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ORIGINAL INVESTIGATION

Midazolam does not inhibit association formation, just its storage and strengthening

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Abstract
Rationale Although there have been many studies examining the effects of benzodiazepines on memory performance, their effects on working memory are equivocal and little is known about whether they affect the efficacy of practice of already learned material.
Objectives The objectives in two experiments were to examine (a) whether midazolam impairs performance on a working memory task designed to minimize mnemonic strategies such as rehearsal or chunking of information to be recalled and (b) the effect of midazolam on repeated practice of paired associates that were learned before drug administration.
Materials and methods Both experiments involved subcutaneous administration of 0.03 mg/kg of body weight of saline or midazolam in within-subject, placebo-controlled designs, involving 23 subjects in (a) and 31 in (b).
Results The drug had no effect on the ability to recall the digits in serial order even though the encoding task prevented the digits from being rehearsed or maintained in an articulatory buffer. Paired associates that were learned before the injection showed a benefit of subsequent practice under saline but not under midazolam.
Conclusions The results suggest that (a) midazolam does not affect the formation of new associations in short-term memory (STM) provided that the presentation rate is not too fast to form these associations when sedated, despite the evidence that the drug blocks long-term memory (LTM) retention of associations; and (b) the potential for over-learning with practice of learned associations in LTM is adversely affected by midazolam such that repeated exposures do not strengthen new learning.

Keywords Benzodiazepine · Working memory · Memory · Binding · Paired associate learning · Practice · MODS task · Midazolam · Over-learning · Digit span

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Researchers concerned with understanding human memory have sometimes relied on studies of patients with anterograde amnesia to provide insights and constraints on theories of memory mechanisms (Milner 2005). Although this research on patients with amnesia can use accidents of nature to provide insights, the difficulties associated with the patient population (access to participants, finding suitable controls, and ability to perform complex experiments) limit what can be learned. Many of these problems inherent in patient populations have recently been finessed by investigators who use pharmacological interventions that create temporary, synthetic anterograde amnesia. These studies have employed benzodiazepines such as triazolam (Mintzer 2003; Mintzer et al. 2001; Mintzer and Griffiths 2003b), lorazepam (Bacon et al. 1998; Blin et al. 2001; Mintzer and Griffiths 2003a), diazepam, (Ghoneim and Mewaldt 1975; Rich et al. 2006), and midazolam (Curran and Birch 1991; Hirshman et al. 1999, 2001, 2002; Park et al. 2004). The time course of these drugs varies but the general behavioral effects on performance are quite similar.

The general finding from memory studies using benzodiazepines is a sharp reduction in the amount of new learning, but no effect on retrieval of information already learned. That pattern mirrors the clinical population of

anterograde amnesiacs. Another similarity with amnesic patients is that not all new experiences are affected by the drug. Specifically, acquisition of episodic memories are affected (i.e., facts that are associated with the context in which they were acquired) while acquisition of new implicit memories (i.e., memories that affect behavior without awareness of the influence) is generally thought to be unaffected (Gabrieli et al. 1997; Goshen-Gottstein et al. 2000; Nissley and Schmitter-Edgecombe 2002). Likewise, new skill learning has been shown to be unaffected by benzodiazepines (e.g., Park et al. 2004). One explanation for this pattern of data is that the drug specifically affects the binding process (Park et al. 2004; Ghoneim 2004a,b) such that, when the task requires the storage of a new LTM association, midazolam will impair performance.

It is noteworthy that it is often difficult to tell whether a participant has received the drug or placebo by observing his or her behavior while under the drug's influence: cognition seems otherwise unaffected and performance on tasks seems very close to normal (although somewhat slowed due to the conscious sedation). What makes this methodological approach particularly exciting is that this manipulation is quite powerful in its ability to quickly and temporarily induce anterograde amnesia. The effects of midazolam are almost immediate and dissipate faster than other benzodiazepines. The same participant can serve as his or her own control, thereby finessing many of the problems inherent with clinical populations. In short, this methodology enables new insights into the mechanisms of memory as well as provides strong constraints on theorizing.

The goal of this paper is to further our understanding of what behaviors are or are not affected by benzodiazepines (specifically midazolam) and thereby help shed more light on memory mechanisms. We address two new questions about the effects of midazolam on performance: First, does midazolam actually block the formation of new associations or only the storage of these associations? That is, if a task requires information to be associated (bound) but that binding only has to be retained for a short period (i.e., in working or short-term memory, STM), will performance be adversely affected by midazolam just as it is for LTM bindings? Second, if an association was learned before the injection, will successive test–study trials strengthen memory for the already established bindings to the same degree as associations learned and practiced in the saline condition?

What do we mean by "binding"?

By binding we mean the creation of an association or link between a concept and its context or another concept/stimulus that was experienced. A number of studies have also suggested that benzodiazepines impair attention (Buffett-Jerrott et al. 2003; Fleishaker et al. 1995; Loke et al. 1985; Rich et al. 2006; Vidailhet et al. 1994) which we also believe is implicated in the binding process (Diana and Reder 2006).

Theorists have recently begun to distinguish between two kinds of information that can be tapped when assessing LTM: item vs relational memories (Davachi and Wagner 2002; Eichenbaum and Cohen 2001; Hunt and Einstein 1981; Ryan et al. 2000). Relational memories require the binding process in their formation. Anytime a new association is formed, either to link a context to a study item to create an episode or to associate two items together, we call these association formations "bindings." Recent work by Blumenfeld and Ranganath (2006) and Davachi et al. (2003) have provided neuroimaging and patient data that support the involvement of the frontal lobes (and presumably working memory) in the ability to form new bindings or associations.

Study 1: is working memory affected by midazolam?

The performance of almost any cognitive task requires that the person maintain and retrieve information during processing. Working memory is the mechanism that enables a person to maintain and manipulate information retrieved from LTM or encoded from the environment. It is well known that performance degrades (measured by errors or response time) as demands on working memory increase either by increasing the number of items in a "pure" memory task or by increasing the difficulty of concurrent processing in a dual-task situation (e.g., Anderson et al. 1996; Baddeley 1986; Caplan et al. 1992; Oberauer et al. 2004). It is also well established that there are individual differences in working memory capacity (Barrett et al. 2004; Conway and Engle 1996; Lovett et al. 1999).

Given that forming new episodic memories is strongly affected by benzodiazepines, it is worth exploring whether working memory performance is also affected. The literature is mixed on this point. There are studies that indicate no effect of benzodiazepines on working memory (e.g., Blin et al. 2001; Ghoneim and Mewaldt 1975; Hennessy et al. 1991; Kirkby et al. 1995; Knopman 1991; Mallick et al. 1993) and several studies that indicate that there is an effect of benzodiazepines on working memory (Fisher et al. 2006; Mintzer and Griffiths 2003a,b). Given that many factors can contribute to these different results, including differences in the nature of the task and the pharmacology of the drug, it is useful to try to collect more data to help tease apart what variables affect the conclusions drawn. We will discuss these factors later in the paper.

We have developed a successful paradigm for studying working memory (Lovett et al. 1997; Daily et al. 2001; Lovett et al. 2000) and we decided to use it with midazolam to compare the results with other studies that have used other paradigms to study the effect of benzodiazepines on working memory. Our working memory task is intended to minimize the use of compensatory strategies and prior knowledge (e.g., chunking the numbers into running times and covert rehearsal). We call it the modified digit span (MODS) task because it is a variant of one developed by Yuill et al. (1989) that is similar in spirit to other span tasks that require subjects to perform a concurrent task along with the test of memory span (e.g., Daneman and Carpenter 1980; Turner and Engle 1989). The task requires the subject to hold in working memory a variable number of digits that are blocked from remaining in the echoic or articulatory buffer because of the concurrent requirement of reading letters aloud at a rapid pace. We expected to see a strong effect of the string length on performance, but we were unsure whether this paradigm would show an effect of drug condition on performance as well.

Method

Participants

Twenty-three healthy participants (11 males, 12 females) between the ages 18–35 and a maximum body weight of 84 kg[1] received US$120 upon completion of the experiment. All were screened by a medical doctor (MD) and gave their written informed consent for a protocol approved by the Institutional Review Boards (IRBs) of Carnegie Mellon University and the University of Pittsburgh.

Procedure and design

A within-subject design was used, with the saline and midazolam sessions 1 week apart. The assignment of drug condition to session was counterbalanced and double-blind. At each session, the subject received a single intravenous (IV) injection of either 0.03 mg/kg (to a maximum of 2.5 mg) of midazolam or a matching volume of saline. We used such a low dose because it had already been shown to be effective in creating temporary amnesia (e.g., Hirshman et al. 1999).

The MODS task was administered approximately 15 min after injection, after completing an encoding task for another study. Smith et al. (1981) provide a curve of IV midazolam that shows that, at 15 min, plasma concentration is still very close to the peak. Trial difficulty was randomly intermixed such that shorter- and longer-digit spans occurred throughout the testing period. Each trial consisted of a series of "sentences" in which the final character of the sentence was a digit that would have to be remembered in the correct position in the set of sentences for that trial. Each sentence consisted of a variable number of letters (from two to five) presented one at a time on the computer screen before the final digit of the sentence was presented. The subjects were instructed to read aloud each letter as it appeared but to remember the sentence final digits for recall at the end of the trial. The trials varied in the number of sentences, and hence the number of digits to be recalled from three to six. At the end of each trial, the subjects were prompted to enter the digits from that trial *in the exact order that they appeared.* The general procedure of a trial is illustrated in Fig. 1.

The letters in each sentence were presented at a rapid pace (two characters per second). The requirement to read these characters aloud as they appeared was intended to prevent the subjects from engaging in mnemonic strategies such as chunking digits into meaningful units or even rehearsing the previous digits in the trial. This MODS task yields a relatively pure estimate of working memory capacity. That is, we have minimized the contributions of prior knowledge and different strategies for encoding numbers. There were 35 trials (series of sentences) per session and each of the two hospital sessions used different materials.

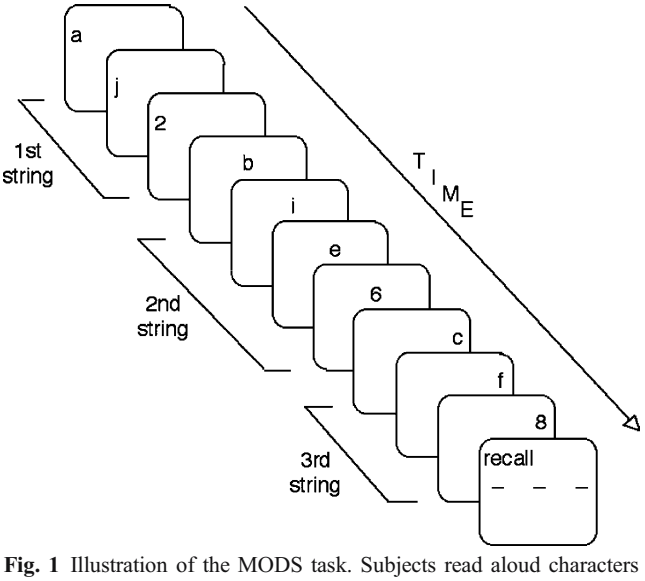

Fig. 1 Illustration of the MODS task. Subjects read aloud characters until they were prompted to recall the final of each string in the order presented

[1]The weight cutoff was a conservative value approved by the IDS of the University of Pittsburgh), We could have used a more liberal (higher weight) cutoff without compromising safety.

Results and discussion

One subject's data were lost due to technical error. Subjects' performance was evaluated according to their accuracy in recall. Each trial can be scored strictly such that each digit must be correctly recalled in its proper serial position or loosely such that the mean number of digits correctly recalled in the appropriate serial position on a trial is computed. Figure 2 presents the serial position curves for the two drug conditions as a function of the number of digits to be recalled (string length) on the trial and the digit's serial position in the trial. The curves are strikingly similar for the two drug conditions. Figure 3 presents the same information, collapsed over serial position. Figure 3a presents these means using a strict criterion of perfect recall of a string and Fig. 3b shows this same information using a loose criterion of proportion of correctly recalled digits in their correct position.

We ran two ANOVAs using drug condition and string length for the two measures of accuracy, strict and loose, shown in Fig. 3a and b, respectively. There was a reliable effect of string length in both analyses, $F(3, 63)=176$ and 179, $p<.001$, for the strict and loose criteria, respectively. In contrast, neither analysis showed a reliable effect of drug condition on performance, both Fs <1.0 nor was there a reliable interaction of drug and string length, $F \sim 1.0$.

We do not consider our null effect to be a problem of statistical power given the robust serial position and string length effects in the experiment. Nor could this null effect be due to a ceiling or floor effect given that performance differed as a function of string length but did not interact with drug condition. The result that there was no effect of drug condition on our MODS task is consistent with a number of studies that also have failed to find an effect of benzodiazepines on working memory performance (Blin et al. 2001; Kirkby et al. 1995; Mallick et al. 1993). Nonetheless, it is useful to understand our results in light of previous research that has found an effect of drug on STM. Fisher et al. (2006) showed a small, but significant, drop in performance on a traditional digit span task when subjects were required to give back the digits in reverse order. Drug condition did not affect performance when digits were recalled in the forward order. Given that the recency items were recalled first and the primacy items were recalled last, the beginning of the list may have been sufficiently delayed in recall such that long-term effects were contaminating their estimates (cf. Hinrichs et al. 1982).

Mintzer and Griffiths (2003a,b) found larger effects of drug on working memory performance than did Fisher et al. They used different benzodiazepines (lorazepam and triazolam) that have a slower onset of effect but last much longer and they used oral capsules instead of IV administration. As in our study, Fisher et al. used midazolam, which is a fast-acting benzodiazepine with a much shorter half-life than those used by Mintzer and Griffiths. Fisher et al. started their reversed memory span task 12 min after injection and we started our working memory task 15 min after injection. We considered the possibility that our null result and the small effect for Fisher et al. could be

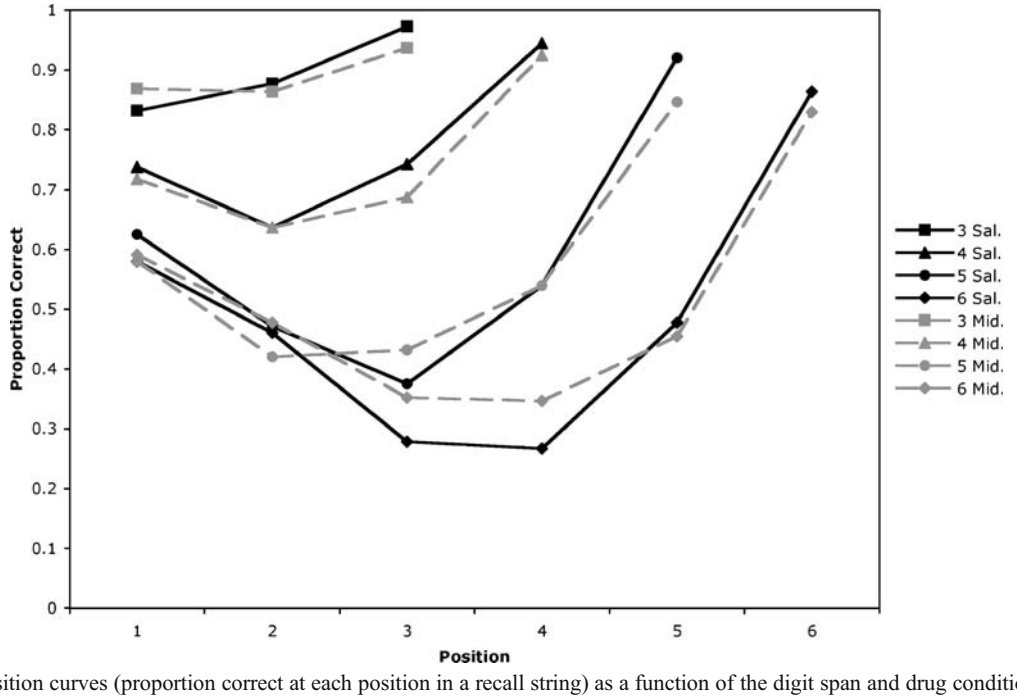

Fig. 2 Serial position curves (proportion correct at each position in a recall string) as a function of the digit span and drug condition. *Dashed gray lines* are midazolam; *black lines* are saline

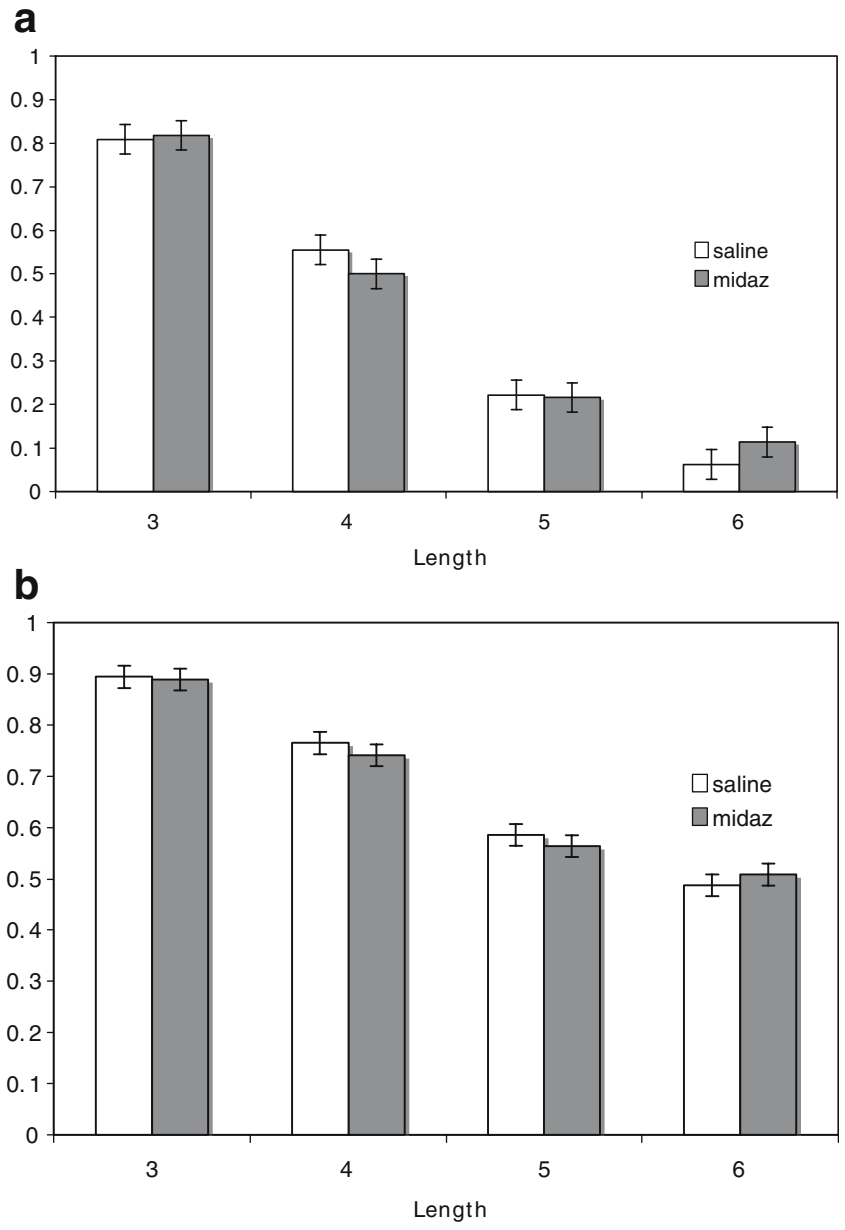

Fig. 3 Proportion correct in the MODS task as a function of digit span and drug condition. **a** Plot of these data using a strict criterion (everything must be perfect in a trial to be counted as correct). **b** Plot of the same results using a less strict criterion (calculating mean number of digits correctly recalled per trial)

attributed to the drug losing its potency. Although that is possible, it is worth noting that our episodic memory results from learning at that same delay after injection still showed strong effects of the drug.[2]

If the explanation for our null result is not due to the drug losing potency, we need to examine why we failed to find an effect of benzodiazepines on working memory when some other researchers have found such effects. Mintzer and Griffiths used the 2-back task that requires subjects to respond when the digit just presented matches one presented before the previous one (i.e., two digits ago). In their task, subjects had to update memory every 1.5 s, leaving two digits in working memory (the current target and the one that will become the target on the next trial) and responding within that same 1.5 s as to whether the current digit matches the one that is being dropped

[2]We examined the episodic memory effects at 17 min in a different study (Reder et al., in press). Paired associates that were studied for the first time were recalled correctly 33% of the time in the saline condition but only 9% of the time in the midazolam condition. It should be noted, however, that it is possible that the same drug has different windows for its effects on various cognitive functions (e.g., a longer window of action for its effects on episodic memory than for its effects on working memory).

from the buffer. Although our task suppressed covert rehearsal by requiring continual oral reading of displayed letters (two per second), there was more time to associate the number to a serial position in the new string to recall and presumably easier than the 2-back task. Our subjects were only required to link a digit to its appropriate serial position approximately every 2.5 s and the serial position for a digit did not change during the trial (unlike the constant updating in the 2-back task). The letters to be read aloud varied from two to five before the single digit appeared to end the "sentence". There was an additional 0.25-s pause (over and above the 0.5 s for letters) after the terminating digit before the next sentence was initiated. This meant that subjects had 0.75 s to process the digit before a new string began. Furthermore, before the next digit was presented, there were more letters to read aloud. Therefore, we estimate that, on average, subjects had 2.5 s to associate the digit to its serial position before the next digit appeared (0.5 s×3.5 letters+ 0.75 s=2.5 s).

The MODS task is quite challenging given that the numbers have to be recalled in order and the letter shadowing task precludes rehearsal. On the other hand, it differs from the 2-back task that requires updating two numbers and judging one of them and responding within a short time frame of 1.5 s. The 2-back task required much faster critical mental operations than the MODS task. Perhaps ability to operate quickly is the vulnerable part of the 2-back task with respect to the drug. In fact, Mintzer and Griffiths (2003b) examined performance in the 2-back task when the benzodiazepine triazolam was paired with the non-specific stimulant d-amphetamine to dissociate the sedative and memory-impairing effects of the benzodiazepine. They found that, when the drug was combined with non-specific stimulant d-amphetamine, the difference in 2-back performance compared with the placebo disappeared. Perhaps the amphetamine sped up processing enough to facilitate the updating process. We should note that our subjects did show evidence of slower processing in the MODS task under midazolam, which is similar to the behavior of Mintzer and Griffiths' subjects without the stimulant. Although the digit encoding time was determined by the experimenter, the time to output the string of digits was self-paced. Subjects were faster in the saline condition: 6.5 s for saline (SD=1.63) and 7.6 s (SD=1.72) for midazolam. This difference in output speed was highly reliable, $F(1, 21)=26.5$, $p<.001$, providing evidence that they were sedated although quite able to perform the MODS task.

Mintzer and Griffiths (2003b) also used a different task to assess the effects of benzodiazepines on working memory. They used an eight-digit reproduction task that required subjects to remember an eight-digit number for immediate or delayed (10-s delay) recall. At those short delays, their subjects were marginally worse under the drug compared to under a placebo, $0.05<p<0.10$. Subjects were only asked to remember an eight-digit number when they could correctly type it from the number displayed on the screen (when they failed to correctly transcribe it, a new eight-digit number appeared). Conceivably their subjects were marginally worse than ours were because their task allowed covert rehearsal and a rehearsal would have been slower in the midazolam condition due to sedation. There is evidence that digit span is affected by the speed of rehearsal (Baddeley 1986). Why did Fisher et al. (2006) find an effect on the backward digit span task, $p<0.05$ between the two drug conditions, when they did not in the forward direction? The reverse digit span subject averaged 7 in the midazolam condition and 7.7 in the saline condition. The digits were presented one per second. Reverse recall tends to be more effortful and slower than forward recall. Output was likely even slower in the midazolam condition under sedation. Therefore, the first digits of the list (which need to be recalled last) probably need to be retrieved from LTM rather than STM as the delay is exceptionally long. Furthermore, we know that the associations that must be retrieved from LTM are vulnerable to midazolam.

Conclusion

Our results suggest that people's ability to remember digits in serial order is equivalent under midazolam and saline when the retention of these digits cannot be supported by an articulatory loop process and the retention duration is short enough not to require long-term storage. The ability to maintain the serial order of these numbers requires temporarily binding them (associating them) to spatial positions in STM. It is noteworthy that short-term bindings were constructed and remained intact under midazolam in this task that required them to last for about 10–12 s without opportunities for covert rehearsal. Subjects' success at creating these temporary bindings was probably due to the fact that the bindings did not have to be created quickly in contrast to the 2-back task used by Mintzer and Griffiths. We believe that this is a novel finding because the other working memory tasks that also failed to find an effect of benzodiazepines on working memory involved tasks that did not preclude rehearsal or keeping the digits in an articulatory buffer (Ghoneim and Mewaldt 1975; Hennessy et al. 1991; Knopman 1991). An interesting speculation based on our finding is that a STM binding is assembled in the frontal lobes but that the registration or storage of the binding occurs in the hippocampus (e.g., Ryan and Cohen 2003, 2004). It is known that the frontal lobes and the hippocampus are critical for episodic memory formation.

It is generally accepted that the frontal lobes are largely responsible for working memory performance (D'Esposito et al. 1995; Miller et al. 2003; Prabhakaran et al. 2000). Given that good performance in the MODS task requires a binding of the digits onto different serial positions, it seems plausible that this formation occurs in the frontal lobes. We know that long-term retention (on the order of several minutes to much longer) is severely compromised by midazolam and it is thought that the hippocampus is responsible for the storage of new LTM bindings (Cohen et al. 1996; Cohen and O'Reilly 1996; McClelland et al. 1995). Our results lead us to speculate that the actual formation of associations occurs in the frontal lobes while the hippocampus is only responsible for the storage. Recent evidence from neuroimaging (Blumenfeld and Ranganath 2006) provides additional support for this conjecture.

Study 2: do previously formed memory traces strengthen at the same rate under midazolam?

It is well established that the retrieval of learned information is unaffected by midazolam (see Ghoneim 2004a,b, for a review). What is less clear is whether previously learned LTM associations can be strengthened as easily under midazolam as under saline. Hirshman et al. (2001) suggest that the previous associations can be primed. Therefore, it seemed reasonable to hypothesize that, for learned associations, midazolam should not impact further learning and that its function is strictly for blocking the formation of new associations.

We were able to test this hypothesis by performing a fine-grained analysis of data collected for another study that used midazolam in a paired-associate learning task (Reder et al., in press). That study compared the retention of three types of word pairs learned over three successive lists: pairs practiced on all three lists, pairs studied on only one list, and pairs that involved recombining cue and response terms from one list to the next. The injection of midazolam or saline was given just before word pairs for List 2 were presented for the initial study. The comparison of interest in that study was final test performance for control pairs from List 1 (not seen on any other list) vs interference pairs from List 1 (stimulus and response terms were recombined on Lists 2 and 3) as a function of drug condition.

The practice pairs that were repeated from list to list were not critical to that study and were not analyzed except to note that, on average, performance improved across lists as the pairs continued to be practiced regardless of drug condition. That is, the two drug conditions did not differ very much in their final performance. The invited inference was that if the pairs are already learned, midazolam had no effect on performance.

In this paper, we more carefully examine the effect of drug on practice pairs. As with any experiment involving study of many word pairs, not all pairs were successfully learned during the first list presentation even though they had been studied and tested on List 1. We are interested in the fate of the subset of the practice pairs that did seem to be mastered on List 1. The drug injection occurred after List 1 so we can compare the over-learning effects for these pairs as a function of whether the subject received midazolam or saline before List 2. Will pairs that were successfully learned before the drug was administered be affected the same way by practice in the midazolam condition as in the saline condition?

Method

Our interest is only in a subset of the word pairs in one of the three conditions described below; however, we briefly describe the method for the entire experiment to explain the context in which the practice pairs were learned.

Subjects

Thirty-one healthy participants (17 males, 14 females) between the ages 18–35 and a maximum body weight of 84 kg received US$150 upon completion of the experiment. All were screened by an MD and gave their written informed consent for a protocol approved by the IRBs of Carnegie Mellon University and the University of Pittsburgh.

Design, materials, and procedure

We used a double-blind cross-over design with assignment of drug condition to session randomly permuted. Words were randomly assigned to pairs and condition for each subject. Subjects studied 45 word pairs on each of three separate lists, with 15 word pairs of each type per list: practice pairs (repeated on each list), control pairs (seen on only one list), and interference pairs (response terms interchanged from one list to the next). For each list, subjects studied each word pair for 3 s. This was followed by a cued recall test for each of the 45 word pairs. Subjects could hit the return key if unsure of the response. The word pair was then presented for an additional 2.5 s of study, regardless of the response. After all pairs were tested, the 45 pairs were tested again in a different random order.

The IV catheter was already in place before the List 1 word pairs were presented for study. After the test–study cycles for List 1, the injection was administered over a 2-min period. Immediately after the injection was com-

pleted, subjects studied the pairs for List 2 and the same test–study procedure was repeated twice before going on to List 3. Each test–study phase lasted approximately 17 min. There was a break before the final test.

Approximately 1 h after the injection, subjects began the final test phase. A test trial consisted of the first word (cue) of a studied pair plus the name of the list on which the pair had appeared. Each pair was tested only once with no feedback concerning accuracy. Since practice pairs appeared on all three lists, the practice pairs were randomly assigned to be tested with one of the three list cues such that an equal number of pairs were tested with each of the three list names.

Results and discussion

The results of interest concern the fate of the practice pairs that were already learned on List 1, as a function of whether saline or midazolam was injected before continued practice on List 2. We categorized word pairs as learned if they were correctly recalled at least once out of the two opportunities on List 1 that occurred before the injection. We were forced to drop three subjects who did not have any observations in that cell. If we limited ourselves to pairs that were recalled correctly exactly two times on List 1, there were not enough observations (most subjects had very few pairs that were learned perfectly on List 1).

Even though these pairs had been learned, research shows that such items continue to benefit from further practice (over-learning) in normal conditions (Ebbinghaus 1913). One way this benefit manifests itself is by higher probability of recall in later tests. The recall probabilities will be high in any case, but they slowly converge to 100% with increased over-learning.

Figure 4 shows the cued recall performance on List 1 and the final test for those practice pairs that were correctly recalled at least once on List 1. Because the data approach the ceiling on performance, the ANOVA was conducted on arcsine-transformed data. There was no difference in accuracy for the pairs for the two drug conditions before injection (which is good as the drug treatment had not yet occurred), $F<1.0$. On the other hand, there was an effect of drug condition on the final test, $F(1, 27)=4.8$, $p<0.05$, and an interaction of drug condition with list, $F(1, 27)=4.6$, $p<0.05$, such that the effect of the drug on these highly practiced pairs only had an effect after the injection. In other words, even though these pairs were equivalent in performance and already learned prior to the injection, the over-learning only occurred in the saline condition.

Conclusion

We are unaware of any past research that has examined whether benzodiazepines affect the potential benefits of over-learning for items learned prior to injection. Our hypothesis (before conducting this analysis) was that those paired associates that were well learned would be strengthened at the same rate regardless of drug condition. The data suggest otherwise.

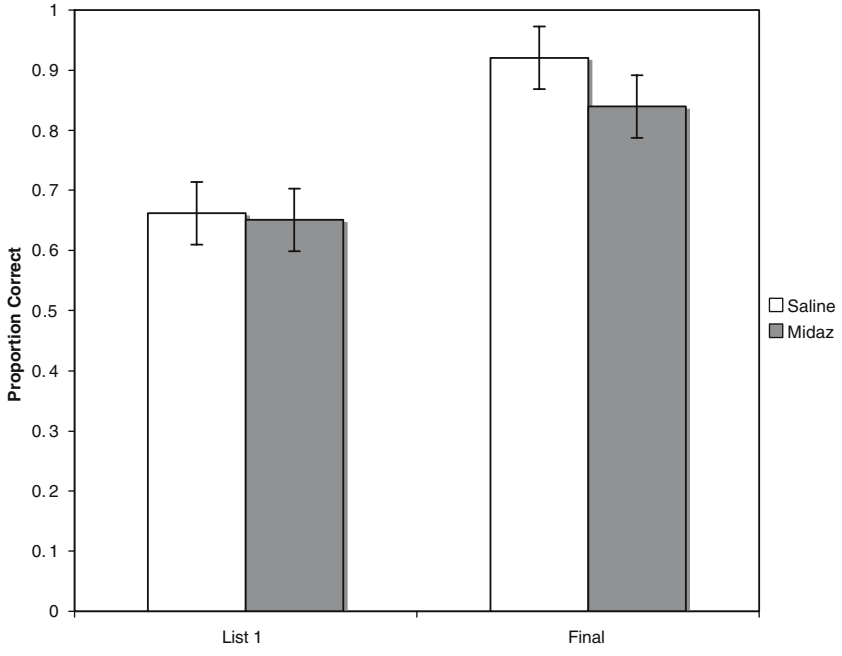

Fig. 4 Proportion correct as a function of drug condition on test–study trials before injection and on the final test for paired associates that had been learned before the injection

General discussion

This paper reported two findings. The first study presented evidence that midazolam does not affect working memory capacity as defined by the MODS task, thus corroborating past research (Ghoneim and Mewaldt 1975; Hennessy et al. 1991; Knopman 1991). The novel contribution of this finding is that this digit span task minimizes the ability to rehearse the digits given the secondary task of pronouncing letters aloud at a rapid pace. (While the secondary task of reading letters aloud is fast-paced, the time required to bind a digit to its serial position in the trial is relatively slow.) Success at this task requires that the subject temporarily associate (or bind) the digits to their respective serial position and to hold on to them for approximately 12 s without benefit of rehearsal. The binding process is given 0.75 s uninterrupted and approximately 2.75 s before the next digit is presented. This task contrasts with the 2-back task that required faster binding that was affected by a benzodiazepine; however, that effect disappeared when the drug was combined with an amphetamine, suggesting that the deficit might have been in the speed of processing rather than in an inability to update (rebind) the digits. Therefore, it appears that midazolam does not block the formation of STM associations but rather their long-term storage.

In a second study, we used a fine-grained analysis of individual items learned prior to injection to ask the question of whether midazolam affects rehearsal or over-learning of already learned memory traces. Our comparison of learned paired associates (correctly recalled at least once out of two opportunities) that were then practiced four more times and tested five more times indicated that even already learned traces are at a disadvantage when the practice occurs under the influence of midazolam.

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References

Anderson JR, Reder LM, Lebiere C (1996) Working memory: activation limitations on retrieval. Cogn Psychol 30:221–256

Bacon E, Danion JM, Kauffmann-Muller F, Schelstraete MA, Bruant A, Sellal F, Grande D (1998) Confidence level and feeling of knowing for episodic and semantic memory: an investigation of lorazepam effects on metamemory. Psychopharmacology 138:318–325

Baddeley AD (1986) Working memory. Oxford University Press, Oxford, England

Barrett LF, Tugade MM, Engle RW (2004) Individual differences in working memory capacity and dual-process theories of the mind. Psychol Bull 130(4):553–573

Blin O, Simon N, Jouve E, Habib M, Gayraud D, Durand A et al (2001) Pharmacokinetic and pharmacodynamic analysis of sedative and amnesic effects of lorazepam in healthy volunteers. Clin Neuropharmacol 24(2):71–81

Blumenfeld RS, Ranganath C (2006) Dorsolateral prefrontal cortex promotes long term memory formation through its role in working memory organization. J Neurosci 26(3):916–925

Buffett-Jerrott SE, Stewart SH, Finley GA, Loughlan HL (2003) Effects of benzodiazepines on explicit memory in a paediatric surgery setting. Psychopharmacology 168:377–386

Caplan D, Rochon E, Waters GS (1992) Articulatory and phonological determinants of word length effects in span tasks. Q J Exp Psychol 45(2):177–192

Cohen JD, O'Reilly RC (1996) A preliminary theory of the interactions between prefrontal cortex and hippocampus that contribute to planning and prospective memory. In: Brandimonte M, Einstein GO, McDaniel MA (eds) Prospective memory: theory and applications. Erlbaum, Mahwah, NJ, pp 267–295

Cohen JD, Braver TS, O'Reilly RC (1996) A computational approach to pre-frontal cortex, cognitive control, and schizophrenia: recent developments and current challenges. Philos Trans R Soc Lond B Biol Sci 351:1515–1527

Conway AR, Engle RW (1996) Individual differences in working memory capacity: more evidence for a general capacity theory. Memory 4(6):577–590

Curran HV, Birch B (1991) Differentiating the sedative, psychomotor and amnesic effects of benzodiazepines: a study with midazolam and the benzodiazepine antagonist, flumazenil. Psychopharmacology 103(4):519–523

Daily LZ, Lovett MC, Reder LM (2001) Modeling individual differences in working memory performance: a source activation account. Cogn Sci 25:315–353

Daneman M, Carpenter P (1980) Individual differences in working memory and reading. J Verbal Learn Verbal Behav 19:450–466

Davachi L, Wagner AD (2002) Hippocampal contributions to episodic encoding: insights from relational and item-based learning. J Neurophysiol 88:982–990

Davachi L, Mitchell JP, Wagner AD (2003) Multiple routes to memory: distinct medial temporal lobe processes build item and source memories. Proc Natl Acad Sci USA 100:2157–2162

D'Esposito M, Detre JA, Alsop DC, Shin RK, Atlas S, Grossman M (1995) The neural basis of the central executive system of working memory. Nature 378:279–281

Diana RA, Reder LM (2006) The low frequency encoding disadvantage: Word frequency affects processing demands. J Exp Psychol Learn Mem Cogn 32(4):805–815

Ebbinghaus H (1913) Memory: a contribution to experimental psychology. Teachers College, Columbia University, New York (reprinted Thoemmes, Bristol, 1999)

Eichenbaum H, Cohen NJ (2001) From conditioning to conscious recollection: memory systems of the brain. Oxford University Press, New York

Fisher J, Hirshman E, Henthorn T, Arndt J, Passannante A (2006) Midazolam amnesia and short-term/working memory processes. Conscious Cogn 15(1):54–63

Fleishaker JC, Garzone PD, Chambers JH, Sirocco K, Weingartner H (1995) Comparison of the spectrum of cognitive effects of alprazolam and adinazolam after single doses in healthy subjects. Psychopharmacology 120:169–176

Gabrieli JDE, Keane MM, Zarella MM, Poldrack RA (1997) Preservation of implicit memory for new associations in global amnesia. Psychol Sci 8(4):326–329

Ghoneim MM (2004a) Drugs and human memory (part 1): clinical, theoretical, and methodologic issues. Anesthesiology 100 (4):987–1002

Ghoneim MM (2004b) Drugs and human memory (part 2): Clinical, theoretical, and methodologic issues. Anesthesiology 100 (5):1277–1297

Ghoneim MM, Mewaldt SP (1975) Effects of diazepam and scopolamine on storage, retrieval and organizational processes in memory. Psychopharmacologia 44(3):257–262

Goshen-Gottstein Y, Moscovitch M, Melo B (2000) Intact implicit memory for newly formed verbal associations in amnesic patients following single study trials. Neuropsychology 14(4):570–578

Hennessy MJ, Kirkby KC, Montgomery IM (1991) Comparison of the amnesic effects of midazolam and diazepam. Psychopharmacology 103(4):545–550

Hinrichs JV, Mewaldt SP, Ghoneim MM, Berie JL (1982) Diazepam and learning: assessment of acquisition deficits. Pharmacol Biochem Behav 17(1):165–170

Hirshman E, Passannante A, Henzler A (1999) The effect of midazolam on implicit memory tests. Brain Cogn 41:351–364

Hirshman E, Passannante A, Arndt J (2001) Midazolam amnesia and conceptual processing in implicit memory. J Exp Psychol Gen 130(3):453–465

Hirshman E, Fisher J, Henthorn T, Arndt J, Passannante A (2002) Midazolam amnesia and the dual-process models of the word-frequency mirror effect. J Mem Lang 47:499–516

Hunt RR, Einstein GO (1981) Relational and item-specific information in memory. J Verbal Learn Verbal Behav 20:497–514

Kirkby KC, Montgomery IM, Badcock R, Daniels BA (1995) A comparison of age-related deficits in memory and frontal lobe function following oral lorazepam administration. J Psychopharmacol 9 (4):319–325

Knopman D (1991) Unaware learning versus preserved learning in pharmacologic amnesia: similarities and differences. J Exper Psychol Learn Mem Cogn 17(5):1017–1029

Loke WH, Hinrichs JV, Ghoneim MM (1985) Caffeine and diazepam: separate and combined effects on mood, memory, and psychomotor performance. Psychopharmacology 87:344–350

Lovett MC, Reder LM, Lebiere C (1997) Modeling individual differences in a digit working memory task. Proceedings of the Nineteenth Annual Cognitive Science Conference. Erlbaum, Mahwah, NJ, pp 460–465

Lovett MC, Reder LM, Lebiere C (1999) Modeling working memory in a unified architecture: an ACT-R perspective. In: Miyake A, Shah P (eds) Models of working memory. Cambridge University Press, pp 135–182

Lovett MC, Daily LZ, Reder LM (2000) A source activation theory of working memory: cross-task prediction of performance in ACT-R. Journal of Cognitive Systems Research 1:99–118

Mallick JL, Kirby KC, Martin F, Philip M, Hennessy MJ (1993) A comparison of the amnesic effects of lorazepam in alcoholics and nonalcoholics. Psychopharmacology 110(1–2):181–186

McClelland JL, McNaughton BL, O'Reilly RC (1995) Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. Psychol Rev 102:419–457

Miller EK, Freedman DJ, Wallis JD (2003) The prefrontal cortex: categories, concepts and cognition. In: Parker A, Derrington A, Blamore C (eds) The physiology of cognitive processes. Oxford University Press, New York, NY, pp 252–273

Milner B (2005) The medial temporal-lobe amnesic syndrome. Psychiatr Clin North Am 28(3):599–611

Mintzer MZ (2003) Triazolam-induced amnesia and the word-frequency effect in recognition memory: support for a dual process account. J Mem Lang 48:596–602

Mintzer MZ, Griffiths RR (2003a) Lorazepam and scopolamine: a single-dose comparison of effects on human memory and attentional processes. Exp Clin Psychopharmacol 11(1):56–72

Mintzer MZ, Griffiths RR (2003b) Triazolam–amphetamine interaction: dissociation of effects on memory versus arousal. J Psychopharmacol 17(1):17–29

Mintzer MZ, Griffiths RR, Contoreggi C, Kimes AS, London ED, Ernst M (2001) Effects of triazolam on brain activity during episodic memory encoding: A PET study. Neuropsychopharmacology 25(5):744–756

Nissley HM, Schmitter-Edgecombe M (2002) Perceptually based implicit learning in severe closed-head injury patients. Neuropsychology 16(1):111–122

Oberauer K, Lange E, Engle RW (2004) Working memory capacity and resistance to interference. J Mem Lang 51(1):80–96

Park H, Quinlan JJ, Thornton ER, Reder LM (2004) The effect of midazolam on visual search: Implications for understanding amnesia. Proc Natl Acad Sci 101(51):17879–17883

Prabhakaran V, Narayanan K, Zhao Z, Gabrieli JDE (2000) Integration of diverse information in working memory within the frontal lobe. Nat Neurosci 3:85–90

Reder LM, Oates JM, Thornton ER, Quinlan JJ, Kaufer A, Sauer J (2006) Drug induced amnesia hurts recognition, but only for memories that can be utilized. Psychological Science. Psychol Sci 17(7):562–567

Reder LM, Oates JM, Dickison D, Anderson JR, Gyulai F, Quinlan JJ, Ferris JL, Dulik M, Jefferson B (in press) Retrograde facilitation under midazolam: The role of general and specific interference. Psychon Bull Rev

Rich JB, Svoboda E, Brown GG (2006) Diazepam-induced prospective memory impairment and its relation to retrospective memory, attention, and arousal. Hum Psychopharmacol 21:101–108

Ryan JD, Cohen NJ (2003) The contribution of long-term memory and the role of frontal-lobe systems in on-line processing. Behav Brain Sci 26(6):756

Ryan JD, Cohen NJ (2004) Processing and short-term retention of relational information in amnesia. Neuropsychologia 42(4): 497–511

Ryan JD, Althoff RR, Whitlow S, Cohen NJ (2000) Amnesia is a deficit in relational memory. Psychol Sci 11:454–461

Smith MT, Eadie MJ, O'Rourke Brophy T (1981) The pharmacokinetics of midazolam in man. Eur J Clin Pharmacol 19:271–278

Turner ML, Engle RW (1989) Working memory capacity: an individual differences approach. J Mem Lang 28:1–28

Vidailhet P, Danion JM, Kauffmann-Muller F et al (1994) Lorazepam and diazepam effects on memory acquisition in priming tasks. Psychopharmacology 115:397–406

Yuill N, Oakhill J, Parkin A (1989) Working memory, comprehension ability and the resolution of text anomaly. Br J Psychol 80(Pt 3):351–361