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14 How midazolam can help us understand human memory: Three illustrations

Lindsay W. Victoria and Lynne M. Reder

In the study of the complex cognitive process of human memory, an investigation of specific memory deficits can help elucidate the functioning of normal memory. One such way to implement controlled memory deficits is with the use of the drug midazolam. Midazolam is an anxiolytic drug that creates temporary and reversible anterograde amnesia. The drug operates by facilitating the negative neurotransmitter gamma-aminobutyric acid (GABA), resulting in the blocking of neural long-term potentiation. Midazolam specifically targets the $GABA_A$ receptors that are prominent in the hippocampus, a neuroanatomical region with a primary role in explicit memory function (Park, Quinlan, Thornton, & Reder, 2004).

Midazolam provides an effective and efficient way to study human memory because its related temporary amnesia eliminates the need to use amnesic patients. Cases of clinical amnesia are often accompanied by other cognitive deficits, making it difficult to tease apart the exact impact of amnesia on the brain. Alternatively, with the use of midazolam in an experimental setting, healthy subjects can be tested, these subjects can effectively act as their own controls, and complex memory experiments can be executed.

The damage to the delicate process of human memory is often manifested in the form of amnesia. Amnesia is conventionally described as a memory disorder that results in the selective impairment of explicit memory, while sparing implicit memory. This conventional belief assumes that since implicit and explicit memory performance are affected differently by amnesia, they are separate memory systems. Alternatively, we propose that amnesia does not affect memory as differently as formerly proposed but, instead, affects the ability to bind stimuli, regardless of whether the information is available to consciousness (Park et al., 2004; Reder, Park, & Kieffaber, 2009).

The present chapter lays forth three specific illustrations of how the use of midazolam can inform current topics in human memory research. The first illustration describes an experiment that provides additional support against the modal view of separate implicit and explicit memory systems. The second example shows how midazolam can provide support for the hypothesis that recognition is affected by the ease of binding stimuli to context. The last

illustration of the use of midazolam to study memory tests the theoretical position that forgetting is the result of a failure to consolidate information.

Example 1: Contextual cuing under midazolam

The effect of midazolam on the visual search (Park, Quinlan, Thornton, & Reder, 2004)

Chun and Jiang (1998) conducted a visual search task, in which subjects searched a display of composed letter Ls rotated 90° for the target, a single rotated T (see Figure 14.1). Once the subjects located the target in the visual field, their task was to indicate whether the T was pointing to the left or the right. Subjects viewed 24 different displays for 30 trials. Unbeknownst to them, half of the displays were repeated patterns of Ts and Ls. Chun and Jiang (1998) found that there was general speed-up during the process of the task, as well as specific speed-up for the repeated, previously viewed configurations. This specific speed-up in target identification during the test period was the result of a learned association between the repeated context and the location of the target. Although the subjects were not aware of having seen the repeated fields during the study phase, their faster reaction

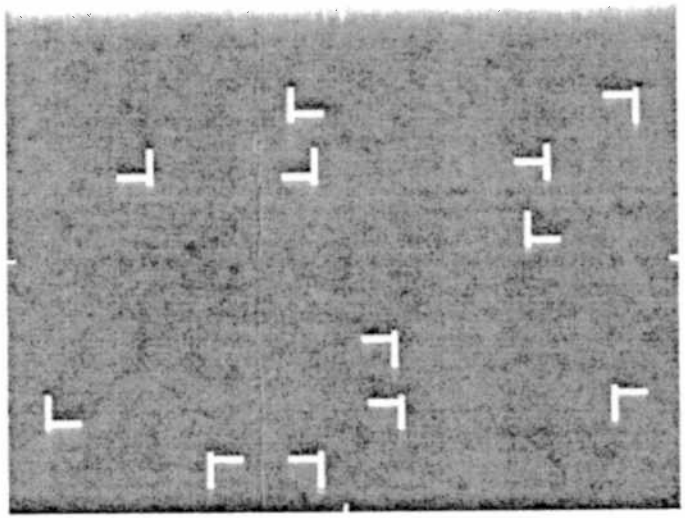

Figure 14.1 Rotated T & L visual search task. Adapted from Chun and Jiang (1998).

times indicated that they had unconsciously processed the location of the target within the field. These findings indicate the presence of an implicit contextual cuing effect for this visual search task.

Chun and Phelps (1999) repeated this visual search task with amnesic patients. The subjects with amnesia got faster with practice over blocks, but did not show the benefit of faster reaction time for the repeated, previously viewed configurations, indicating that there was no effect of contextual cuing. In other words, the subjects with amnesia did show context-independent learning over time, performing increasingly better on the task with time as a result of practice, but not learning that depended on the contextual cuing of the target's location (see Figure 14.2). These results provide support for the notion that not all forms of implicit learning are affected by specific brain damage.

The results of Chun and Phelps (1999) challenged the conventional notions of the deficits that occur with anterograde amnesia, leading Manns and Squire (2001) to suggest that the Chun and Phelps findings were caused by brain damage outside the region typically associated with clinical amnesia. We decided to use pharmacologically induced amnesia to adjudicate between

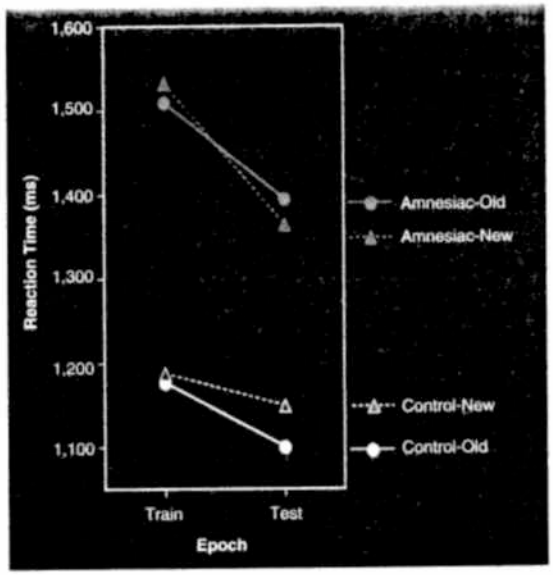

Figure 14.2 Reaction times on visual search task for control and amnesic patients. Adapted from Chun and Phelps (1999).

these positions. Park et al. (2004) replicated the Chun and Phelps (1999) study using college students as subjects with midazolam-induced amnesia. A within-subject, double blind, cross-over design involved the administration of midazolam in one session and saline in the other. The same T/L visual search task was used in one session and a similar 2/5 search task in the other session, counterbalanced on order and drug condition assignment. Immediately after injection, subjects studied a list of paired associates that were tested at the end of the day's session as a manipulation check on the amnestic effects of the drug. Immediately after studying the list of paired associates, the visual search test consisting of 24 blocks of 24 trials commenced.

Following these 24 blocks of trials, subjects were given a quadrant guessing task in which they were shown the repeated displays and novel displays, with the target replaced with another distractor. Subjects were asked to guess which quadrant should contain the target. In both the drug and saline conditions, subjects were at chance guessing the target quadrant, replicating previous results that the knowledge of target location is implicit.

Figure 14.3 plots the response time (RT) to locate the target in a display of distractors as a function of practice at the task, whether the display was repeated across blocks of trials and drug condition. Each epoch is the average of four blocks of 24 trials. In both the saline and midazolam conditions, subjects showed a general speed-up effect with practice. However, the faster RTs for target identification in repeated configurations were only seen in the saline condition, and not under the administration of midazolam. In other words, when subjects were injected with midazolam, they did not demonstrate

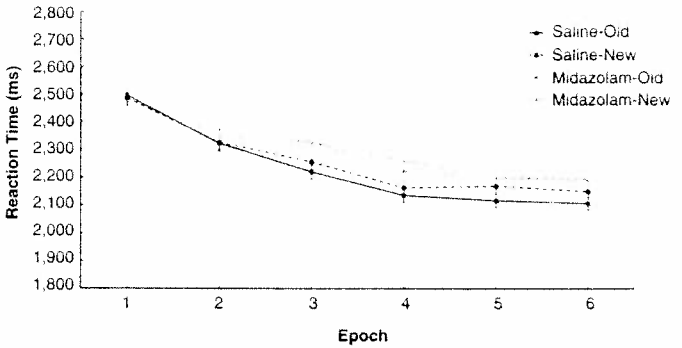

Figure 14.3 Reaction times on visual search task as a function of drug condition and visual field repetition. Reproduced from H. Park et al., The effect of midazolam on the visual search: Implications for understanding amnesia. *Proceedings of the National Academy of Sciences, USA*, 2004, *101*(51), 17879–17883.

the implicit contextual cuing effect, instead demonstrating an implicit memory impairment.

In summary, our findings supported the conclusions of Chun and Phelps (1999) that amnesia can lead to impairment on implicit tasks, in addition to the established impairment of explicit memory tasks.

Example 2: Not all stimuli can be bound to context

Drug-induced amnesia hurts recognition, but only for memories that can be unitized (Reder et al., 2006)

The previous example illustrated that amnesia can affect learning that is implicit in nature. The present example illustrates that amnesia does not always impair explicit memories. The goal of this study was to test the thesis that explicit recognition can be affected by the ease of generating a unique label. We assume that there are two ways to recognize a stimulus seen earlier in an experiment, one based on recollection (retrieval of details of encoding context) and the other based on the familiarity of the stimulus (see Diana, Reder, Arndt, & Park, 2006; Yonelinas, 2002, for reviews). According to the SAC model of memory (e.g., Reder et al., 2000), recollection requires the formation of an association of the stimulus concept with the encoding context; however, when recollection fails, recognition can sometimes occur based on the familiarity of the stimulus concept.

Our working hypothesis is that midazolam affects memory performance by blocking the formation of new associations or binding (Park et al., 2004). We propose that subjects administered midazolam will be unable to use associations to make recollections, and they will have to rely exclusively on familiarity judgments in an experimental setting. The use of midazolam affects explicit memory for new information when those judgments require recollection of context. On the other hand, when explicit memory judgments can be based on familiarity (i.e., binding to context is not a requirement), midazolam should not affect memory performance.

Reder et al. (2006) used midazolam to test two hypotheses. The first hypothesis was that stimuli that are not sufficiently familiar to be *unitized* (formed into a "chunk") cannot be bound to context and therefore cannot be recollected later. Therefore, any stimulus that cannot be bound to context in normal conditions will suffer less when studied under midazolam. The other hypothesis we examined was whether recollection would show less impairment from midazolam relative to the saline control when the stimuli could not be labeled with unique descriptors. In other words, even if the label representing a stimulus could be bound to context, there would be no advantage of binding for those stimuli that do not evoke a unique label (one that distinguishes the stimulus from foils). Therefore those stimuli that evoke a generic label will be relatively unimpaired in the midazolam condition because the ability to bind to context does not help with recollection.

To test these hypotheses, subjects studied lists consisting of three types of stimuli: abstract pictures, concrete words, and photographs of (unfamiliar) faces and outdoor scenes. Subjects were told that they would see a series words and pictures to rate each item on its pleasantness using a Likert scale. After the instructions, subjects were injected with saline or midazolam, depending on the session, since this study was also a within-subject, double-blind, cross-over design. Assignment of stimuli to treatment condition was randomized for each subject such that there was an equal number of each stimulus type for both targets and foils for each session, with no overlap. There were 100 words, 100 photographs, and 50 abstract pictures on each study list.

Figure 14.4 displays memory performance, measured in d', as a function of stimulus type and drug condition. As expected, memory was worse in the midazolam condition than the saline condition. Memory was best overall for words; however, there was also a strong interaction between stimulus condition and drug condition, such that words showed the biggest drop in performance, while abstract pictures were least affected by midazolam. Our explanation for this pattern is that under saline, it is easy to bind words to their context, enabling an accurate recollection judgment. On the other hand, subjects were unfamiliar with the abstract stimuli making the association of the stimulus to context very difficult. Midazolam is thought to only

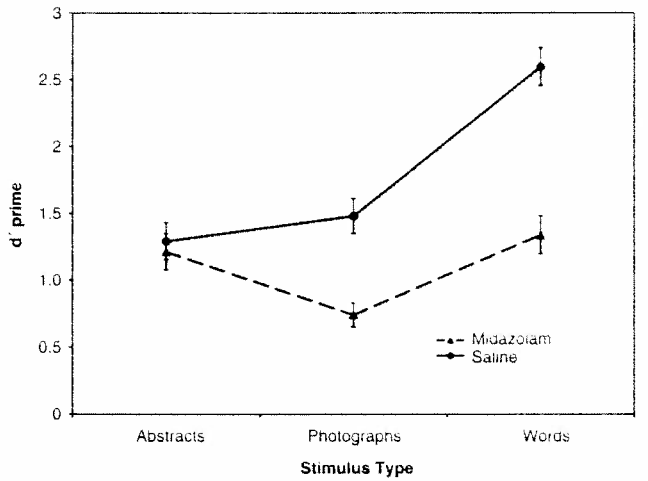

Figure 14.4 Memory sensitivity as a function of drug condition and stimulus type. Reproduced from L. M. Reder et al., Drug-induced amnesia hurts recognition, but only for memories that can be unitized. *Psychological Science*, 2006, *17*(7), 562–567.

affect binding and creating new associations, so abstract stimuli are relatively unaffected by the drug condition (Reder et al., 2006). Although photographs of unknown faces or places are easy to bind to context with generic labels, these labels will have a "high fan," having been associated with many other stimuli. Their "high fan" status will not enable discrimination between a studied picture of an unknown city scene with a foil that generates the same label.

Figure 14.5 presents the same data as Figure 14.4 as a function of hits and false alarms. Notably, there are many more hits for words than the pictures and photographs in the saline condition. We attribute the advantage for words over photographs and pictures to recollection. That is, words have a stable conceptual representation in memory and therefore can be bound to an episode node. When binding is not possible, all three types of stimuli rely on familiarity and in the midazolam condition, the three stimulus types have the same hit rate. Consistent with differential ability to use recollection for different classes of stimuli, the difference in hit rate was much smaller for photographs than words and was very small for abstract pictures. Regardless of drug condition during encoding, subjects were unable to make recollection-based judgments for abstract pictures during the test phase. As discussed, the

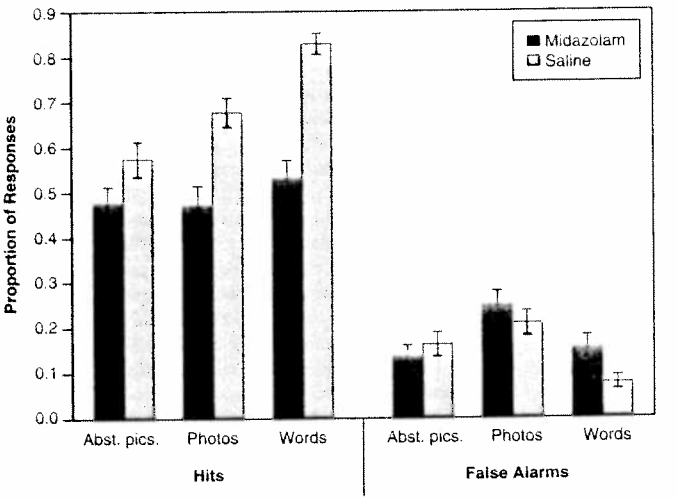

Figure 14.5 Hits and false alarms as a function of drug condition and stimulus type. Reproduced from L. M. Reder et al., Drug-induced amnesia hurts recognition, but only for memories that can be unitized. *Psychological Science*, 2006, *17*(7), 562–567.

inability to generate a unique label for photographs of unknown faces or places made accurate recollection difficult. First, to the extent that the label was generic (e.g., "blond female" or "mountain stream"), the fan from the label might be high, making it more difficult to access the episode node (see Reder, Donavos, & Erickson, 2002; Reder et al., 2000); second, a generic label could apply to foils as well as targets and lead to spurious recollection as well as spurious familiarity based responding.

In Example 1, we demonstrated that midazolam-induced amnesia had a detrimental effect on some forms of implicit memory performance (contextual cuing) that requires binding of spatial relations, but not others (task speed up) with practice at the skill. In the present example, we provided support for the flip side: midazolam impaired only those explicit memories that were based on association-specific recollections, while subjects had the same memory performance for familiarity-based judgments (see Reder et al., 2009). The present results demonstrate the importance of binding and association for accurate memory recall and indicate that midazolam negatively affects memory by preventing the creation of associations and preventing the recollection of contextual information.

Example 3: The link between consolidation and forgetting

Retrograde facilitation under midazolam (Reder et al., 2007)

Recent memory research has considered the role of consolidation in forgetting previously processed information. Wixted (2004) posited that memory theorists have failed to appreciate the role of consolidation in explaining whether or not information is forgotten. Consolidation requires effort, and when mental exertion interferes with consolidation, this exertion can lead to forgetting. On a neurological level, Wixted (2004) suggested that the limited capacity of the hippocampal system may also contribute to the impact of interference on memory formation. He proposed that a major source of forgetting is the disruption of consolidation that occurs when new incoming information competes with the older information for limited hippocampal resources. An example of support he offered for his position came from a benzodiazepine study that was purported to show *retrograde facilitation* for information acquired prior to the injection. This facilitation was a comparison of recall performance of items from the list studied prior to injection for the saline (control) compared with the benzodiazepine group. Those subjects who received saline recalled more of the second list items than those who received the benzodiazepine, but they recalled fewer items from the first list. Reder et al. (2007) tested an alternative explanation for the difference in performance on the first list that did not postulate a role for differential consolidation: Better performance on the pre-injection list was the result of less interference from the second list that was very poorly recalled in the amnesia group.

To test our explanation, we used a modified version of the experiment

described by Wixted (2004). We used a cued recall paradigm involving three lists of word pairs, one list presented prior to injection, two lists studied post injection. Each list (of 45 word pairs) consisted of three types of word pairs (15 of each type): one third of the pairs were repeated across all three lists (practice pairs); one third of the pairs (control pairs) were only shown on one of the lists; the final third of the word pairs (interference pairs) were shuffled from list to list such that the left-hand word of a pair (stimulus word) was reassigned to a different right-hand word (response term) across lists. If the effect of midazolam was to enhance consolidation of material learned prior to the injection, then all types of pairs should benefit equally. On the other hand, if the effect of midazolam is to block the formation of new associations, then the benefit of the drug condition should be greatest for those word pairs that would otherwise experience the most interference from the formation of competing associations (the interference pairs).

For each subject, words were randomly paired with other words, as well as randomly assigned to pair condition and list. The 45 word pairs on a list were presented first for two seconds each and were tested individually by asking the subject to type the response term to the stimulus word. After the attempted recall, the word pair was re-studied for three seconds and another pair was tested. Each pair was tested twice in this manner for each list.

After completing the study–test cycle for List 1, subjects received an injection of either saline or midazolam. They then studied a new list of paired associates followed by two study–test cycles for List 2, followed by the same procedure for List 3. After studying all three word lists, subjects were given a snack, and their monitoring devices were removed. After the snack and rest, subjects were given a final cued-recall test consisting of all word-pairs from the three lists in a random order. In this case, cued recall included both the stimulus word and the list number in which the pair had been studied. For practice pairs, any of the three lists could be mentioned, but one was randomly selected with the constraint that all three lists were tested equally often for the practice pairs.

Figure 14.6 shows the acquisition data for the three lists of words. Understandably, there were no differences for drug condition for List 1, which was studied pre-injection. Likewise, there were no differences among pair types, since the differences among types of pairs was defined in relation to all three lists. However, the data for List 2 and List 3 do show differential effects of drug condition and stimulus type. When administered midazolam, subjects had difficulty learning word pairs. Notably, this difficulty was only seen for interference and control pairs. Since the practice pairs were studied before the injection, they were less affected by midazolam. Figure 14.7 presents the final recall data. Subjects were reliably better at recall in the saline than the midazolam condition. Recall was also best for practice pairs and worst for interference pairs.

Of particular interest is the comparison of recall for List 1 items in the midazolam versus the saline condition. Specifically, would we replicate the

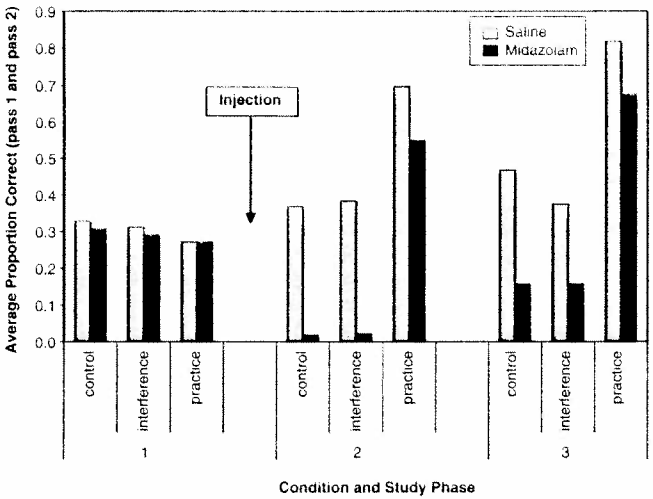

Figure 14.6 Acquisition of word pairs as a function of drug condition and type of pair. Adapted from Reder et al. (2007).

result of retrograde facilitation in the presence of midazolam? When Lists 2 and 3 were studied in the midazolam condition, the List 1 control pairs did not differ from the List 1 interference pairs; however, when the pairs for Lists 2 and 3 were studied in the saline condition, performance on interference pairs from List 1 was not as good as recall for the control pairs.

Retrograde facilitation had been defined as the difference in performance between the midazolam and saline condition performance. Such facilitation was only found for the interference word pairs, even though performance on those pairs did not differ from performance on the control pairs. The same pattern was observed with latency. List 1 word pairs that were studied prior to a saline injection were recalled slower if they ended up being interference pairs than if they were control pairs. On the other hand, word pairs that were studied prior to a midazolam injection were responded to equally fast, regardless of the assignment of those pairs to control vs. interference condition. Our explanation for this pattern of findings is that under midazolam subjects did not suffer from the effects of interference because they could not form new associations to words studied after the injection. Rather than interpreting the pattern as *retrograde facilitation* due to enhanced consolidation, the pattern can be understood as differing amounts of interference. We modeled these effects, fitting the acquisition and recall accuracy, errors in

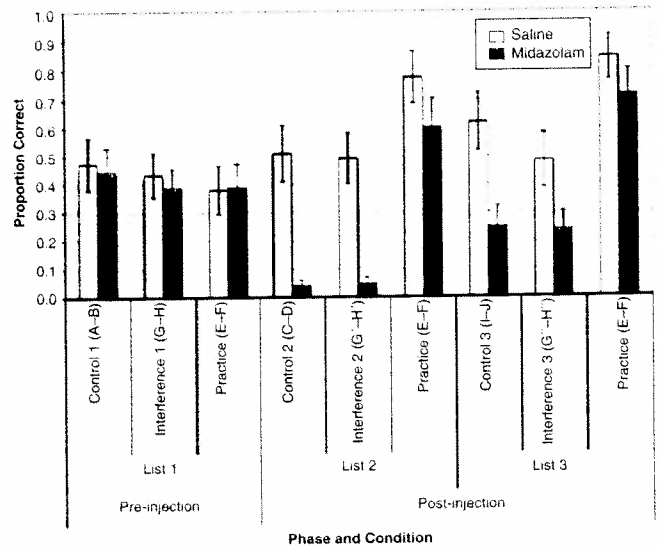

Figure 14.7 Final recall of word pairs as a function of drug condition and type of pair. Adapted from Reder et al. (2007).

recall, and latencies for both the drug and the saline conditions (see Figures 14.8 and 14.9). We explained the pattern by assuming different probabilities of forming an association between the words in a pair and between the pair and the list and general context. We assumed that the probability of forming a new association from the stimulus word to the response term and to the list context and general experimental context is affected by midazolam, which affects the hippocampal system. As the drug wears off, the probability of forming a new association increases. There was no need to postulate a consolidation mechanism to get excellent fits (model fits can be seen at http://memory.psy.cmu.edu/model_fits.php).

Conclusion

Memory is a complex system that performs many functions and relies on a range of neurological structures. The system is highly integrated, and damage to different parts of the brain that results in amnesia disrupts the same underlying functional loop. The specific memory deficits seen in drug-induced anterograde amnesia can provide further understanding of the

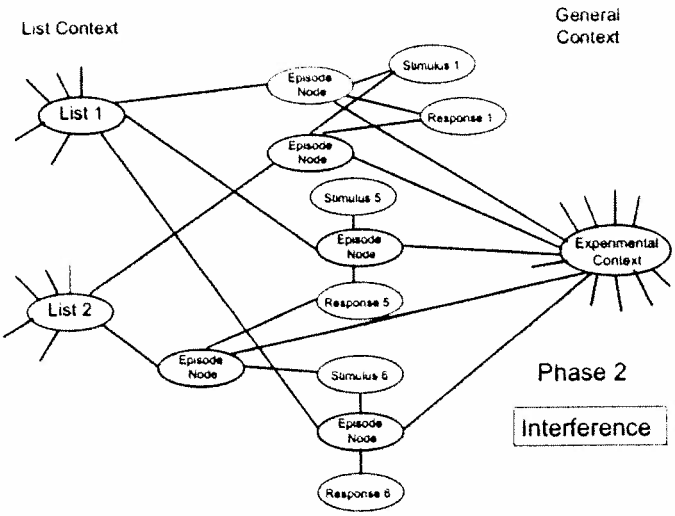

Figure 14.8 Stimulus and response model. Adapted from Reder et al. (2007).

human memory system, both for individuals with memory deficits and for those with normally functioning systems. Memory studies employing midazolam can elucidate the roles of different aspects of the memory process, while defining which aspects are specifically targeted and spared by anterograde amnesia. The drug's focused impairment of binding (i.e., association formation) can make it especially useful for a range of experimental tasks.

The controlled administration of midazolam to create anterograde amnesia in experimental settings can be particularly useful to test various hypotheses concerning memory functioning. It is also potentially useful for isolating the brain regions that appear to be essential for memory function by combining the use of the drug with neuroimaging. By using midazolam, subjects can serve as their own controls, and we can study the same brain with and without anterograde amnesia, thus eliminating the individual differences that make it difficult to study patients with organic amnesia. The examples presented demonstrate how midazolam can be used to specifically investigate current issues in the field of memory research.

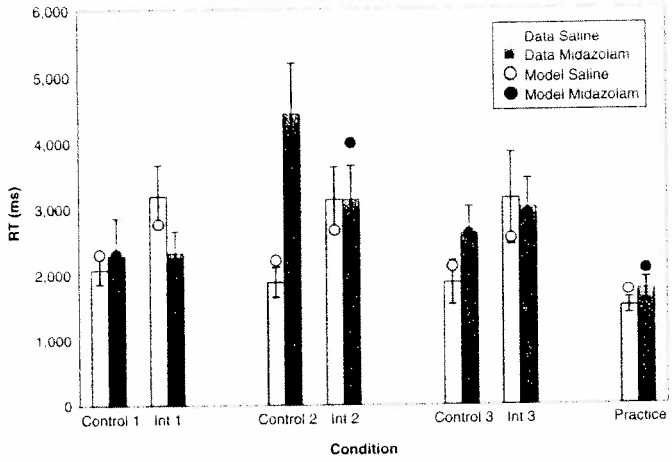

Figure 14.9 Model fits for final test response time as a function of drug condition, type of pair, and list. Reproduced from L. M. Reder et al., Retrograde facilitation under midazolam: The role of general and specific interference. *Psychonomic Bulletin and Review*, 2007, *14*(2), 261–269.

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Section IV

Fundamental general issues