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Metamemory without the memory: are people aware of midazolam-induced amnesia?

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Abstract *Rationale:* Midazolam is a benzodiazepine which produces a dense anterograde amnesia, while permitting relatively well-preserved short-term memory, semantic retrieval, and other higher cognitive functions. Given these preserved abilities, we were interested in whether or not participants given midazolam would be aware of this anterograde amnesia. *Method:* In the present experiment, participants were given midazolam in one testing session and a saline placebo in another. Participants provided judgments-of-learning (JOLs) immediately following study of cue-target pairs. During the test phase of the experiment, confidence levels and feeling-of-knowing (FOK) judgments were collected. *Results:* Although cued recall performance was substantially impaired in the midazolam condition, mean JOLs were unaffected, indicating participants had little insight into their impairment during the study phase. Participants were relatively accurate in confidence levels and FOK judgments in the midazolam condition. *Conclusion:* When studying items under the influence of midazolam, participants are unaware that their memory will be impaired. Implications for clinical practice and pharmacological studies of amnesia are discussed.

Keywords Benzodiazepines · Midazolam · Metamemory · Cued-recall · Judgments-of-learning · Feeling-of-knowing · Confidence levels · Amnesia

Introduction

Benzodiazepines are well known for producing anterograde amnesia (Mewaldt et al. 1983). The benzodiazepine, midazolam, produces an exceptionally dense, albeit temporary, anterograde amnesia. For example, Hirshman et al. (2001) demonstrated that administering midazolam prior to a study episode reduced free recall from an average of 12 items to an average of less than one item, with many participants recalling no items.

In clinical settings, midazolam is used to provide conscious sedation for surgical procedures. Administered in conjunction with narcotic analgesics and other anesthetics, it results in a conscious, but heavily sedated patient. Such procedures allow for relatively normal communication with patients who generally have little or no memory of the surgical procedure.

Taking these surgical procedures as a model, recent research (e.g. Hirshman et al. 1999) has used midazolam amnesia to explore a variety of theoretical questions about memory processes. Midazolam is particularly well-suited for this purpose because it has relatively limited side effects (Stoelting 1991) and a brief duration of action. Midazolam's estimated elimination half-life is 1.5–3.5 h (Greenblatt et al. 1984; Mandema et al. 1992). With short-term administration, the drug's effects dissipate relatively rapidly due to the redistribution of midazolam away from its site of action into peripheral tissues and its rapid metabolic clearance (Evers and Maze 2004). Given intravenously, midazolam causes a rapid onset of amnesia allowing for short intervals between drug administration and the start of study episodes (e.g. 5 min). Rapid elimination also facilitates quick recovery allowing for relatively short intervals between study and test (e.g. 1 h). These properties are extremely beneficial for use in the

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large non-clinical samples typically used in memory research.

Prior research (Polster et al. 1993) has established that midazolam amnesia arises from the disruption of encoding, but not retrieval processes and is not state-dependent. Prior studies (Veselis et al. 1997) have also demonstrated that midazolam amnesia is largely independent of sedation. These properties substantially constrain interpretations of experimental results.

A pivotal question concerns whether individuals who are given midazolam are aware during study that their memory will be severely impaired. Whether or not an individual is aware of midazolam's amnesic effects has important implications for the use of midazolam in both clinical and experimental settings.

In clinical settings, midazolam is widely used in a variety of in-patient and out-patient procedures. Given that patients administered midazolam are awake, able to engage in normal conversation and can show minimal appearance of sedation, it is possible that neither the patient nor some members of the hospital staff would be aware that a patient's memory will be impaired. This problem might be particularly important when patients are receiving postoperative instructions. Under these circumstances, a patient might indicate they understood the presented instructions even though they would not remember them later, producing significant complications.

From a research perspective, participant's understanding of their memory impairment might have important implications for interpreting results of experiments using midazolam. If participants are aware that their memory has been impaired by midazolam, they might alter their encoding strategies with consequent effects on the experimental results. To give a specific example, participants in a midazolam condition who believed their memory would be impaired might have less motivation to use effortful encoding strategies, thereby exacerbating their memory impairment.

Interestingly, some theoretical accounts of metamemory (e.g. Schwartz et al. 1997) predict that although participants are densely amnesic following administration of midazolam, they could be unaware of these impairments during study. While early theories (Hart 1967) suggested that participants directly evaluate the state of memory traces during study, Schwartz (1994) and Koriat (1997) have argued that participants predict their later memory performance from cues such as the ease with which an item is processed, the perceived difficulty of an individual item or the task itself. In this view, participants are able to accurately predict their later memory performance only when the information obtained from such cues is correlated with memory performance.

Importantly, many factors that have been postulated to underlie metamemory judgments are relatively unaffected by midazolam. For example, retrieval from short-term memory during study, which might be used to predict later memory performance (Dunlosky and Nelson 1992), is relatively unaffected by administration of midazolam (Henessey et al. 1991). Similarly, retrieval of semantic

information about to-be-learned items during study, which might also be used to predict later memory (Koriat 1997), is relatively unaffected by midazolam (Jackson et al. 1993).

While the foregoing suggests that participants might not be aware of their later memory impairment, they possess a significant cue to this impairment. Midazolam produces sedation and participants are aware of this sedation (Veselis et al. 1997). Participants may use information about a specific study context in making metamemory judgments, as well as information regarding their current state and how it relates to their memory performance (Koriat 1997; Nelson et al. 1998). Thus, participants might infer that sedation would harm their later memory. A central question of the current study then is whether participants are able to infer the depth of their amnesia from sedation or other associated cues during a study episode.

To explore these issues, participants studied cue-target pairs after receiving midazolam in one session, and a saline placebo in another. During the study phase of the experiment, participants provided a judgment of learning immediately following the presentation and study of each cue-target pair. Judgments of learning (JOLs) are often used to assess whether or not participants are able to accurately predict their performance on a later memory test (Lovelace 1984). In the present study, participants rated on a scale from 0 to 100 the likelihood that they would be able to recall the target when presented with the cue.

In addition to measuring participant's awareness of midazolam induced amnesia during study, we also examined whether participants knew they were impaired during testing. Participants rated on a scale from 0 to 100 the likelihood that a response was correct for each item produced in a forced response cued-recall test. Comparing these confidence levels across drug conditions provides a measure of participant's awareness of their impairment during testing (Shimamura and Squire 1988; Metcalfe and Shimamura 1994).

Last, we examined participant's feeling-of-knowing judgment (FOK) when they failed to recall the correct item in cued recall. When an incorrect response was given, participants provided a FOK in which they rated on a scale from 0 to 100 the likelihood that they would be able to choose the correct target in a four-item cued recognition test. FOK judgments are thought to be derived from information about the likelihood that the target is available to the participant (Nelson and Narens 1990).

While there is no prior literature on whether participants administered midazolam are aware of their memory impairment during study, there are two relevant studies. Nelson et al. (1998) found that acute alcohol intoxication impaired memory and participants were relatively unaware of this impairment during study for immediate judgments of learning. Similarly, Weingartner et al. (1993) found that participants administered the benzodiazepine, triazolam, were not aware of their memory impairment during study. These results occurred even though the drug conditions produced detectable sedation, suggesting that participants

may not use perceived sedation as a cue to memory impairment. While these initial results are suggestive (cf. Dunlosky et al. 1998), it is not necessarily the case that they will replicate with the much denser amnesia typically found in studies using intravenously administered midazolam (Hirshman et al. 2001).

In contrast to the results of the studies examining awareness during study, Bacon et al. (1998), Nelson et al. (1986, 1998) and Mintzer and Griffiths (2003) demonstrated that confidence levels in forced or free recall remain at least somewhat accurate when amnesia is induced pharmacologically. The FOK data from these studies are mixed. The accuracy of FOK judgments was unaffected by alcohol (Nelson et al. 1986) but reduced to chance by lorazepam (Bacon et al. 1998).

Materials and methods

Participants

There were 17 participants from the Washington DC area, each of whom 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 (e.g. cancer, schizophrenia); they were pregnant; they reported drinking more than one alcohol-containing drink per day; or reported a history of drug abuse. The current experiment was approved by the George Washington University Institutional Review Board. The data from one participant was not included in the analyses below because he was extremely sedated in the midazolam condition, making it difficult for him to properly complete the JOL task.

Design and materials

Type of drug (midazolam versus saline) was manipulated within participant. For the cued-recall task, 130 word pairs were generated by randomly pairing one-to-three syllable, high-frequency, concrete nouns (Kucera-Francis >60, MRC >400), with the constraint that no pair be directly associated. The word pairs were then randomly assigned to two lists of 65 pairs (five practice pairs and 60 test pairs). The pairs were counterbalanced such that each word appeared as a cue and a target equally often. The lists were counterbalanced across drug conditions.

For the recognition memory task, three distracter items were randomly chosen from the targets within each list. Targets were chosen from the same list to equate the familiarity of the target and distracters for each trial.

Stimuli were presented and participant's responses collected via a Dell Latitude laptop computer using the E-Prime software.

Procedure

Each participant was tested individually in two sessions, 1 week apart. Sessions were run in the preoperative area of the George Washington University Hospital. All equipment necessary for advanced cardiopulmonary resuscitation, including a defibrillator, is available in these areas. Prior to each session, an intravenous catheter was inserted and participants were administered an injection of either 0.03 mg/kg body weight of midazolam diluted to a total volume of 10 ml or 10 ml saline. Intravenous administration was used to ensure rapid action of the drug. If a participant received a midazolam injection in the first session, they received a saline injection in the second session and vice versa. The order of these injections was counterbalanced across participants. Both the participant and the experimenter were blind to the nature of the injection. Participants were monitored as if they were undergoing a diagnostic procedure under conscious sedation. Arterial oxygen saturation and heart rate were continuously monitored with a pulse oximeter. In addition, participant's blood pressure was monitored. No adverse events occurred during or following the experiment.

Five minutes following the injection the study phase began. Participants were asked to rate how strongly they felt the drug's effects from 0 to 100 (Bacon et al. 1998). Participant's were shown a scale from 0, no effect; 25, slightly sedated; 50, moderately sedated; 75, heavily sedated; to 100, extremely sedated and entered their response on the computer. Participants were then given instructions for the study phase. They were told they would be presented with pairs of words on the computer screen and that they would later be presented with the first word (the cue) and asked to remember the second word (the target). They were instructed to form an association between the words so that when presented with the cue, they would think of the target. They were told they would be asked to rate how well they thought they had learned each word pair on a scale of 0, definitely will not remember, to 100 definitely will remember. Participants were then given a practice list of five word pairs to determine whether they could perform the JOL task. For both the practice lists and the study lists the word pairs were presented for 5 s. After each pair was presented, participants completed the JOL task. Following the five practice list pairs, the 60 study list word pairs were presented and self-paced JOLs collected for each pair. The order of pairs in the study list was randomly determined for each participant.

Following the study list, participants completed a selective visual attention task, a digit-span task, and word-search puzzles for the duration of the retention interval.

At the end of the 70-min retention interval, participants were asked to rate their level of sedation. The cued-recall task followed this rating. Participants were instructed that they would be presented with the first word from a studied pair and they should try to recall and type the word with which it was paired. The instructions indicated that a

Table 1 Mean sedation ratings given by participants at study and test as a function of type of drug (midazolam versus saline)

Sedation ratings	Midazolam		Saline	
	<i>M</i>	SD	<i>M</i>	SD
Study	41.63*	24.49	10.19	15.14
Test	23.00* ⁺	19.13	6.75	10.34

*Indicates a significant difference from saline, $P<0.001$, ⁺Indicates a significant difference from study, $P<0.01$

Table 2 Mean proportion correct in cued-recall and the four-choice recognition task as a function of type of drug (midazolam versus saline)

Memory effects	Midazolam		Saline	
	<i>M</i>	SD	<i>M</i>	SD
Cued recall	0.03*	0.03	0.23	0.13
Recognition memory	0.34* ⁺	0.07	0.56 ⁺	0.10

*Indicates a significant difference from saline, $P<0.001$, ⁺indicates a significant difference from chance (0.25), $P<0.001$

response was required and that they should guess if necessary. They were told they would be asked to rate how confident they were in their response on a scale from 0 to 100 and that they would be given feedback regarding the correctness of their response. For incorrect responses, they would be asked to rate how likely it was on a scale from 0 to 100 that they would be able to pick the correct answer out of four possible answers in a cued recognition task. They were informed that a four-alternative cued recognition task would follow this rating.

Following these instructions, participants were given a series of five practice trials to familiarize them with the test task, followed by the 60 item test list. Each test trial proceeded as outlined above. The test session was self-paced, with the order of test items randomly determined for each participant.

At the conclusion of each session, all participants were discharged as if they had received midazolam. They received a ride home and were instructed not to drive until the next day. All participants were debriefed following their second session.

Results and discussion

All statistical tests were conducted with an alpha level of 0.05. We began all analyses by including type of drug (midazolam versus saline) as a within-subjects factor and drug order (midazolam first versus midazolam second) as a between subjects factor. The factor of drug order produced significant effects only on the JOLs, so it is not discussed in any of the other analyses.

Table 3 Mean ratings and difference scores for JOLs, retrospective confidence and FOK, as a function of type of drug (midazolam versus saline)

Metamemory measures	Midazolam		Saline	
	<i>M</i>	SD	<i>M</i>	SD
<i>Judgments of learning</i>				
Mean	46.93	18.00	44.50	22.40
Difference scores ^a	0.44* ⁺	0.17	0.22 ⁺	0.19
<i>Confidence level</i>				
Mean	6.62*	10.31	28.47	17.90
Difference scores ^a	0.04	0.08	0.06 ⁺	0.07
<i>Feeling-of-knowing</i>				
Mean	27.61*	18.03	55.95	23.92
Difference scores ^b	-0.06	0.19	-0.0004	0.23

*Indicates a significant difference from saline, $P<0.01$, ⁺Indicates a significant difference from zero, $P<0.01$

^aDifference scores [(mean JOL or confidence level)/100-(proportion correct cued recall)]

^bDifference scores=[(mean FOK)/100-(proportion correct recognition)]

Sedation ratings

To investigate whether participants were aware of their sedation, and if their sedation was diminished at test, a 2×2 within-subjects ANOVA using the factors of type of drug (midazolam versus saline) and time of rating (prior to study versus prior to test) was conducted on sedation ratings.

Mean sedation ratings are presented in Table 1. Participants rated their sedation as being greater in the midazolam than the saline condition [$F(1,15)=25.31$, $P<0.001$]. Participants also rated their sedation as being higher at study than test [$F(1,15)=15.88$, $P=0.001$]. These effects interacted such that sedation ratings decreased from study to test in the midazolam, but not the saline condition [$F(1,15)=10.69$, $P=0.005$]. Contrasts demonstrated that midazolam produced sedation during both study and test.

Effects of midazolam on memory

The mean proportions of items recalled and recognized are presented in Table 2.

Cued recall

A one-way within-subjects ANOVA using the factor of type of drug (midazolam versus saline) was conducted on the cued recall scores. This analysis demonstrated that participants were densely amnesic in the midazolam condition [$F(1,15)=36.72$, $P<0.001$]. While participants recalled, on average, approximately 14 items in the saline condition, they recalled, on average fewer than two items in the midazolam condition, with five participants recalling no items.

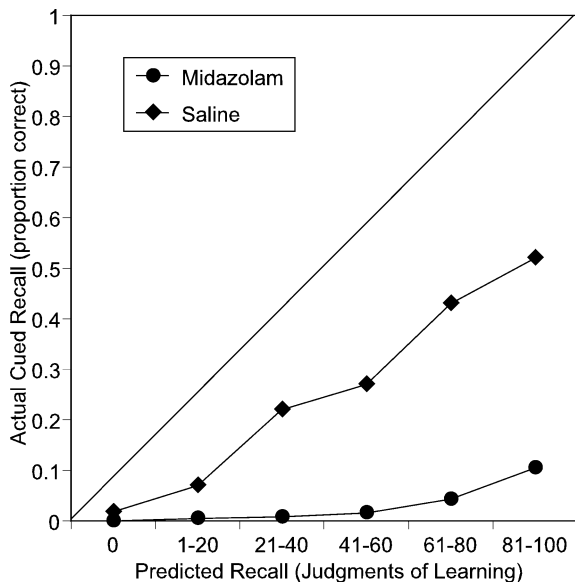


Fig. 1 Calibration curves for judgments-of-learning (*JOL*), mean proportion correct in cued-recall is plotted as a function of *JOL*, collapsed across intervals of 20 for the saline and midazolam (0.03 mg/kg) conditions ($n=16$). The main diagonal represents perfect prediction, with points below the diagonal representing overconfidence in participants *JOLs*

Recognition memory

A one-way within-subjects ANOVA using the factor of type of drug (midazolam versus saline) was conducted on the recognition memory scores. This analysis confirmed that participants were densely amnesic in the midazolam condition [$F(1,15)=95.81$, $P<0.001$]. As in cued recall, there was evidence for some residual memory in recognition memory. Recognition performance was significantly above chance in the midazolam, as well as the saline, condition ($P<0.001$).

Metamemory measures

We focus our analyses on accuracy of *JOLs*, confidence levels and *FOKs*. We present Hart's difference score (see Table 3) as an *ordinal* measure of accuracy (positive values indicate over confidence and negative values indicate under confidence). When appropriate, we also present calibration curves to illustrate *absolute accuracy* in our findings (Nelson 1984). While it is traditional to use gamma correlations to measure *relative accuracy* or *resolution* of metamemory judgments (Nelson), there are an insufficient number of correct trials for *JOLs* and confidence levels in the midazolam condition, precluding the use of this measure to compare results from the saline and midazolam conditions.

Judgments of learning

Mean *JOLs* are presented in Table 3. A 2×2 within-subjects ANOVA using the factors of type of drug (midazolam versus saline) and drug order (midazolam first versus midazolam second) was conducted on participant's mean *JOLs*. Our most important result is that although midazolam produced dramatic amnesia effects, *JOLs* were approximately equal in the midazolam and saline conditions ($F<1$). Thus, participants were unaware of their memory impairment during study.

Hart's difference scores (*JOLs*/100–cued recall), representing accuracy of *JOLs*, are presented in Table 3. The difference scores are significantly greater than zero, indicating over-confidence in both the midazolam and saline conditions. Moreover, as one would anticipate from the cued recall and *JOL* results, over-confidence was substantially greater in the midazolam condition.

Figure 1 presents calibration curves illustrating the relation between *JOLs* and actual recall (overconfidence is reflected in calibration curves below the diagonal). The curves are plotted in accordance with procedures used in a typical calibration study (Koriat 1997). The *JOLs* are grouped into six intervals, 0, 1–20, 21–40, ...81–100. The mean proportion correct in cued recall is plotted against *JOLs*, computed across participants. Figure 1 represents that the combination of midazolam's amnesic effect and its null effect on *JOLs* produces dramatic over-confidence in the midazolam condition. For the saline condition, Fig. 1 demonstrates that while participants were overconfident in their *JOLs*, the shape of the curve suggests participant's absolute accuracy was relatively intact. Figure 1 also demonstrates participants were using the full scale of possible responses (i.e. they were not simply anchoring their judgments at the scale median as might be inferred from the mean *JOLs* in Table 3). Further analysis of the data showed this was the case for both session 1 and session 2.

A question raised by the equality of *JOLs* in the saline and midazolam condition concerns the accuracy of *JOLs* in the saline condition. Perhaps participants simply make random ratings in the saline condition. Under these circumstances, a comparable process in the midazolam condition resulting in equal *JOLs* across conditions would not be surprising. Two pieces of evidence speak to this issue. First, the calibration curve for the saline condition in Fig. 1 demonstrates a systematic increase in actual recall with increasing *JOLs*. Second, the mean gamma correlations for the saline condition was 0.43, significantly and substantially above chance [$t(15)=7.02$, $P<0.001$].

One final result from our analyses of *JOLs* merits mention. While, there was no effect of type of drug on *JOLs*, there was a significant interaction effect of type of drug and drug order on *JOLs* [$F(1,14)=14.98$, $P=0.002$]. This interaction effect is characterized by significantly reduced mean *JOLs* in the saline condition for participants who received midazolam in the first session ($M=34.12$, $SEM=6.95$) relative to those receiving saline in the first

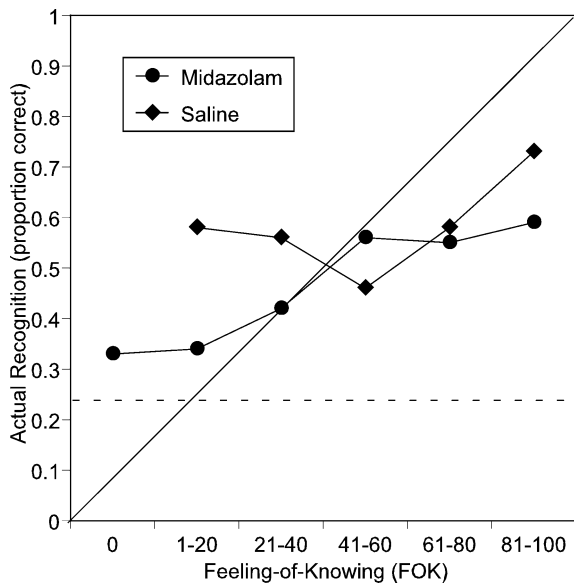


Fig. 2 Calibration curves for FOK, mean proportion correct in four-choice recognition is plotted as a function of FOK, collapsed across intervals of 20 for the saline and midazolam (0.03 mg/kg) conditions ($n=16$). The main diagonal represents perfect prediction with points below the diagonal representing overconfidence in participants FOK. The dashed line represents chance performance in recognition memory

session ($M=54.89$, $SEM=7.92$). This result raises some concerns about the data that required further analysis.

One interpretation of this interaction effect is that participants were retrospectively aware of their amnesia (see immediately below) and their poor performance in the midazolam condition during the first test session may have led them to reduce their JOLs in the saline condition during the second test session. This may be due to participants misattributing their poor performance in the midazolam session to other factors such as the difficulty of the task or perceptions of their own memory performance, consistent with current views of the cues used in making JOLs immediately following study (Koriat 1997).

To ensure that our central results were independent of these adaptation effects, we completed a second analysis using only data from the first session. An independent-samples t -test was conducted comparing mean JOLs (midazolam versus saline) in session 1. There was no evidence that JOLs differed in the midazolam and saline conditions ($P>0.50$). Thus, our core findings are independent of adaptation effects.

Confidence levels: cued recall

Mean confidence levels for cued recall are presented in Table 3. Although subjects were unaware of their memory impairments during study, they were aware of their amnesia during the test session. This effect may arise because the influence of midazolam is minimized during test (see introductory remarks on midazolam's metabolism and sedation ratings) and/or because metamemory judg-

ments at test can be accurate even when midazolam is administered to participants. A one-way within-subject ANOVA using the factor of type of drug (midazolam versus saline) on confidence levels confirmed that mean confidence levels were substantially and significantly lower in the midazolam than the saline condition [$F(1,15)=28.03$, $P<0.001$].

Regarding accuracy, mean difference scores (confidence level/100—cued recall) are presented in Table 3. Comparing these difference scores to zero, provided evidence of modest over-confidence, with mean difference scores being significantly above zero in the saline condition, but not the midazolam condition. Thus, the accuracy of confidence levels was at least as good, if not better, in the midazolam condition. Calibration curves are not provided for confidence levels because almost all responses in the midazolam condition were at the lower end of the scale (92% of the ratings were 20 or below), making the calibration curve uninterpretable.

FOK: recognition memory

Mean FOK judgments are presented in Table 3. FOK judgments were substantially and significantly lower in the midazolam than the saline condition [$F(1,15)=21.56$, $P<0.001$]. Thus, the FOK results provided converging evidence that participants are retrospectively aware of their memory impairment. Interestingly, these results further demonstrate that *prospective* FOK judgments (e.g. how will I perform on the recognition memory test?) are affected by retrospective awareness of memory performance (e.g. Schwartz 1994).

Regarding accuracy of FOK judgments, mean difference scores (FOK/100—recognition memory accuracy) are also presented in Table 3. Comparing the difference scores to zero demonstrated that subjects were generally accurate (neither over or under confident), with mean difference scores not significantly different from zero in both the saline ($P>0.50$) and midazolam ($P>0.20$) conditions. Calibration curves for FOK judgments are presented in Fig. 2.

The shape of the curves illustrates that even though overall accuracy of FOKs is good, *absolute accuracy* (i.e. the ability to generally determine which items will be recognized) is poor in the saline and midazolam conditions. Examination of gamma correlations further support the finding that relative accuracy was poor in both the saline ($M=0.11$, $SEM=0.07$) and midazolam ($M=0.11$, $SEM=0.09$) conditions. This latter result replicates previous findings of poor relative FOK accuracy when only a single study-test trial is used (Nelson and Narens 1990) and when performance is poor in forced-choice recognition tests (Koriat and Goldsmith 1996). Close examination of the FOK calibration data suggests that not only are participants aware of their impairment, they may have slightly underestimated their performance on the recognition memory test in the midazolam condition. Participants gave 577 items ratings between 0 and 20, while mean

recognition memory performance for these items was above 0.30, suggesting mild under-confidence.

Effects of sedation on memory

The results reported above suggest that the dense amnesia reported here may be related to increased sedation in the midazolam condition. To address this issue, participants were divided into two groups using a median split procedure on the sedation ratings given just prior to study in the midazolam condition. The mean ratings were 55.18 ($n=11$, $SEM=4.52$) and 11.80 ($SEM=3.70$), respectively. Independent samples t -tests conducted on the cued recall and recognition memory results indicated there were no significant differences in cued recall (higher sedation ratings group, $M=0.025$, $SEM=0.009$, lower sedation ratings group, $M=0.032$, $SEM=0.014$, $P>0.50$) or recognition memory performance [higher sedation ratings, $M=0.36$, $SEM=0.021$, lower sedation ratings, $M=0.29$, $SEM=0.026$, $t(14)=1.88$, $P>0.05$]. This suggests that the dense amnesia found is independent of sedation ratings at study.

Participants were also divided into two groups according to their sedation ratings given just prior to testing in the midazolam condition. Using a median split procedure participants were divided into a sedated group ($n=8$, $M=37.5$, $SEM=5.09$) and a non-sedated group ($M=8.5$, $SEM=3.47$). Independent samples t -tests were then conducted on the cued recall and recognition memory results comparing the sedated and non-sedated groups. There was no difference detected in cued recall performance (sedated group, $M=0.028$, $SEM=0.009$, non-sedated group, $M=0.027$, $SEM=0.013$, $P>0.90$). Interestingly, recognition memory performance was significantly better for the sedated group ($M=0.37$, $SEM=0.027$) than the non-sedated group [$M=0.30$, $SEM=0.018$; $t(14)=2.19$, $P=0.046$]. This presumably reflects a correlated participant difference. Together, these results suggest that the dense amnesia reported here is independent of sedation at testing.

Concluding remarks

Our results demonstrate a remarkable lack of awareness of midazolam-induced amnesia at study. At the same time, our results clearly show that participants are aware that their memory is impaired at test. These findings converge with those of previous studies (Nelson et al. 1986, 1998; Weingartner et al. 1993; Bacon et al. 1998; Mintzer and Griffiths 2003) to demonstrate that participants are often unaware of pharmacologically induced memory impairments at study even when they are aware of these impairments at test (Nelson et al. 1986, 1998; Bacon et al. 1998). Importantly, this regularity occurred in the current study where induced amnesia was substantially greater than in previous studies. Similarly, our findings converge with those of prior studies to suggest that information

about sedation levels do not necessarily influence judgments of learning during study even though participants are aware of their sedation. Interestingly, aspects of our procedure bias participants to be aware of their later impairments. During the informed consent procedure, participants are explicitly informed that midazolam produces both sedation and amnesia.

As discussed above, an important limitation of the current study is that our results regarding test judgments may reflect that midazolam is not pharmacologically active during test due to its rapid elimination. An experimental design in which midazolam is administered prior to the memory test or using a brief retention interval is necessary to address this issue.

Our results also provide data relevant to the types of information participants use in making judgments of learning. Previous authors have proposed that when making immediate judgments of learning, participants measure the strength of a memory trace (Hart 1967) or attempt to retrieve the to-be-judged item from memory (Nelson et al. 1998). Our results clearly demonstrate that participants are not accessing a memory trace directly, nor basing their judgments on retrieval from long-term memory. Rather, participants base these decisions on other information such as retrieval from short-term memory, assessments of item strength or task difficulty.

At a general level, our results provide some reassurance for investigators using midazolam to explore memory processes. It appears that, at least in initial learning sessions, participants are relatively unaware that midazolam produces amnesia. As such, they are unlikely to engage in alternative encoding strategies in response to their perceived memory impairment. One caveat to this finding is that our results apply only to a single use of midazolam. As suggested by the effect of drug order on JOLs described here, we cannot rule out that adaptation processes could result in changes in the accuracy of judgments of learning when midazolam is administered multiple times.

At the same time, our results raise concerns regarding the clinical use of midazolam, and possibly other benzodiazepines. In addition to uses in surgical procedures, benzodiazepines similar to midazolam are also regularly given to treat sleep and psychiatric disturbances (Rivas-Vazquez 2003), with 20% of patients being treated for depression receiving a benzodiazepine (Stafford et al. 2000). Recent proposals have also argued for the use of midazolam in treating acute seizure disorders (Knoester et al. 2002). Given the failure of metamemory during study documented here, it is absolutely critical that patients receiving midazolam (and possibly other benzodiazepines) be clearly informed of its amnesic effects prior to treatment.

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