The Problem with Amnesia

THE article published in this issue of ANESTHESIOLOGY by Hayama *et al.*[1] highlights important issues in understanding anesthetic effects on human memory, terminology included. Terms such as "amnesia" seemingly become more ill-defined as more sophisticated models of memory are employed. Prototypically, "amnesia" refers to organic amnesias resulting from some pathologic process or lesion. Amnesia induced by drugs entered the lexicon as Mickey Finn drinks established a presence in film noir, and became more entrenched with the widespread use of benzodiazepines. One person's annoying side effect became another's therapeutic response, and the use of amnesic drugs became widespread in anesthesia for exactly this reason. Propofol, having similar effects on memory as the benzodiazepines, is in many ways an ideal drug to study this peculiar effect on memory.[2,3] There is a crucial need to understand mechanisms underlying this effect, as lack of memory for intraoperative events is one of the key pillars of the triad (or pentad) of anesthesia.

"Terms such as 'amnesia' seemingly become more ill-defined as more sophisticated models of memory are employed."

Anesthetic-induced lack of memory consists of two highly interrelated but separate processes, as illustrated by the cultural references above. These represent the nonspecific sedation common to most centrally depressant drugs, and a specific benzodiazepine-type effect that produces lack of memory for events even when sedation is largely absent.[4] Recently Pryor *et al.* modeled memory impairment induced by various intravenous drugs using a negative power function to separate drug actions on initial memory formation (encoding) from memory loss over time.[3] The question is how to refer to this latter effect, and that is the problem with "amnesia."

Amnesia has been and is used to refer to a multiplicity of effects on memory depending on a particular context, frequently not delineated by the authors in question. It is helpful to conceptualize drug actions within a cogent framework of memory systems. A similar, but less pervasive, fuzziness surrounds "consolidation," those processes necessary to retain a memory over time – with the question being, when does consolidation begin after stimulus perception?

Hayama *et al.* examined the effects of dexmedetomidine on conscious (episodic) memory. Conscious memory starts as working memory, a seconds-long "scratchpad" for incoming information. Successful encoding has occurred once a memory is able to be accessed using processes other than working memory.[5] Because of the complexity of their study, Hayama *et al.* did not document successful encoding *per se*, but one can imply this by the fact that memories were able to be retrieved 4 days later. However, the study design provides no information on the temporal dynamics of memory between encoding and retrieval. In other words, we don't know if dexmedetomidine impaired encoding, in line with Pryor's work, or resulted in memory impairment characterized by memory loss over time, akin to the benzodiazepine amnesic effect. Greater missed responses during dexmedetomidine along with a diminished hippocampal response soon after stimulus presentation points to impaired encoding.

As the hippocampus is critical to conscious memory, drug effects on hippocampal activity are potentially revealing. Memory-related hippocampal activity was imaged during stimulus presentation by comparing subsequently remembered with nonremembered items based on recognition 4 days later. Hayama *et al.* further refined retrieval from episodic (conscious) memory into two distinct qualities of recollection and familiarity. Recollection is a memory where contextual details are clearly remembered, and these are the memories lost over time when propofol or midazolam are present.[4] Memory processes associated with familiarity recognition ("I remember the face, but not the name") are more difficult to clearly identify, as there is less confidence associated with such judgments. Hayama *et al.*

Image: ©Thinkstock.

Accepted for publication July 17, 2012. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

 Anesthesiology 2012; 117:940–1

◆ This Editorial View accompanies the following article: Hayama HR, Drumheller KM, Mastromonaco M, Reist C, Cahill LF, Alkire MT: Event-related functional magnetic resonance imaging of a low dose of dexmedetomidine that impairs long-term memory. ANESTHESIOLOGY 2012; 117:981–95.

used the "remember/know" paradigm to assess recollection *versus* familiarity recognition memory, respectively, at retrieval. After 4 days it is not surprising that there were too few "remember" responses to allow neuroimaging analysis of encoding of recollection memories. The authors thus collapsed recognition across remember/know, but it should be noted that the majority of responses were familiarity recognitions. Whether familiarity is a different memory process than recollection is somewhat controversial, but as this is a potential issue, future studies should focus on recollection, for example by using a shorter learn-test interval.[6,7]

One final note of caution is needed. The most informative neuroimaging results were those that imaged hippocampal activity (figs. 4 and 6 from the accompanying article), as these represent the task upon which the study was designed. Results from the placebo group were congruent with existing literature, and results from the dexmedetomidine group related well to behavioral data. However, the analyses of the "main"* effect of drug on blood oxygenation level-dependent response throughout the brain (figs. 1 and 2) should be interpreted with caution, and not only for the reasons mentioned by the authors. Subtleties in global-normalization procedures used in image analysis, which equate different conditions to a common denominator for use in formal comparisons, can produce quite different results based purely on different assumptions about the data set and imaging signals.[8,9] The effect of dexmedetomidine, and other drugs, on these assumptions is currently still unknown.[10–13] The hard-to-explain "main" effect of drug in the right but not left hippocampus also points to the need for caution in interpreting this analysis.

Hayama *et al.*[1] are to be commended in embracing more sophisticated understanding of memory processes. Neuroimaging of the interaction of a drug with a specific memory process provides a different viewpoint to better understand anesthetic actions on conscious memory. A limited interpretation may seem to be a small step for such a complex study, but if we are to untangle the mechanisms that underlie the temporary ablation of memory by anesthesia, we need to focus on one piece of the puzzle at a time.d

Robert A. Veselis, M.D., Department of Anesthesiology and Critical Care, Memorial Sloan–Kettering Cancer Center, New York, New York, and Department of Anesthesiology, Weill Cornell Medical College, New York, New York. veselisr@mskcc.org

* "Main" in this context is used in a statistical sense.

References

1. Hayama HR, Drumheller KM, Mastromonaco M, Reist C, Cahill LF, Alkire MT: Event-related functional magnetic resonance imaging of a low dose of dexmedetomidine that impairs long-term memory. Anesthesiology 2012; 117:981-995
2. Veselis RA, Reinsel RA, Feshchenko VA, Wroński M: The comparative amnestic effects of midazolam, propofol, thiopental, and fentanyl at equisedative concentrations. Anesthesiology 1997; 87:749-64
3. Pryor KO, Reinsel RA, Mehta M, Li Y, Wixted JT, Veselis RA: Visual P2-N2 complex and arousal at the time of encoding predict the time domain characteristics of amnesia for multiple intravenous anesthetic drugs in humans. Anesthesiology 2010; 113:313-26
4. Veselis RA, Pryor KO, Reinsel RA, Li Y, Mehta M, Johnson R Jr: Propofol and midazolam inhibit conscious memory processes very soon after encoding: An event-related potential study of familiarity and recollection in volunteers. Anesthesiology 2009; 110:295-312
5. Veselis RA, Reinsel RA, Feshchenko VA, Johnson R Jr: Information loss over time defines the memory defect of propofol: A comparative response with thiopental and dexmedetomidine. Anesthesiology 2004; 101:831-41
6. Yonelinas AP, Parks CM: Receiver operating characteristics (ROCs) in recognition memory: A review. Psychol Bull 2007; 133:800-32
7. Wixted JT: Dual-process theory and signal-detection theory of recognition memory. Psychol Rev 2007; 114:152-76
8. Desjardins AE, Kiehl KA, Liddle PF: Removal of confounding effects of global signal in functional MRI analyses. Neuroimage 2001; 13:751-8
9. Gavrilescu M, Shaw ME, Stuart GW, Eckersley P, Svalbe ID, Egan GF: Simulation of the effects of global normalization procedures in functional MRI. Neuroimage 2002; 17: 532-42
10. Shtoyerman E, Arieli A, Slovin H, Vanzetta I, Grinvald A: Long-term optical imaging and spectroscopy reveal mechanisms underlying the intrinsic signal and stability of cortical maps in V1 of behaving monkeys. J Neurosci 2000; 20:8111-21
11. Qiu M, Ramani R, Swetye M, Rajeevan N, Constable RT: Anesthetic effects on regional CBF, BOLD, and the coupling between task-induced changes in CBF and BOLD: An fMRI study in normal human subjects. Magn Reson Med 2008; 60:987-96
12. Masamoto K, Kim T, Fukuda M, Wang P, Kim SG: Relationship between neural, vascular, and BOLD signals in isoflurane-anesthetized rat somatosensory cortex. Cereb Cortex 2007; 17:942-50
13. Carhart-Harris RL, Erritzoe D, Williams T, Stone JM, Reed LJ, Colasanti A, Tyacke RJ, Leech R, Malizia AL, Murphy K, Hobden P, Evans J, Feilding A, Wise RG, Nutt DJ: Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci U S A 2012; 109:2138-43