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Midazolam amnesia and retrieval from semantic memory: Developing methods to test theories of implicit memory☆

Elliot Hirshman,[a,*] Julia Fisher,[b] Thomas Henthorn,[c] Jason Arndt,[d] and Anthony Passannante[e]

[a] *Department of Psychology, George Washington University, Washington, DC 20052, USA*
[b] *Department of Psychology, University of Colorado at Denver, USA*
[c] *Department of Anesthesiology, University of Colorado Health Sciences, USA*
[d] *Department of Psychology, Middlebury College, USA*
[e] *Department of Anesthesiology, University of North Carolina, USA*

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Abstract

Studies of organic anterograde amnesia have been central to the development of theories of implicit memory. Pharmacological amnesia provides an additional method for exploring implicit memory, allowing for the experimental manipulation of amnesia and the testing of more participants. A significant concern with pharmacological amnesia is whether its cognitive effects are specific to explicit memory. The current research examines the effects of the benzodiazepine, midazolam, on retrieval from semantic memory and encoding in explicit memory. We focus on midazolam because it holds significant advantages over other benzodiazepines in inducing pharmacological amnesia and prior research suggests it may be useful for testing theories of implicit memory. Our results demonstrate that midazolam does not impair accuracy of retrieval from semantic categories, even when it produces anterograde amnesia for retrieved category items on a later recall test. These results suggest ways midazolam can be used to help test theories of implicit memory.

Keywords: Midazolam; Pharmacological amnesia; Implicit memory; Semantic memory; Benzodiazepines; Category generation

1. Midazolam amnesia and retrieval from semantic memory

Studies of organic amnesia have been central to the development of theories of implicit memory (Blaxton, 1995; Graf, Shimamura, & Squire, 1985; Graf, Squire, & Mandler, 1984; Schacter, 1987). Demonstrations of preserved memory capacities in organic amnesiacs have suggested the existence of multiple forms of memory, with the distinction between explicit (i.e., conscious) memory and implicit (i.e., unconscious) memory being central to contemporary approaches. Pharmacological amnesia (Curran & Birch, 1991; Ghoneim & Mewaldt, 1990; Hennessy, Kirkby, & Montgomery, 1991; Hirshman, Passannante, & Arndt, 1999; Mintzer & Griffiths, 2001) provides an alternative methodology for testing hypotheses about implicit memory. In studies of pharmacological amnesia, participants are administered a drug that induces a brief anterograde amnesia and their memory is tested. The performance of these participants can be compared to their performance in a placebo condition to understand the effects of pharmacological amnesia on explicit and implicit memory.

Studies of pharmacological amnesia have important methodological advantages over studies of organic amnesia. There are a larger number of potential participants, enhancing opportunities to replicate findings and amnesia can be experimentally manipulated, mitigating problems that arise because of the correlational nature of organic amnesia. Moreover, participants can act as their own controls when administered a placebo.

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* Corresponding author. Fax: 1-202-994-1602.
E-mail address: ellioth@gwu.edu (E. Hirshman).

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Coupled with the larger number of participants, this substantially increases the statistical power to detect experimental effects. As a further contrast to organic amnesia, amnesia-inducing drugs can be administered at various times during an experiment, making it possible to identify the stage in processing (i.e., encoding/consolidation or retrieval) that mediates experimental effects.

A significant concern in using pharmacological amnesia is whether an amnesiac agent produces specific effects on explicit memory or general effects on a range of cognitive processes. For many drugs (e.g., fentanyl, Veselis, Reinsel, Feschenko, & Wronski, 1997), the dosage necessary to produce substantial anterograde amnesia will produce extreme sedation, significantly impairing attention, short-term memory, retrieval from semantic memory and implicit memory. Drugs that produce such general patterns of cognitive impairments have limited uses in the exploration of theories of implicit memory.

The purpose of the experiment presented here is to explore the cognitive specificity of the benzodiazepine, midazolam (Curran & Birch, 1991; Evans & Viola-McCabe, 1996; Hennessy et al., 1991; Hirshman, Passannante, & Arndt, 2001). Midazolam is a safe, fast-acting benzodiazepine used in anesthesiology (e.g., surgical pre-medication) and psychiatry (e.g., treatment of anxiety). Specifically, we focus on the question (Tulving, 1984) of whether midazolam spares retrieval from semantic memory, while it impairs encoding in explicit memory.

We investigate midazolam because it may have significant methodological advantages over other benzodiazepines in producing pharmacological amnesia. Because it is water soluble, midazolam is metabolized substantially faster than other benzodiazepines such as diazepam and lorazepam (Stoelting, 1991). This rapid metabolism is convenient for investigations of implicit and explicit memory because it allows one to examine test performance at relatively brief retention intervals (e.g., 1 h) with the assurance that performance on baseline or new items will be equal in the midazolam and placebo conditions. This assurance mitigates concerns about scale effects that often arise when baseline or new performance is substantially lower in an amnesiac than a control condition (Ostergaard, 1998). Similarly, the amnesiac effect of midazolam has a more rapid onset than that of other benzodiazepines (Stoelting, 1991). This rapid onset permits a much shorter interval between the administration of midazolam and the study period, shortening the length of experiments substantially. Midazolam's water solubility is also important to its use in a non-clinical population because water solubility minimizes the side effects of intravenous administration. Intravenous injection of midazolam, in contrast to intravenous injection of non-water soluble benzodiazepines, is painless and is unlikely to cause venuous irritation or thrombophlebitis (Stoelting, 1991).

Motivation for examining the specific question of whether midazolam spares retrieval from semantic memory arises from our prior investigations of midazolam's effect on explicit and implicit memory (Arndt, Passannante, & Hirshman, in press; Hirshman et al., 1999; Hirshman, Passannante, & Henzler, 1999; Hirshman et al., 2001; Hirshman, Fisher, Henthorn, Arndt, & Passannante, 2002). The cited studies have demonstrated that midazolam has substantial effects on encoding in explicit memory, but has limited effects on implicit memory performance. For example, Hirshman et al. (2001) demonstrated that midazolam administered prior to the study period substantially diminished generation effects on the explicit memory tests of free and cued recall, as well as overall performance on these tests, but had no detectable effect on generation effects found in the implicit memory test of cued perceptual identification. Such findings suggest that midazolam can be used to examine implicit memory test performance that is relatively uncontaminated by the effect of explicit memory processes.

This novel use of midazolam holds great promise for exploring prominent theories of implicit and explicit memory (e.g., Roediger & Blaxton, 1987; Roediger & Weldon, 1987; Schacter, Church, & Treadwell, 1994, 1995) if it can be demonstrated that administration of midazolam prior to the study period spares retrieval from semantic memory during this period. Specifically, the cited theories assert that semantic processing during the study period should influence performance on explicit memory tests, but not on implicit memory tests (see Richardson-Klavehn & Gardiner (1998) for a review). It has been difficult to test this assertion using normal subjects in the past because results (e.g., Masson & MacLeod, 1992) demonstrating effects of semantic processing during study on an implicit memory test may have been attributable to contamination by explicit memory (see Jacoby (1991) for a discussion of these methodological issues). Thus, if midazolam spares semantic retrieval during the study period, we can use it to test whether semantic processing during study can influence implicit memory, independently of explicit memory contamination. In this context, the current experiment is part of a larger research enterprise (e.g., Jacoby, 1998) dedicated to developing methods to test theories of implicit memory.

Empirical research on other benzodiazepines suggests that midazolam may spare retrieval from semantic memory. Other benzodiazepines, such as diazepam and lorazepam, impair encoding in explicit memory, but produce minimal effects on retrieval from semantic memory (Curran, Schiwy, & Lader, 1987; Danion, Zimmerman, Willard-Schroeder, Grange, & Singer, 1989; Fang, Hinrichs, & Ghoneim, 1987; Ghoneim &