Olsen KL (1993): Sex and the mutant mouse: Strategies for understanding the sexual differentiation of the brain. In: *NATO Advanced Research Workshop: The Development of Sex Differences and Similarities in Behaviour*, Haug M, Whalen R, Aron C, Olsen KL, eds. London: Kluwer Academic Publishers, pp. 255–278

Symposium on Brain and Steroids (1994): *Hormones and Behavior* 28(4) (Special Issue):303–558

Webb P, Lopez GN, Uht RM, Kushner PJ (1995): Tamoxifen activation of the estrogen receptor/AP-1 pathway: Potential origin for the cell-specific estrogenlike effects of antiestrogens. *Mol Endocrinol* 9:443–456

See also Gonadotropins; Sexual behavior, brain control; Sexual differentiation; Steroid hormone effects on the brain; Sex differences in human brain and behavior

Anesthesia, effects on cognitive functions

John F. Kihlstrom, Lawrence J. Couture, Daniel L. Schacter and Randall C. Cork

Surgical anesthesia is intended to render the patient insensitive to pain. In a typical clinical procedure, known as balanced anesthesia, the patient is premedicated with a sedative intended to relieve pre-operative anxiety and facilitate the induction of anesthesia itself (often this is a benzodiazepine such as diazepam or midazolam; otherwise, a barbiturate such as thiopental or nonbenzodiazepine such as propofol may perform this function). Sedation is followed by the induction of general anesthesia by intravenous injection of a sedative, narcotic (e.g., morphine, fentanyl, alfentanyl), or ketamine. In addition, a nondepolarizing curare-like derivative (e.g., vecuronium, d-turbocurarine) or a depolarizing drug (e.g., succinylcholine) is administered to induce muscle paralysis. After intubation and connection to a ventilator for artificial respiration, general anesthesia may be maintained by a mixture of oxygen and nitrous oxide, volatile agent (e.g., halothane, enflurane, or isoflurane) or intravenous drug. At the conclusion of the surgery, muscle relaxation is reversed (e.g., by neostigmine or other anticholinesterase), and normal (unassisted) breathing is restored. In addition, the patient may be given an analgesic agent (e.g., morphine) to manage any acute pain experienced postoperatively.

General anesthesia operates directly on the central nervous system, producing (at least in theory) a temporary inhibition on synaptic transmission that results in a general loss of consciousness that affects sensory awareness in all modalities and at all body loci. This "controlled coma" is indicated by: (1) the lack of motor response to instructions; (2) suppression of autonomic and skeletal responses to intraoperative stimuli such as incisions; (3) absence of retrospective awareness of pain; and (4) postoperative amnesia for surgical events such as conversations among the medical team. Thus, by definition, adequately anesthetized patients rarely show any conscious recall or recognition of surgery. Nevertheless, there is some evidence that surgical events may be processed to some degree even by adequately anesthetized patients, resulting in the encoding of memory traces of experience that can affect postsurgical experience, thought, and action.

Prima facie evidence for information-processing during general anesthesia is provided by studies of classical conditioning in animals: conditioned fear responses can be acquired during anesthesia, and displayed after recovery. This evidence is mitigated, however, by the empirical fact that conditioned responses can be established in almost any organism that has a nervous system, including decorticate animals. This primitive form of learning should not be confused with the higher cognitive processes involved in intelligent perception, memory, and thought.

Other evidence indicates that adequately anesthetized patients continue to show event-related potentials (ERPs) to auditory and tactile stimulation. In fact, intact ERPs constitute one way in which the patient's status is monitored during surgery. However, the ERP is very complex: for example, the first 10 ms of the auditory ERP reflect brainstem activity, those arising within 10–100 ms the activity of the primary auditory cortex, and those observed after 100 ms the activity of the cortical association areas. Only the early components of the ERP are clearly unaffected by anesthetic agents (these are the only components routinely monitored during surgery); the later, perceptual-cognitive components exhibit dose-related suppression of activity. To date, there have been few studies of the fate of later components of the cognitive ERP, such as the P300 response to the omission of an expected event, or the N400 response to semantic anomalies.

In the absence of definitive studies of cognitive ERPs, online evidence of complex mental activity comes primarily from studies using the "isolated forearm technique", in which muscle relaxant is prevented from affecting one arm by means of a tourniquet. In some (but not all) cases, the patient retains the ability to make a motor response with the spared limb in accordance with instructions from the anesthetist. Moreover, patients can respond after recovering consciousness to instructions given during anesthesia. In either case, such responses provide evidence that the instructions themselves were heard during surgery. However, adequately anesthetized patients have no conscious recollection of having been given these instructions.

Evidence of information processing *during* anesthesia is often sought in signs of memory *afterwards*. Of course, a failure to remember surgical events is part and parcel of the definition of adequate anesthesia. However, recent studies of both brain-damaged patients and intact subjects support a distinction between explicit memory, which requires the conscious recollection of a previous episode; and implicit memory, as revealed by a change in task performance that is attributable to such an event. Explicit and implicit memory are dissociable. For example, amnesic patients typically fail to recall or recognize the items studied in a list of words; however, they generally show priming effects attributable to the study episode when they are asked to identify words presented under degraded conditions, or to words as completions of stems or fragments. By definition, adequate general anesthesia abolishes explicit memory for surgical events; but the possibility remains that some degree of implicit memory may be spared.

Although the evidence is still rather mixed, recent studies employing procedures derived from the laboratory study of normal and pathological memory suggest that a dissociation between explicit and implicit memory may be obtained under certain conditions of adequate anesthesia. For example, patients (maintained on nitrous oxide–oxygen and, in some cases, halothane) who were presented a list of low-frequency words during surgery showed no memory for the list on a post-operative recall test; but when encouraged to guess on a recognition test, showed greater accuracy than control subjects. In another study, anesthetized patients (isoflurane) who were presented with a list of extremely low-frequency words were unable to remember these words following recovery; however, they did rate these items as more familiar than carefully matched control words (this effect was not observed when the anesthetic was switched to fentanyl). Finally, patients (maintained on isoflurane) who were presented paired associates showed no subsequent free recall, cued recall, or recognition of the items; but they were more likely to produce list items on a free-association task, compared to controls. We note, however, that several well-designed studies have failed to find such effects. One important factor determining outcome may be the selection of the anesthetic agent: the positive outcomes described have all been obtained with inhalant anesthetics.

The preservation of information-processing functions during adequate general anesthesia has some potential practical implications. For example, there is some evidence (again, controversial) that at least some patients respond positively to hypnosis-like therapeutic suggestions administered during anesthesia, showing speeded postoperative recovery, diminished requests for pain medication, and the like, although the patients do not remember receiving the suggestion. These psychosomatic effects also count as evidence of information-processing during anesthesia, as well as of implicit memory. Unfortunately, as in hypnosis, the mechanism by which such effects are achieved is presently unknown.

Many surgical procedures are performed under conscious sedation, an alternative anesthetic technique in which the patient receives a barbiturate, benzodiazepine, or nonbenzodiazepine sedative plus a local or regional anesthetic. As its name implies, conscious sedation does not entail a general loss of consciousness on the part of the patient. Nevertheless, the centrally acting drugs do produce a dense amnesia for the surgery and surrounding events. Once again, however, this amnesia tends to dissociate explicit and implicit memory. In a study of midazolam, for example, subjects showed a profound deficit in recognition memory, but intact levels of priming on a test of perceptual identification. And in a study of propofol, patients who studied paired associates during surgery showed poor postoperative cued recall, but intact priming when asked to generate free associations. Thus, the drugs involved in conscious sedation seem to impair explicit memory, while sparing implicit memory.

The distinction between general anesthesia and conscious sedation underscores the fact that "general anesthesia" is not a single, monolithic construct. It seems likely that the various types of anesthetics in current use have different psychological effects as well. Detailed study of the cognitive effects of the various classes of anesthetic agents, coupled with a more detailed psychopharmacological theory of anesthetic effects, may yield important insights into the biological substrates of conscious and nonconscious cognitive processes.

Acknowledgements The point of view represented in this article is based on research supported in part by NIMH Grants MH-35856 and MH-45398. We thank Randall C. Cork, Monica W. Furlong, and Martha L. Glisky for their comments during the preparation of this paper.

Further reading

Cork RL, Couture LJ, Kihlstrom JF (1997): Memory and recall. In: *Anesthesia: Biologic Foundations*, Yaksh TL, Lynch C, Zapol WM, Maze M, Biebuyck JF, Saidman LJ, eds. New York: Lippincott-Raven, pp. 451-467

Couture LJ, Edmonds HL (1989): Monitoring responsiveness during anaesthesia. In: *Depth of Anaesthesia. Bailliere's Clinical Anaesthesiology: International Practice and Research, vol. 3, no. 3*, Jones JG, ed. London: Bailliere Tindall, pp. 547–558

Ghoneim MM, Block RI (1992): Learning and consciousness during general anesthesia. *Anesthesiology* 76:279–305

Hindmarch I, Jones JG, Moss E (1987): *Aspects of Recovery From Anaesthesia*. London: Wiley

Kihlstrom JF (1993): Implicit memory function during anesthesia. In: *Memory and Awareness in Anesthesia*, Sebel PS, Bonke B, Winograd E, eds. Englewood Cliffs, NJ: Prentice-Hall, pp. 10–30

Kihlstrom JF, Schacter DL (1990): Anaesthesia, amnesia, and the cognitive unconscious. In: *Awareness and Memory during Anaesthesia*, Bonke B, Fitch W, Millar K, eds. Amsterdam: Swets and Zeitlinger, pp. 21–44

Polster MR (1994): Drug-induced amnesia: Implications for cognitive neuropsychological investigations of memory. *Psychol Bull* 114:477–493

Rosen M, Lunn JN (1987): *Consciousness, Awareness and Pain in General Anaesthesia*. London: Butterworths

Schacter DL (1987): Implicit memory: History and current status. *J Exp Psychol: Learn Mem Cognit* 13:501–518

Schacter DL, Chiu C-Y P, Ochsner DN (1993): Implicit memory: A selective review. *Annu Rev Neurosci* 16:159–182

See also Anesthesia, mechanisms of; Anesthesia, nerve block; Learning and memory

Author's website (JFK) socrates.berkeley.edu/~kihlstrm

Update (April 1998)

Implicit memory for events occurring during general anesthesia remains controversial. However, a recent meta-analysis by Merikle and Daneman (1996) reviewed 44 studies involving 2,517 patients and found clear evidence that repetition priming is relatively spared under such conditions; however, there is little evidence for spared semantic priming. These results do not imply that ostensibly anesthetized patients are in fact aware of surgical events as they occur, but rather that some perceptual processing of the surgical environment goes on outside of awareness. Despite the relative sparing of priming, there was no evidence for the effect of intraoperative suggestions on postoperative recovery. For comprehensive coverage of this debate, see Bonke et al. (1996).

Bonke B, Bovill JG, Moerman N, eds. (1996): *Memory and Awareness in Anaesthesia III*. Assen, The Netherlands: Van Gorcum

Merikle PM, Daneman M (1996): Memory for unconsciously perceived events: Evidence from anesthetized patients. *Consciousness & Cognition* 5:525–541.

REPRINTED FROM

Elsevier's Encyclopedia of Neuroscience

2nd enlarged and revised edition

Edited by
George Adelman
Barry H. Smith

Editorial Manager
Jennifer De Pasquale

Visit the Encyclopedia's website for supplementary information and details regarding the CD-ROM version:

http://www.elsevier.com/locate/encneu