IMPLICIT AND EXPLICIT MEMORY WITH ISOFLURANE COMPARED TO SUFENTANIL/NITROUS OXIDE

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INTRODUCTION

By definition, patients receiving adequate general anesthesia fail to remember the events and experiences that transpired during surgery. At the same time, numerous anecdotal accounts, and some experimental data, suggest that surgical events might be processed to some degree by such patients, and influence them in various ways, even though they are not consciously remembered. The suggestion has garnered additional strength from neuropsychological studies of amnesic patients: although they cannot recall or recognize words from a previously studied list, they are nevertheless more likely than would be expected by chance to complete appropriate word stems and fragments with list items. These sorts of priming effects motivate a distinction between two forms of memory, explicit and implicit.[1] Explicit memory entails conscious recollection of some event; implicit memory refers to any change in the subject's experience, thought, and action that is attributable to such an event. Research shows that explicit and implicit memory are dissociable in at least two senses: explicit memory can be impaired but implicit memory spared, as in the amnesic syndrome and other disruptions of memory, such as posthypnotic amnesia; and experimental variables such as encoding activity or modality shifts have different effects on explicit and implicit memory. Accordingly, we have sought to determine whether general anesthesia also dissociates explicit and implicit memory. An early study, by Eich and his colleagues, answered in the negative.[2] But a number of subsequent studies did find some evidence of spared implicit memory.[3,4] This paper compares the results of two experiments involving, respectively, isoflurane and nitrous/sufentanil anesthesia. Because of our concern that the amnesic effects of anesthesia not be confounded with those of sedation, none of the patients received benzodiazepine premedication. Aside from the anesthetic technique, we attempted to keep the methods of the two experiments identical.

METHOD AND RESULTS

Experiment 1: Isoflurane

Our first experiment[3] involved 30 surgical patients who consented to participate in the study. We prepared two lists of paired associates, each consisting of 15 stimulus terms and the most frequent response given to them, as indicated by standard word-association norms. For each patient, one list served as the targets, the other as controls. A number of repetitions of each list were recorded in an unfamiliar voice on auto-reverse cassette players. Anesthesia was induced with sodium thiopental, accompanied by vecuronium, and was maintained with isoflurane. Neither nitrous oxide nor benzodiazepines were administered during surgery. The tape was played through earphones from the first incision to the last stitch, at which time the patients received intravenous morphine sulphate for postoperative pain control. Memory testing was conducted in the recovery room, and again two weeks later, by assistants who, like the anesthesiologist, did not know which tape had been played to the patient. On the initial free recall test, the patients were reminded that they had been played some words during surgery, and were asked what they were. There followed tests of cued recall and free association, administered in counterbalanced order. For cued recall, the patients were given the stimulus terms from both lists, and were asked to recall the items associated with them on the tape-recorded list; for free association, they were read the stimuli, and asked to give the first word that came to mind. Testing concluded with a recognition test, in which the patient was read the word pairs, and asked which had appeared on the tape. Testing was completed for 25 of the 30 patients.

None of the 25 patients had any free recall of the paired associates, or any other intraoperative event. The left panel of Figure 1 shows the results of cued-recall testing (the right panel shows the corresponding results of Experiment 2, discussed below). The filled bars show the percentage of targets produced from the critical list, presented during surgery; the hatched bars show the comparable percentage from the neutral list, which served as a control. A repeated-measures ANOVA showed no difference between critical and neutral lists, on either immediate or delayed testing.

As Figure 2 indicates, the same results were obtained with the recognition test. In other words, the patients showed no explicit memory for the paired associates presented during surgery.

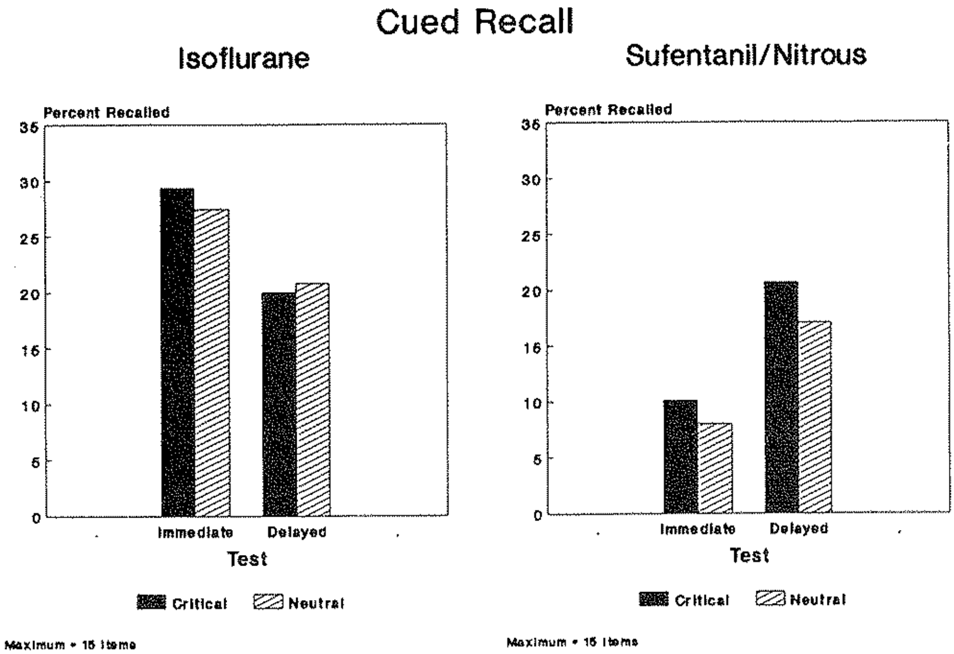
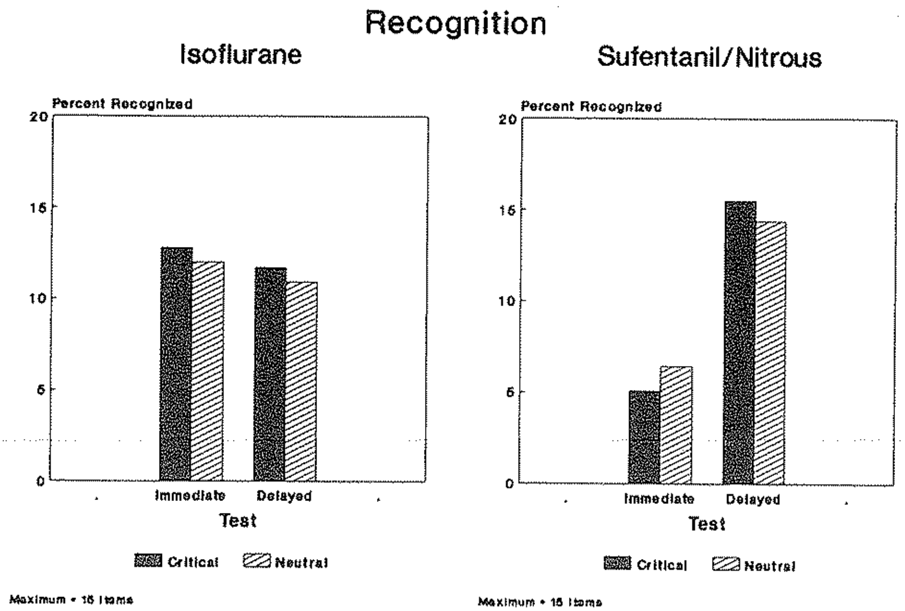
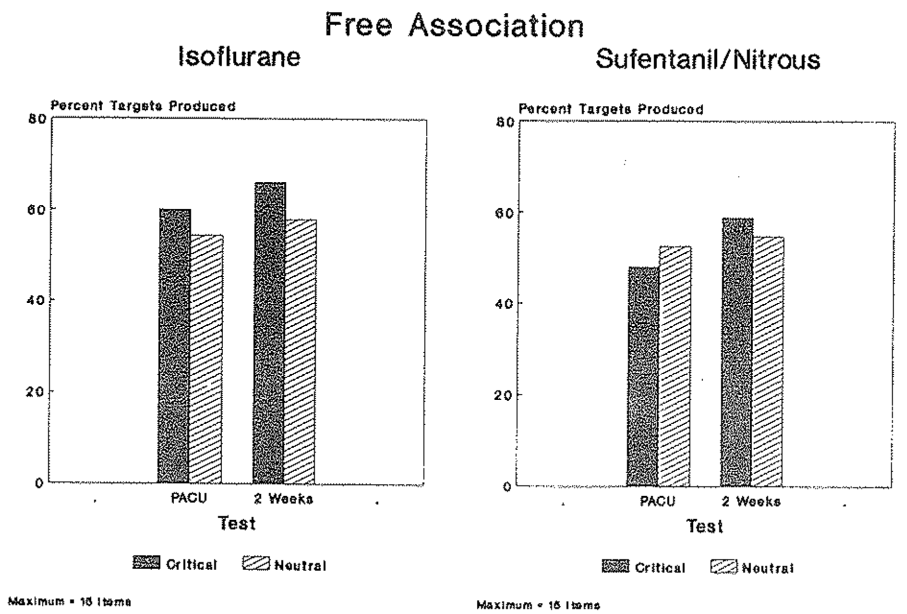


Fig.1

Rather different results were obtained on the free-association test of implicit memory. As Figure 3 shows, and ANOVA confirmed, the patients were significantly more likely to produce target items from the critical list, presented during surgery, than they were from the control list -- in other words, they showed a significant priming effect. A similar level of priming was observed on the delayed test, although this might have been a test-priming effect -- that is, an effect of the immediate test, rather than of the surgical presentation itself.

We should note that there was an order effect on priming: greater priming was observed when the free-association test preceded the cued-recall test, rather than the reverse. Considering only those patients who completed the implicit test before the explicit one, 84.6% showed evidence of priming; in the other condition, only 50% did so. The magnitude of priming was unrelated to anesthetic and surgical variables measured in this experiment.


Recognition
Isoflurane
Sufentanil/Nitrous
Percent Recognized
20
15
10
5
0
Immediate
Delayed
Test
Critical
Neutral
Maximum = 15 Items


Free Association
Isoflurane
Sufentanil/Nitrous
Percent Targets Produced
80
60
40
20
0
PACU
2 Weeks
Test
Critical
Neutral
Maximum = 15 Items

Figs 2 and 3

Experiment 2: Sufentanil/Nitrous Oxide

Our second experiment was a conceptual replication of the first, except for a change in anesthetic agents.[4] For a total of 30 patients, anesthesia was induced by sodium thiopental, with vecuronium, and maintained by sufentanil and nitrous oxide in oxygen; again, no benzodiazepines were administered before or during surgery. Testing could not be completed for eight patients, and another three showed some degree of explicit memory for the word list; eliminating these individuals reduced the final sample to 25 subjects who showed no free recall for the wordlist presented during surgery.

The fact that the procedures for testing memory in the two experiments were identical permits a direct comparison of their results by means of a mixed-design ANOVA with anesthetic agent, isoflurane or sufentanil, added as a grouping variable. In the within-subjects ANOVAs described for first experiment, the principal evidence for post-surgical memory was a main effect of targets, obtained for the implicit test of free association, but not the explicit tests of cued recall or recognition. Accordingly, differences between the two experiments are indicated by an interaction involving agent and targets. In overall 2x2x3x2 mixed-design ANOVA, with one between-groups factor (agent) and three within-subjects factors (targets, measures, and delay), the critical agent x measure x targets interaction was significant, $F(2,96 = 4.03$, $MSE = 0.028$, $p < 0.05$. This indicates that the outcomes of the two experiments differed with respect to some, but not all, of the measures of memory. This interaction was explored in three follow-up 2x2x2 mixed-design ANOVAs, with one between-groups factor (agent) and two within-subjects factors (targets and delay), each performed on a different measure of memory.

The right panel of Figure 1 shows the results for cued recall: there was no difference between critical and neutral lists. ANOVA showed no interaction of agent by targets, $F(1,48) = 1.26$, n.s. Figure 2 shows the results for recognition. Again, the interaction was nonsignificant, $F < 1$. In other words, there was no difference between the two experiments with respect to either cued recall or recognition measures of explicit memory. Figure 3 shows the results of the free-association test. This time, the critical interaction was statistically significant, $F(1,48) = 4.91$, $MSE = 0.062$, $p < 0.05$. A significant priming effect was observed under isoflurane, but not under sufentanil/nitrous oxide. There was no order effect on priming in the nitrous/narcotic experiment; nor was priming correlated with any anesthetic or surgical variables.

DISCUSSION

To summarize, our experiments have demonstrated a dissociation between explicit and implicit memory with isoflurane anesthesia, but not with sufentanil/nitrous oxide. In the isoflurane study, patients who could neither recall nor recognize paired-associates presented during their surgery nevertheless showed an enhanced tendency to respond to the cue term with the target with which it had been associated on the stimulus tape. By contrast, sufentanil/nitrous oxide impaired free association as well as cued recall and recognition.

Taken together, these findings suggest a resolution to the current situation, in which some studies give evidence for implicit memory following surgical anesthesia, while others do not. That is, those studies yielding negative results may have used anesthetic agents that abolish both explicit and implicit memory; or, alternatively, the use of variable anesthetic regimes may have created a situation where the negative effects of one technique swamped the positive effects of another. On the other hand, some investigators have found evidence of implicit memory with both volatile and narcotic regimes.[5] Still, it seems wise to standardize anesthetic techniques (including the use of benzodiazepine premedication[6]) until implicit memory has been brought under tighter experimental control.

It is possible that the differing results of these two studies are an artifact of anesthetic depth. Although all patients in the experiment were adequately anesthetized by all clinical criteria, it is difficult if not impossible to insure that the 'depth' of anesthesia was the same for the nitrous/narcotic technique as it was for the inhalant. Thus, it is possible that sufentanil/nitrous oxide anesthesia abolished implicit as well as explicit memory because it was in some sense 'deeper'.

On the other hand, the different outcomes may be of theoretical interest. Anesthetic effects on explicit and implicit memory are interesting for the light they can shed on basic brain-behavior relations -- providing an alternative to brain-injured patients for neuropsychological investigation. If, for example, the receptor sites differ from one anesthetic agent to another, and the effects on explicit and implicit memory differ as well, the resulting pattern will shed light on the biological substrates of memory and consciousness.

AUTHOR NOTES

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