a word stem completion task.**

Results: **There were no differences between groups for relevant demographic, preoperative, or supplemental drug variables. Ninety-eight percent of words were presented within a bispectral index range of 40–60, with values averaging 48.8 (SD = 5.7) during word presentation. Neither the process dissociation procedure nor standard measures of conscious recall and recognition memory showed evidence of explicit or implicit memory. Preoperative stress levels did not correlate with postoperative memory test scores in either study group.**

Conclusions: **In contrast to the results of their previous study, the authors found no evidence of memory function with close control of hypnotic state. This suggests that hypnotic state fluctuations are important to memory activation under anesthesia. Other variables may contribute to preserved memory function as well. Propofol and isoflurane block memory equally well during adequate anesthesia.**

WE have previously described memory function in trauma patients at varying levels of anesthesia (as determined by bispectral index, BIS).[1] To determine memory function, we used a word stem completion task and process-dissociation procedure.[2,3] Over the range BIS 96–40, a steady decline in implicit (unconscious) memory function with increasing depth of hypnosis was observed. We were surprised to find preserved implicit memory function at a level of anesthesia generally considered adequate for surgery, BIS in the range 40–60.[4] At BIS values of less than 40, no evidence of memory was found.[1]

Other studies have failed to confirm evidence of memory function in the BIS range of 40–60.[5–7] All used different memory tasks (free association, category generation, and preference ratings) and included elective surgical patients. In addition, propofol was used to maintain anesthesia, as opposed to isoflurane in the trauma study. Furthermore, two of three negative studies guided anesthesia to a BIS between 40 and 60.[6,7]

To explain residual memory function during BIS 40–60 as observed in the trauma study, we hypothesized that fluctuations in hypnotic state, in particular too light anesthesia (BIS >60), affects memory formation. Such fluctuations occurred naturally in the trauma sample. We also speculated that propofol is a potentially more amnesic drug than isoflurane based on the studies mentioned above and one in which recall curves suggested a higher probability of memory at BIS <60 when isoflurane was used.[8] Third, differences in study group, in particular the stress level associated with trauma *versus* elective surgery, may explain variation in memory formation. Stress creates a neuromodulatory influence regulating consolidation of several forms of memory.[9–11] Finally, the test procedure used in trauma patients could be more sensitive to memory effects.

In the current study, therefore, we replicated the trauma study,[1] using the same memory task, with two important modifications: close control of hypnotic state to BIS 50–55 and maintenance of anesthesia with either propofol or isoflurane. To assess a possible effect of stress on memory function during anesthesia, we measured preoperative anxiety and stress levels in each individual patient.

Materials and Methods

After institutional review, 106 consenting male patients, American Society of Anesthesiologists physical status I or II, scheduled for elective (ambulatory) surgery were enrolled. All patients were fluent in English and reported intact hearing. We excluded 16 patients because of anesthetic (drug) protocol violations (n = 8), because critical stimuli could not be presented during anesthesia (n = 4), or because patients had left the hospital before they were tested (n = 4), resulting in 90 evaluable patients. Study group size was chosen to approximate the same number of patients (n = 96) as in our previous study.[1] For replication purposes we studied

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only males, who constituted the majority (85%) of our previous sample. Elective patients rather than trauma patients were included to allow close control of hypnotic state in all patients. Stress levels were assessed preoperatively using various measures.

Stress Assessment

On the day of surgery, while waiting to be taken to the operating room, patients filled out the Spielberger State-Trait Anxiety Inventory[12] and the Horowitz Impact of Event Scale (IES).[13] The Spielberger State-Trait Anxiety Inventory is a self-report measure assessing state and trait anxiety. The State scale consists of 20 statements about how respondents feel right now; the Trait scale contains an equal number of items evaluating how people generally feel. Each statement is accompanied by a four-point rating scale ranging from "not at all" to "very much" (State items) or "almost never" to "almost always" (Trait items). A weighted score of 1 to 4 for each item results in a sum (scale) score ranging from 20 to 80, indicating increasing levels of anxiety. In accordance with the development of the instrument and normative data, patients first completed the State questionnaire and then the Trait questionnaire.

The IES is a measure of subjective stress experienced as the result of a specific life event. It is broadly applicable to any life event; in our study the event was "having surgery under general anesthesia." Psychological responses to stressful events tend to carry two qualities that the IES aims to assess.[13] Intrusion is characterized by unbidden thoughts or images, troubled dreams, strong waves of feelings, and repetitive behaviors. Avoidance pertains to denial of the event's meaning and its consequences, blunted sensation, behavioral inhibition, and emotional numbness. The IES describes 15 emotional reactions (seven intrusion, eight avoidance) for which respondents indicate how frequently they experienced each during the past week, using a four-point scale ranging from "not at all" to "often." Weighted item scores of 0, 1, 3, or 5 add to a sum score of 0 to 35 (intrusion) or 0 to 40 (avoidance). The IES was constructed and validated using various clinical and nonclinical samples.[13,14]

Anesthetic Protocol

Patients arrived unpremedicated in the operating room where they were randomly assigned to one of two treatment groups: maintenance of anesthesia with propofol (propofol group, n = 48) or isoflurane (isoflurane group, n = 42). In both groups, after lidocaine (1 mg/kg) administration, anesthesia was induced with fentanyl (2 μg/kg) and propofol (2 mg/kg). Succinylcholine (1.5 mg/kg) was used to facilitate intubation after which neuromuscular blockade was maintained at the discretion of the anesthesiologist, using vecuronium as needed to maintain a train-of-four at 1:4. The lungs were ventilated with nitrous oxide in oxygen (F_{IO_2} = 0.4). Anesthesia was maintained with propofol or isoflurane according to group assignment. In both groups, the anesthetics were titrated as close to BIS 50–55 (mean BIS during word presentation in the trauma study had been 54). Additional fentanyl (50–100 μg) was administered if heart rate or blood pressure changed as described previously.[15] Throughout cases, the following parameters were automatically recorded to a laptop: mean arterial blood pressure and heart rate every 5 min, BIS (v. 3.4) every 5 s.

BIS Measurement

Electrical brain activity was measured using an A1050 monitor (Aspect Medical Systems Inc., Newton, MA) with a two-referential montage. After proper cleansing of the skin, four self-prepping electrodes (Zipprep; Aspect Medical Systems, Inc.) were attached to the following sites: channels 1 and 2 to the left and right outer malar bone (At1; At2), a referential electrode high on the forehead (Fpz), and a ground electrode approximately 2 cm to the right of the reference electrode (Fp2). Electrode impedance was maintained at less than 5 kΩ during data acquisition.

Memory Test

We used the same memory paradigm as in our previous studies consisting of a word stem completion test with 32 common five-letter English words dispersed over four lists as study material.[1,16] Words were equally likely to be used for stem completion without previous word presentation (*i.e.*, homogenous base rates or chance performance).[1,16] As in our previous studies, we presented patients with two of the lists during anesthesia (16 targets) and incorporated all 32 words in the postoperative test, thus including the two lists not presented during anesthesia (16 distractors). Observers were blinded to list assignment and the nature of word presentation during anesthesia. Once hypnotic state approximated BIS 50–55, words were played to patients *via* closed headphones connected to a Macintosh PowerBook G3 (Apple, Cupertino CA). A computer program generated a different random target sequence for each patient and played each target 30 times consecutively with a 2-s delay between repetitions. Because data were logged automatically, target word presentation could be associated with corresponding BIS values and hemodynamic parameters.

As soon as patients were sufficiently responsive after surgery, memory was tested. A short structured interview assessed recall of perianesthetic events,[17] after which a word stem completion (WS) test was administered. To separate implicit (unconscious) from explicit (conscious) uses of memory, we administered the WS test in combination with the process-dissociation procedure as described previously[1,16] and elsewhere.[2,3,18,19]

In short, the process-dissociation procedure entails testing of memory under two similar conditions that differ in one respect: participants are instructed to either use previously presented words for stem completion (inclusion test part) or such words are not to be used (exclusion test part). If recall fails, the first word coming to mind may be used in both parts. The process-dissociation procedure enables investigators to evaluate, within a single test, the extent to which conscious and unconscious perceptual processes contributed to the observed memory effect.

The WS test inclusion and exclusion parts included 16 word stems each, of which eight corresponded to a list presented during anesthesia whereas eight others (randomly mixed) did not. Counterbalancing of lists assured that all study words appeared equally often as a target and distractor in both test parts. Stems were presented aurally (twice) and visually on the computer screen (until response was entered) using the same laptop and headphones as during anesthesia. As a measure of cued recall, patients were asked, and reminded twice during test, to report words they recalled hearing during anesthesia. In contrast to our previous studies[1,16] we also assessed recognition memory by showing patients a list of all 32 study words and asking them to select those 16 presented under anesthesia.

Statistical Analysis

Data analysis focused on observed hit frequencies in the two conditions of the WS test, a "hit" being stem completion with a study word. Analysis of variance was used to determine whether reliable differences were established between hit rates for targets and distractors in either test condition (within-subjects factor) or treatment group (between-subjects factor). If so, this was considered evidence of memory. Implicit (unconscious) memory function would be evident from target hit rates higher than base rate in both parts of the WS test. Explicit (conscious) memory function, by contrast, is evident from target hit rates less than the base rate in the exclusion test part. We then calculated correlations between hit scores for targets in the inclusion test condition and preoperative stress scores to see if variation in stress could account for differences in test scores. Target inclusion hit scores can be considered a measure of general memory performance as they indiscriminately reflect both implicit and explicit uses of memory.[1,19] Data are reported as mean ± SD; $P < 0.05$ was considered significant.

Results

Demographic data are shown in table 1. Preoperative measures (table 2) indicated that patients in both the propofol and the isoflurane groups experienced mild stress anticipating their surgery under general anesthesia, which is consistent with moderate state-anxiety scores. Compared with normative IES data, our patients showed more stress than male medical students before a first confrontation with cadaver dissection but were markedly less stressed than male adults suffering from stress syndromes resulting from bereavement or personal injury.[13] For state and trait anxiety, our sample scored slightly below average (46th to 48th percentile) compared with normative data from general medical/surgical patients and slightly above average (55th percentile) compared with normal male adults of 19 to 39 yr of age.[12] Taken together, these data suggest that patients experienced appropriate, nonpathological levels of anxiety and stress before surgery.

Table 1. Demographic Data

	All (N = 90)	Propofol (n = 48)	Isoflurane (n = 42)
Age (yr)	35 ± 10	36 ± 10	33 ± 9
Weight (kg)	84 ± 15	84 ± 15	84 ± 16
Height (cm)	179 ± 8	178 ± 7	180 ± 8
ASA status I/II (n)	23/67	12/36	11/31
Orthopedic/General (n)	62/28	29/19	32/10

Data are displayed as mean ± SD or observed frequency. Patients underwent orthopedic surgery or general surgery. There were no significant differences between groups.

ASA = American Society of Anesthesiologists.

To determine whether preoperative data displayed sufficient variation, we calculated the median score for each measure and contrasted high performers (top 50%) with low (bottom 50%) performers. Analysis of variance of IES (intrusion, avoidance) and Spielberger State-Trait Anxiety Inventory (state, trait) data yielded four significant main effects of high/low performance, demonstrating that scores on all measures varied substantially. No interactions with study group or main effects of study group were found, indicating that patients in both the propofol and isoflurane groups displayed variation although their average scores did not differ significantly. Groups were thus comparable in terms of stress and anxiety before surgery.

Anesthetic data for the two groups (table 3) showed no significant differences in supplemental drugs administered or duration of surgery and anesthesia. During anesthesia, 1440 words were presented (90 subjects × 16 words). BIS during word presentation was 48.8 ± 5.7 (range, 37.4–69.8) and 98% of words were presented between BIS 40 and 60. Thirteen words were presented at BIS <40 (minimum, 37.4) as opposed to sixteen at BIS >60 (maximum, 69.8). Outliers occurred as frequently in the propofol as isoflurane group and did not alter memory test performance. During word presentation BIS was higher in the isoflurane group (49.5 ± 5.9 *versus* 48.2 ± 5.4) and mean arterial blood pressure increased in the propofol group (90.2 ± 18.2 *versus*

Table 2. Preoperative Stress Measures

	Overall (N = 90)	Propofol (n = 48)	Isoflurane (n = 42)
STAI state-anxiety score	42.0 ± 13.1	41.3 ± 12.7	42.7 ± 13.6
STAI trait-anxiety score	40.2 ± 10.4	38.4 ± 9.1	42.3 ± 11.4
IES intrusion score	12.1 ± 8.5	11.8 ± 8.8	12.5 ± 8.2
IES avoidance score	12.7 ± 8.0	13.0 ± 8.2	12.2 ± 8.0

Data are means ± SD.

STAI = State-Trait Anxiety Inventory[12] assessing self-reported feelings of anxiety in general (trait anxiety) and at the time of filling out the questionnaire (state anxiety). IES = Impact of Event Scale[13,14] assessing self-reported stress experienced as the result of having surgery under general anesthesia.

There were no significant differences between groups.

86.5 ± 19.8 mmHg). Heart rate was comparable in both groups (69.0 ± 13.3 beats/min). Memory was tested on the day of surgery or the next day at an average of 11 ± 11 h (range, 1–28 h).

None of the patients consciously recalled the intraanesthetic period on interview. Presentation of the word stems (cued recall) yielded 14 hits (three propofol, 11 isoflurane) *versus* 71 false alarms (36 propofol, 35 isoflurane). Further prompting of memory (recognition test) yielded an average of 7.7 ± 1.3 targets, which was not different from chance performance (8.00). These observations indicate absence of unprompted and prompted conscious recall for words presented during anesthesia. Table 4 shows the observed hit probabilities for targets and distractors in the postoperative WS test. Neither group was inclined to use or avoid target words at better than chance frequency ($P = 0.88$), supporting the absence of both implicit and explicit memory function in this study. Target-inclusion hit scores correlated insignificantly with IES intrusion (Pearson r = 0.03), IES avoidance (r = 0.1), and state and trait anxiety scores (r = 0.09 and r = 0.04, respectively). No group differences were found.

Discussion

Memory function during anesthesia has been the subject of many investigations.[20,21] Not only did the discovery that patients could form memories of which they were unaware (implicit memory) inspire lines of research, the reason for such findings remained to be elucidated as well. Implicit memory suggested that stimuli were perceived unconsciously but an effect of inadequate anesthesia and concurrent awareness could not be excluded. However, this issue was difficult to test without adequate monitoring of hypnotic state. In 1999, we demonstrated an unconsciously mediated memory effect in trauma patients during apparently adequate anesthesia (BIS between 40 and 60).[1,22] This finding, in the absence of any apparent methodological flaw, was not easily reconciled with the null findings in other relevant studies.[5–7] Our hypothesis for the current study was that hypnotic state fluctuations, which occurred naturally in trauma patients, enhanced memory formation in that sample. We attempted to test this hypothesis by replicating the study using the same memory task while controlling hypnotic state within a narrow range.

Table 3. Anesthetic Variables

	Overall (N = 90)	Propofol (n = 48)	Isoflurane (n = 42)
Duration Surgery (min)	104 ± 59	105 ± 63	102 ± 56
Duration Anesthesia (min)	145 ± 70	144 ± 72	145 ± 67
Fentanyl @ induction (μg/kg)	2.06 ± 0.60	2.12 ± 0.50	1.99 ± 0.69
Propofol @ induction (mg/kg)	2.29 ± 0.49	2.31 ± 0.41	2.27 ± 0.57
Succinylcholine (mg/kg)	1.47 ± 0.32	1.49 ± 0.34	1.46 ± 0.29
Additional Fentanyl (μg/kg)	2.19 ± 1.75	2.23 ± 1.99	2.14 ± 1.45
Vecuronium (mg/kg)	0.11 ± 0.06	0.11 ± 0.06	0.11 ± 0.06

Data are displayed as mean ± SD. No significant differences between groups were found.

Table 4. Observed mean (± SD) hit probabilities in the four test conditions

	Target Inclusion	Distractor Inclusion	Target Exclusion	Distractor Exclusion
Propofol (n = 48)	0.34 ± 0.19	0.32 ± 0.22	0.30 ± 0.15	0.30 ± 0.18
Isoflurane (n = 42)	0.33 ± 0.16	0.32 ± 0.14	0.32 ± 0.20	0.33 ± 0.19
Overall (N = 90)	0.33 ± 0.18	0.32 ± 0.18	0.31 ± 0.18	0.31 ± 0.18

A hit means word stem completion to a study word that was either presented during anesthesia (target hit) or not presented during anesthesia (distractor hit). In the inclusion test part patients tried to complete stems to presented words; in the exclusion part such words had to be avoided. Probabilities are based on n (sample size) × 8 (word stems) observations per test condition. No significant memory effects were observed.

To address alternative explanations, such as an effect of anesthetic agent or stress on intraoperative memory formation, we assigned patients to isoflurane or propofol treatment and measured preoperative anxiety.

It is often thought that some element of consciousness is required for memory to function. Indeed, preserved memory is typically (but not necessarily) observed when some form of wakefulness is present.[18–20] However, most studies that contrasted memory performance in waking subjects with that during various drug concentrations did not address the consciousness issue because hypnotic state was not addressed. More convincing evidence for a crucial role of consciousness comes from studies in which patient responsiveness to verbal command was monitored[18,19,23–28] and, more recently, electroencephalographic correlates of unconsciousness.[6,7,19,28,29] From a clinical perspective, targeting prevention of awareness and memory formation in patients during surgery, it is noteworthy that none of the more sophisticated studies other than the trauma investigation[1] and a more recent study[30] demonstrated evidence of memory function during seemingly adequate hypnosis. Our current null findings support the growing body of evidence that consciousness is important to memory function.

Before turning to a discussion of alternative explanations, we consider the possibility that hypnotic state fluctuations may indeed have contributed to preserved memory function in trauma patients.[1] After all, when hypnotic state was controlled for in the current study, the effect could not be replicated. These findings suggest that avoiding light anesthesia may reduce memory formation, a view that is supported by other investigations in which an effect of hypnotic control was addressed retrospectively[6] and prospectively.[7] The case for obliterated memory function during continuous adequate hypnosis does not necessarily invalidate the evidence of memory function observed in trauma patients[1] and can be reconciled with those findings by postulating a mechanism in which episodes of lightened hypnosis, as evidenced by BIS >60, facilitate perceptual-cognitive processes at subsequent deeper levels of anesthesia. Light hypnosis could prime the central nervous system to temporarily process information when it otherwise, under continuous adequate hypnosis, would not, just as long-term potentiation is a (long-term) facilitation of synaptic transmission after high-frequency electrical stimulation of presynaptic neurons. Although "proactive facilitation" of brain function is highly speculative at this point, we argue that hypnotic control should be a key element of memory studies during anesthesia and should be part of routine clinical practice.

Any conclusions must be considered in the light of an important weakness of the current study, in which a direct comparison of fluctuating *versus* nonfluctuating patients was not made. Instead, we base our conclusions on a retrospective comparison of two similar studies, the current study and trauma.[1] It would have been more elegant to randomly assign patients to a fluctuating or nonfluctuating condition but this is unethical for mere study purposes. The use of volunteers raises other issues, and to replicate the study in trauma patients—comparing fluctuating with nonfluctuating subjects—is not only difficult on all involved but may also yield insufficient power, as nonfluctuating subjects are rare. In this study, therefore, we chose a different surgical population to allow for careful anesthetic titration to BIS 50–55 in all participants. This shift in study sample limits our conclusion regarding obliterated memory function to elective surgical patients and does not preclude the possibility that a particular characteristic of trauma surgery contributed to residual memory function in that sample.[1] One such feature, as we and others have argued,[5,6,30] could be the degree of stress that patients are exposed to. Mental and physiologic stress can create a neuromodulatory influence that regulates consolidation of different forms of memory.[9–11] Using self-report measures, we were unable to demonstrate evidence of stress-enhanced memory in the current study. None of the measures varied systematically with hit scores for words presented under anesthesia, which demonstrates that preoperative differences in stress degrees cannot account for differences in postoperative memory task performance. What this implies for the trauma sample is unclear. In general, our observations are in line with the mixed support for stress-induced memory during anesthesia using self-report measures.[30–32]

Deeprose *et al.*[30] recently addressed an effect of surgical stress on memory function by presenting patients under anesthesia with word series either before surgery started or during surgery. A glimpse of memory was observed only in the latter group, supporting the notion that surgical stimulation enhances memory formation. Of further interest is that propofol was used and BIS values during word presentation remained much less than 60 on average. The findings by this group thereby confirm our evidence of memory function during adequate hypnosis in trauma patients[1] and extend the evidence to propofol-based anesthesia. Surgical stimulation is probably not a necessary and sufficient condition for memory function under anesthesia, however. Memory may be observed in volunteers not undergoing surgery and many studies during surgery, including the current study, have yielded null effects. Although surgery ostensibly represents a stressor, the relation with actual stress hormones is unclear. To test the neuromodulatory influence of stress, therefore, it would be fruitful to focus on physiologic stress parameters in different surgical groups or select stress cohorts.

We also hypothesized at the outset of this study that the amnesic properties of isoflurane and propofol differ and thereby explain discrepancies in memory findings at equisedative degrees of anesthesia. Isoflurane and propofol have both been studied extensively for their amnesic effect but seldom in the same study. In comparison with intravenous agents like thiopental and fentanyl, propofol has a marked capacity to impair memory function.[33] Further support for this notion comes from Glass *et al.*,[8] who compared the amnesic properties of propofol, midazolam and isoflurane at equisedative degrees of anesthesia as measured by BIS. Although the authors reported no statistically significant differences between agents, the relatively flat appearance of the recall-sedation curve in volunteers breathing isoflurane drew our attention. In comparison with a steep propofol curve, it indicated a potentially higher probability of memory function during BIS 40–60. Glass *et al.*[8] noted, on the other hand, that an outlier event could account for the visual discrepancy. Our current null findings support their contention that the likelihood of memory function during adequate degrees of hypnosis as measured by BIS does not differ between propofol and isoflurane.

In summary, we conclude from our failure to demonstrate memory under tight hypnotic control that hypnotic state fluctuations, in particular instances of too light anesthesia, are important to memory function under anesthesia. Our observations do not preclude the possibility that particular surgical characteristics other than hypnotic state fluctuations contribute to residual memory function during seemingly adequate degrees of hypnosis.

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