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SCIENCE DIRECT
Brain and Cognition 61 (2006) 219–223
Brain and Cognition
www.elsevier.com/locate/b&c

Brief communication

Episodic representations support early semantic learning: Evidence from midazolam induced amnesia

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Accepted 8 December 2005
Available online 19 January 2006

Abstract

Current controversy exists regarding the role of episodic representations in the formation of long-term semantic memories. Using the drug *midazolam* to induce temporary amnesia we tested participants' memories for newly learned facts in a semantic cue condition or an episodic and semantic cue condition. Following midazolam administration, memory performance was superior in the episodic and semantic condition, suggesting early semantic learning is supported by episodic representations.

Keywords: Midazolam; Semantic memory; Episodic memory; Amnesia

1. Introduction

A central question in our understanding of human memory is the process by which we learn basic semantic information such as the meanings of words and encyclopedic facts (e.g., semantic memory). The contribution of the hippocampus to this process remains controversial (Holdstock, Mayes, Isaac, Gong, & Roberts, 2002; Kitchener, Hodges, & McCarthy, 1998; Manns, Hopkins, & Squire, 2003). While it is clear that the hippocampus has a vital role in memories which are linked to specific times and places (e.g., episodic memory; McClelland, McNaughton, & O'Reilly, 1995; O'Reilly & Rudy, 2001), the relationship between episodic memory and semantic memory and the role of the hippocampus remains elusive. A number of models of memory hold that the hippocampus is involved in the rapid acquisition of semantic information and is critical for the retrieval of semantic information early in the learning process (Kitchener et al., 1998; McClelland et al., 1995; O'Reilly & Norman, 2002; O'Reilly & Rudy, 2001). In the early stages of semantic learning, to-be-learned information is contained in dual-representations—an episodic/hippocampal representation linked to unique contextual information and a semantic/neocortical representation that is independent of such contextual information. Recent imaging data indicate that neocortical areas in the temporal and frontal lobes are active during encoding of new facts (Maguire & Frith, 2004), demonstrating neocortical activation early in semantic learning. Over time, semantic information is consolidated into neocortical regions, is no longer linked to any specific context and is independent of the hippocampus. Prior to consolidation, semantic retrieval may benefit from episodic/hippocampal information (see also Eldridge, Knowlton, Furnanski, Bookheimer, & Engel, 2000; Moscovitch et al., 2005).

Assuming that the episodic/hippocampal and semantic/neo-cortical representations combine to influence performance, this view makes the intriguing prediction that early in the learning process, performance will be enhanced for tasks that access both the episodic/hippocampal and semantic/neo-cortical representations. It is well established that semantic representations influence performance on

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0278-2626/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.bandc.2005.12.001

episodic memory tasks (e.g., Bower, Black, & Turner, 1979; Tulving & Pearlstone, 1966), similarly recent episodes have been shown to facilitate semantic memory retrieval through semantic priming (e.g., Ashcraft, 1976). While this view suggests that performance on tasks that present episodic and semantic cues will be superior to performance on tasks that present only semantic cues, this implication is difficult to test in normal participants because the presentation of a semantic cue alone can cause unintended episodic recognition of this cue in normal participants. This recognition, in turn, can foster the internal generation and use of episodic representations.

Recent advances in cognitive psychopharmacology have provided the opportunity to experimentally investigate the contribution of episodic memory to performance on a variety of memory tasks. Using the benzodiazepine *midazolam*, investigators have been successful in inducing temporary anterograde amnesia in normal, healthy participants (Arndt, Passannante, & Hirshman, 2004; Hirshman, Passannante, & Arndt, 2001; Merritt, Hirshman, Hsu, & Berrigan, 2005; Polster, McCarthy, O'Sullivan, Gray, & Park, 1993). Midazolam is an anxiolytic sedative used in a variety of clinical settings. Midazolam induces amnesia by facilitating the action of γ-amino butyric acid (GABA) (Evers & Maze, 2004). GABA is known to reduce long-term potentiation (LTP) in the hippocampus, an important mechanism by which episodic memories are thought to be formed (Bliss & Collingridge, 1993). Participants given midazolam are slightly sedated, but conscious and able to engage in conversation and complete a variety of cognitive tasks (Hirshman et al., 2001; Merritt et al., 2005; Polster et al., 1993). Midazolam has been shown to substantially reduce, but not eliminate episodic memory (Hirshman et al., 2001; Hirshman, Fisher, Henthorn, Arndt, & Passannante, 2003; Merritt et al., 2005). These procedures have numerous advantages. Within-participant designs allow for participants to act as their own controls in a saline placebo condition. The relative ease of midazolam administration allows for testing of larger numbers of participants, while rapid elimination of midazolam provides for relatively brief study/test intervals. Finally, such procedures allow experimenters to determine whether a reduction in episodic memory, as opposed to other correlates of organic brain damage, is related to effects on other memory tasks (see Hirshman, 2004).

Use of midazolam provides a unique opportunity to test the above-cited models. When participants are administered midazolam they are less likely to experience episodic recognition of a semantic test cue (Polster et al., 1993). Consequently, they are less likely to use episodic representations on a test that only uses semantic cues. In contrast, the use of episodic instructions and semantic cues will bias participants to use both episodic and semantic representations. Thus, in a midazolam condition, performance on a test that uses semantic cues and episodic instructions should be superior to performance on a test that only uses semantic cues. This outcome is less likely to occur in a saline condition due to the episodic recognition of semantic test cues described above. The expectation is that midazolam would impair episodic/hippocampal representations to the point they would not be automatically triggered when only a semantic cue is given. However, when explicitly cued to use episodic representations with an episodic and semantic cue, residual episodic information would be activated supporting superior recall of semantic information.

To examine this prediction, 19 participants studied 50 obscure but true facts after receiving midazolam in one session and saline placebo in another. Pilot testing indicated that participants were unlikely to know these facts.

2. Method

2.1. Methods

2.1.1. Participants

There were 19 participants from the Washington, DC area who received a $100 payment. Participants were excluded during recruitment if: they were older than 35 or younger than 18; they were currently using benzodiazepines, narcotics or amphetamines; their airway was in any way compromised; they had a serious physical or mental illness; they were pregnant; they reported drinking more than one alcohol-containing drink per day; or reported a history of drug abuse. This experiment was approved by the George Washington University Institutional Review Board and all participants gave informed consent.

2.1.2. Design and materials

This study employed a 2×2 mixed design in which type of Drug (midazolam vs. saline) was manipulated within-participant while type of retrieval (episodic + semantic vs. semantic) was manipulated between-participants. Participants were randomly assigned to retrieval conditions.

A series of 290 factual statements were created using a variety of information sources. A pilot study was conducted to select facts unfamiliar to most participants. All 290 facts were converted into "fill-in-the-blank" questions such as "The capital of Botswana is _____." These questions were then presented to 65 George Washington University undergraduates who participated for extra credit in their psychology courses. Of the 290 facts, no participants provided correct answers to 174 questions, only 1 correct response was given for 42 questions, 2 correct responses were given to 20 questions and 3 correct answers to 19 questions. Using this subset of 255 questions, 200 facts were chosen for inclusion in the study. The final set of 200 was chosen to have as little overlap as possible. The mean correct responses given in the pilot study for these questions was less than 1%.

The final set of 200 facts was then randomly assigned to lists of 50 facts. For each participant, one set of facts was presented during the study phase of a session (one set for midazolam, another for saline). Another set of 50 facts was then included as new items during the test phase of each