# When Memory Fails, Intuition Reigns: Midazolam Enhances Implicit Inference in Humans

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Abstract:

People often make logically sound decisions using explicit reasoning strategies, but sometimes it pays to rely on more implicit "gut-level" intuition. The transitive inference paradigm has been widely used as a test of explicit logical reasoning in animals and humans, but it can also be solved in a more implicit manner. Some have argued that the hippocampus supports relational memories required for making logical inferences. Here we show that the benzodiazepene midazolam, which inactivates the hippocampus, causes profound explicit memory deficits in healthy participants, but actually enhances their ability in making implicit transitive inferences. These results are consistent with neurocomputational models of the basal ganglia/dopamine system that learn to make decisions based on positive and negative reinforcement. We suggest that disengaging the hippocampal explicit memory system can be advantageous for this more implicit form of learning.

When told that Zoey is older than Jillian who is older than Allison, one can then infer that Zoey is older than Allison. Some have argued that this ability to flexibly draw novel conclusions based on prior premises — to make transitive inferences in this case — depends on specialized neural properties of the hippocampus (Dusek & Eichenbaum, 1997; Eichenbaum, 2004). These authors showed that even rats can make transitive judgments, but only if their hippocampal system is intact. Others have suggested that simple associative mechanisms can explain transitive responding in animals, and that these mechanisms are independent of (but interact with) the hippocampus (Frank, Rudy, & O'Reilly, 2003; Frank, Rudy, Levy, & O'Reilly, 2005a; Frank, Seeberger, & O'Reilly, 2004). This explains why pigeons with hippocampal damage continue to respond transitively (Strasser, Ehrlinger, & Bingman, 2004), and why humans can do so even when they are prevented from becoming explicitly aware of hierarchical relationships (and therefore from employing logical reasoning) (Frank et al., 2005a). Here we investigate in humans the effects of the drug midazolam, which has potent amnestic properties and transiently deactivates the hippocampus (Thomas-Anterion et al., 1999; Hirshman et al., 2001; Rovira & Ben-Ari, 1993; Poncer et al., 1996; Kristiansen & Lambert, 1996; Kobayashi et al., 2004). We show that midazolam-induced amnesia is accompanied by a marked *enhancement* in implicit transitive inference performance. Thus our results strongly challenge the notion that the hippocampal explicit memory system is necessary for making relational judgments, and instead suggest that hippocampal disengagement allows the implicit system to have full reign on behavior.

Transitive inference (TI) is typically evaluated in the laboratory by first asking participants to select one of two stimuli in a series of "premise" pairs. The correct choice is learned via error feedback. More concretely, four pairs are presented (A+B-, B+C-, C+D-, D+E-; where +/- indicate the reinforced and non-reinforced choice, respectively). Participants are then presented with the novel test pairs AE and BD. Successful AE performance is trivial, because A is always reinforced and E is never reinforced. In contrast, because B and D are equally often reinforced during training, the selection of B over D is taken to indicate that an inference has been made. The question of interest is which neural mechanisms support such inference-like behavior?

Insight into this question comes from analysis of exactly what participants learn during the training procedure. In selecting among the various premise pairs, participants can either explicitly memorize the correct choice associated with each pair, or they can implicitly assign re-

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inforcement values to each of the stimulus elements, and just choose the one with the higher value. Computational models of transitive responding suggest that these two processes occur in parallel, and are formally described by the use of *conjunctive* and *elemental* representations (Frank et al., 2003; Siemann & Delius, 1998), which may be encoded by complementary neural systems. The hippocampus supports explicit memorization of the conjunction of each stimulus pair (AB, BC, etc) by automatically and rapidly binding together individual elements of an event (O'Reilly & Rudy, 2001; Frank et al., 2003; Atallah, Frank, & O'Reilly, 2004; Davachi & Wagner, 2002). In parallel, the basal ganglia/dopamine system learns an implicit elemental reinforcement value for each stimulus depending on how often its selection is associated with positive vs. negative reinforcement (Frank, 2005; Frank et al., 2005a; Frank et al., 2004).

Correct performance on the novel test pair (e.g., BD) depends on the elemental learning system, because this conjunction is novel, but the elements are not (Frank et al., 2003; Siemann & Delius, 1998; Frank et al., 2005a). Although the B and D stimuli are equally often associated with positive and negative reinforcement, they can nevertheless develop asymmetrical associative strengths such that B has a net positive value while D has a negative value (Frank et al., 2003; Frank et al., 2005a; Siemann & Delius, 1998; von Fersen et al., 1991). In brief, because the "anchor" pairs AB and DE can be solved by simply learning that A is always correct and E is never correct, one does not have to learn anything about the companion stimuli (B in AB, and D in DE). As a result, B can take on a more positive association to support BC performance, while D becomes more negative to support CD. Therefore, participants may choose B over D simply because B has a higher dopamine reinforcement value, without having to explicitly perform any logical reasoning. This mechanism explains why participants can respond transitively even when they are prevented from becoming explicitly aware of logical structure (Frank et al., 2005a; Greene et al., 2001), and is consistent with the effects of dopaminergic manipulation on learning in a TI task (Frank et al., 2004). In contrast, a conjunctive strategy that treats each stimulus pair as a distinct event may rapidly produce correct training performance, but would not by itself lead to transitive responding: upon presentation of the BD test pair, the participant does not have a stored memory representation from which to retrieve the correct response. Thus our account suggests that successful choice of B over D in non-explicit TI tasks does not depend on the hippocampus, but on reinforcement learning systems that assign differential associative strengths to these stimuli (Frank et al., 2005a).

This computational framework led us to the counter-intuitive prediction that inactivating the hippocampal explicit memory system would be associated with enhanced implicit transitive inference performance. This prediction stems from various observations that basal ganglia and hippocampal memory systems interact competitively (Packard & McGaugh, 1996; Poldrack & Packard, 2003; Atallah et al., 2004; Poldrack & Rodriguez, 2004; Poldrack et al., 2001; Seger & Cincotta, 2005), such that deactivating hippocampus should lead to greater recruitment of the implicit basal ganglia system. In other words, the more participants memorize stimulus conjunctions during training, the less they may have to learn about individual stimulus reinforcement values, and therefore the worse they will perform on novel test pairs in TI tasks (Siemann & Delius, 1998). This has been formalized in our models, as learning about conjunctive hippocampal representations can actually block learning of elemental associations (Frank et al., 2003).

The present experiments were motivated by the observation that midazolam, by acting on GABA-A receptors densely expressed in the hippocampus (Montpied et al., 1988), transiently but profoundly impairs explicit memory processes while leaving implicit memory intact (Thomas-Anterion et al., 1999). We tested 23 participants in a double-blind within-subjects design. Each participant was tested once on midazolam and once on saline (both intravenous injections; order counterbalanced). To minimize potential learning effects across session, two different cognitive learning tasks were used in each session, with the Session 1 task selected at random. Participants performed the TI task in one session, and a "probabilistic selection" (PS) task in the other session (Frank et al., 2004). This task was used as a control: because probabilistic learning recruits the striatum, and actually disengages the hippocampus (Poldrack et al., 2001), we hypothesized that midazolam would have minimal effects on PS performance. In contrast, midazolam should improve TI test performance by preventing participants from memorizing the stimulus pairs and encouraging greater implicit learning of reinforcement value. Finally, to verify that midazolam was effective in inducing amnesia, following each task participants were given a list of names and were told to remember them for a subsequent recall test.

## Methods

### *Participants*

Our sample was 23 healthy participants, 15 females and 8 males between the ages of 18 and 28 (M = 21).

## *Procedures*

Procedures were approved by the Scientific Advisory Committee of the University of Colorado Health Sciences Center, and the University Human Research Committee. We used a within-subjects double blind design. Participants reported to the Boulder GCRC for lab tests and a medical exam by a physician. Those who met the study criteria and who received medical approval then proceeded to the experimental sessions, which were separated by 1-2 weeks.

## *Drug Administration*

An intravenous catheter was inserted and participants were administered an injection of .03mg/kg of body weight of midazolam diluted to a volume of 10 ml or 10 ml of saline. The injection was given over 2 minutes, with a maximum dose of 2.5mg. 20 minutes after drug administration, cognitive learning tests were administered, followed by the study phase of the explicit name recall task.

## *Stimuli*

Stimulus items were characters selected from the Japanese Hiragana script, as in Greene et al. (2001; Frank et al., 2005a; Frank et al., 2004). The assignment of Hiragana characters to hierarchical elements A-E was randomized across participants (Figure 1a shows one example of a stimulus hierarchy). The characters were presented on a 19" color monitor in 36-point font size. Different Hiragana characters were used across the two tasks.

## *Transitive Inference Task Procedures*

Prior to training, instructions were given as follows: 'Two black figures will appear simultaneously on the computer screen. You are to select the "correct" figure as quickly and accurately as possible.' No instructions were given that would lead the participant to believe that the stimuli were ordered hierarchically.

For each stimulus pair, the "z" and "m" keys were used to select the stimulus on the left or right, respectively. The position of each character was counterbalanced across trials. Feedback was provided with the word "Correct!" written in blue letters or the word "Incorrect" written in red letters. These were the same methods used by Greene et al. (2001; Frank et al., 2005a; Frank et al., 2004).

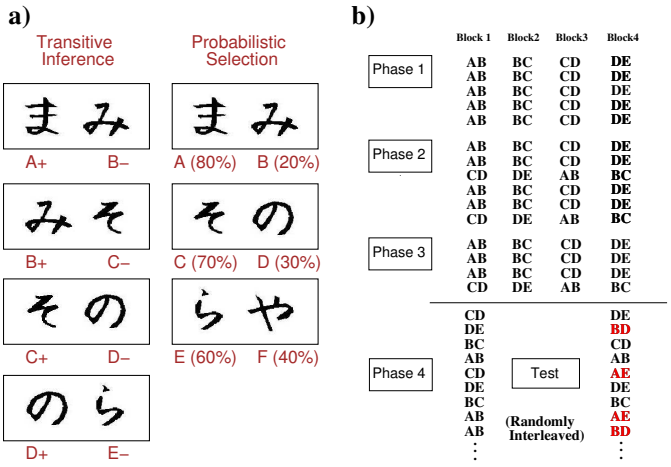


Figure 1: **a)** Example stimulus pairs (Hiragana characters) used in both cognitive learning tasks, designed to minimize verbal encoding. In Transitive Inference, feedback is deterministic as indicated by the +/- signs for each stimulus. In Probabilistic Selection, the frequency of positive feedback for each choice is shown. **b)** The four training phases and the test phase of the TI experiment, showing the number of trials per block in each phase, and where distractor trials were placed.

Training consisted of three phases of blocked trials, followed by a fourth phase of randomly interleaved trials. Each phase was terminated after criterion performance of at least 75% correct across all pairs, and at least 60% on each individual pair. In the first phase, the premise pairs were presented in blocks of 5 trials, such that the first block consisted of AB trials, the second block consisted of BC trials, and so on. In the second phase, blocks of 6 trials were used, but "distractor" trials were inserted into a minority of trials within and between each block (see Figure 1b). These trials disrupt the descending order of hierarchical presentation, making the stimulus hierarchy less obvious, preventing participants from becoming explicitly aware of the stimulus hierarchy (Frank et al., 2005a). A similar procedure was used for phase 3, which included 4 trials per block, while in phase 4 stimulus pairs were randomly interleaved (no hierarchical order at all), for a total of 20 trials before criterion performance was evaluated. If criterion was not met, the random sequence was repeated.

The test phase was similar to the final training phase in that all pairs were randomly interleaved. However, no feedback was provided and the novel test pairs AE and BD were added to the mix of randomly ordered pairs. All pairs were presented 6 times each.

### *Probabilistic Selection Task Procedures*

The Probabilistic Selection (PS) task tests the extent to which people implicitly learn more from positive versus negative reinforcement (Frank et al., 2004; Frank, Woroch, & Curran, 2005b). Three different stimulus pairs (AB, CD, EF) are presented in random order and participants learn to choose one of the two stimuli based on visual feedback. A choice of stimulus A leads to correct (positive) feedback in 80% of AB trials, whereas a B choice leads to incorrect (negative) feedback in these trials (and vice-versa for the remaining 20% of trials). Stimulus C is correct in 70% of CD trials, while E is correct in 60% of EF trials. Over the course of training participants learn to choose stimuli A, C and E more often than B, D, or F. The position of the correct stimulus was randomized across trials, and the assignment of Hiragana character to hierarchical element A-F was randomized across participants.

We enforced a performance criterion (evaluated after each training phase of 60 trials) to ensure that all participants were at the same performance level before advancing to each test segment. Because of the different probabilistic structure of each stimulus pair, we used a different criterion for each (65% A in AB, 60% C in CD, 50% E in EF). 2/11 participants on midazolam, and 3/11 on saline, reached criterion in Phase 2, while the rest did so in Phase 3. After reaching this criterion, participants were subsequently tested with the same training pairs, in addition to all novel combinations of stimuli, in random sequence. They were instructed (prior to the test phase) to use "gut instinct" if they did not know how to respond to these novel pairs. Each test pair was presented 6 times, and no feedback was provided.

### *Name Recall Procedures*

In each session, participants studied a series of 10 names presented sequentially in random order, for four seconds each on a computer monitor. Different lists of names were used across sessions. After a retention interval of 30 minutes, participants attempted free recall of the studied names, writing as many names as he/she could recall on an answer sheet within 2 minutes.

## Results

Midazolam profoundly impaired explicit memory processes (Figure 2a). Compared with saline, midazolam was associated with a significant deficit in the number of

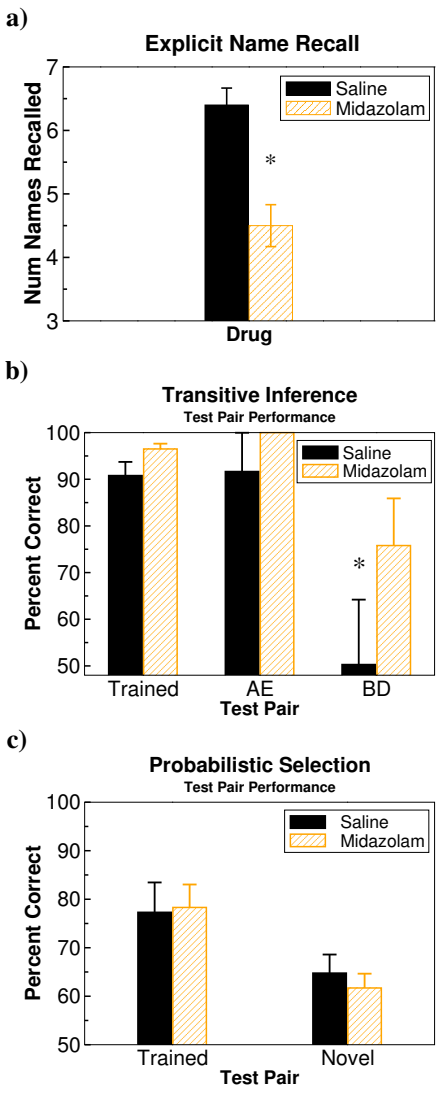


Figure 2: **a)** Explicit name recall results. **b)** Transitive inference performance during the test phase, showing performance on the premise pairs (AB, BC, CD and DE) and novel test pairs (AE and BD). **c)** Probabilistic selection test phase performance on training pairs (AB, CD, EF) and all novel combinations (AC, BC, DF, etc). Error bars reflect SEM.

names recalled in the recall test ($F[1,22] = 13.8$, $p_{rep} = .99$, $\eta^2 = 0.38$), and these effects were similar regardless of the learning task performed in that session (task by drug interaction $F[1,22] = 0.25$). In contrast, midazolam effects on novel test performance in the reinforcement learning tasks interacted with the type of task ($F[1,22] = 4.5$, $p_{rep} = .885$, $\eta^2 = 0.17$). Notably, midazolam was associated with strikingly enhanced transitive inference performance on novel test pairs AE/BD (Figure 2b, $F[1,22] = 5.3$, $p_{rep} = .91$, $\eta^2 = .19$), an effect that was also significant when considering the BD test alone ($F[1,22] = 4.1$, $p_{rep} = .877$, $\eta^2 = .16$). There was no effect of midazolam on novel test performance in the probabilistic selection task (Figure

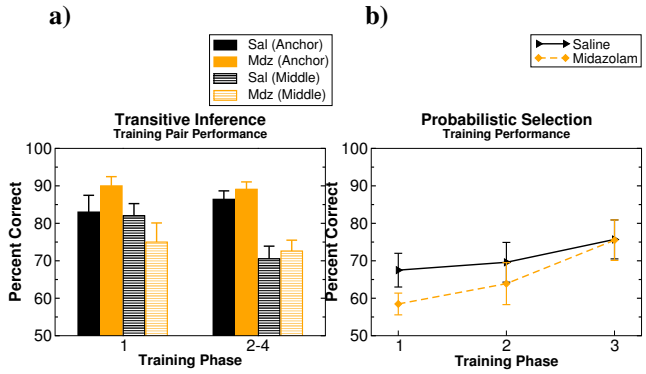


Figure 3: **a)** Training pair performance as a function of training phase (early, late) in the Transitive Inference task. **b)** Probabilistic Selection training performance as a function of training phase. Error bars reflect SEM.

2c, F[1,22] = 0.74). These results are consistent with the conclusions that: (a) midazolam impairs explicit memory processes that depend on the hippocampus; (b) the hippocampus is not necessary and actually hinders transitive responding in associative learning tasks; and (c) the hippocampus is not involved in probabilistic learning.

Our hypothesis that the hippocampus is important for rapidly memorizing stimulus conjunctions makes additional predictions for learning patterns during the training phases of both tasks. For transitive inference, the end "anchor" pairs AB and DE are the easiest to learn because stimulus A is always correct and stimulus E is always incorrect. The middle pairs (BC, CD) are more difficult and may benefit from explicit memorization of stimulus conjunctions to prevent interference. We hypothesized that midazolam should impair memorization of stimulus conjunctions and would be associated with relatively worse performance in the middle pairs. In contrast, the tendency for participants to rely on reinforcement learning systems under midazolam should be associated with relatively *better* performance on the anchor pairs. We further hypothesized that these effects would be apparent very early in training, due to the known role of the hippocampus in automatically and rapidly encoding stimulus conjunctions in very few trials (e.g., O'Reilly & Rudy, 2001). After multiple training trials, the differential reinforcement values learned for each stimulus item A-E should be sufficient to perform well on all pairs.

To test this idea, we performed a 2x2x2 repeated measures ANOVA on drug, training pair (anchor, middle) and training phase (1 vs 2-4). As hypothesized, midazolam was associated with relatively better performance on anchor pairs (AB, DE) than middle pairs (BC and CD) in the early stages of training (Figure 3a). Overall, performance on anchor pairs was better than that on middle pairs (main effect training pair type: F[1,20] = 52.9, $p_{rep} > .998$, $\eta^2$ = .73). Notably, the differentiation between anchor and middle pair performance was greater for midazolam than for saline (drug*pair interaction: F[1,20] = 5.6, $p_{rep}$ = .914, $\eta^2$ = .22), which further interacted with training phase (drug*pair*phase interaction: F[2,20] = 9.2, $p_{rep}$ = .987, $\eta^2$ = 0.48). Planned contrasts confirmed that the drug*pair interaction was significant in training phase I (F[1,20] = 5.94, $p_{rep}$ = .93, $\eta^2$ = .23), but not across all remaining phases (F[1,20] = 0.1). In particular, in phase I anchor performance was better than middle performance under midazolam (F[1,20] = 7.8, $p_{rep}$ = 0.95, $\eta^2$ = .28), but not saline (F[1,20] = 0.58), and midazolam anchor performance was marginally better than saline (F[1,20] = 3.15, $p_{rep}$ = 0.82, $\eta^2$ = .14). These particular interactions, which were predicted by our computational framework, were found despite no main effect of drug on overall training performance (F[1,20] = 0.1), and no interaction between drug and training phase (F[1,20] = 0.02). Overall, these results are consistent with the hypothesis that participants under midazolam relied more on reinforcement learning about individual stimuli (as evidenced by better anchor pair performance), but were relatively impaired at rapidly binding together stimulus elements into conjunctive pairs (as evidenced by impaired middle pair performance). This result is also consistent with recent reports that midazolam impairs learning of configurations in a visual search task (Park et al., 2004).

Similar indications of a role for the hippocampus in rapid learning were also found in the probabilistic selection task (Figure 3b), where midazolam showed a trend toward impairing performance in the first training phase (F[1,20] = 2.8, $p_{rep}$ = .81, $\eta^2$ = .12), but not in the remaining two phases (F[1,20]= 0.07). In addition, performance was better than chance (50%) in the first 10 trials of experience with each training pair for the saline condition (t[1,10] = 3.4, $p_{rep}$ = 0.965), but not for midazolam (t[1,10] = 1.4, n.s). These results are consistent with the notion that probabilistic learning does not depend on the hippocampal explicit memory system, but that there is a subtle benefit of explicit memory in early training periods (i.e., before the implicit system can integrate over multiple trials).

## Discussion

Taken together, our results provide strong support for the idea that the hippocampal explicit memory system is not necessary for making transitive inferences. This is consistent with predictions from our computational

models which suggest that reward associations to individual stimulus elements, supported by the basal ganglia/dopamine system, are critical for correct performance on the novel test pairs (Frank et al., 2003; Frank, 2005; Frank et al., 2004). Furthermore, our detailed analysis of midazolam effects on training performance is consistent with the idea that the hippocampus is critical for rapid learning of stimulus conjunctions (O'Reilly & Rudy, 2001). Overall, these results support the notion that the basal ganglia and hippocampus make distinct contributions to memory (Squire, 1992). Finally, our observation that midazolam actually enhanced transitive inference performance suggests that disengagement of the hippocampal explicit memory system may lead to enhanced basal ganglia learning, supporting the notion that these memory systems interact competitively, and consistent with observations that hippocampal lesions enhance performance in striatal tasks (Packard & McGaugh, 1996; Packard et al., 1989; Poldrack & Packard, 2003; Atallah et al., 2004; Poldrack & Rodriguez, 2004; Poldrack et al., 2001; Seger & Cincotta, 2005).

This account is also consistent with several recent findings. First, neuroimaging studies show that the hippocampus is more activated by conjunctive items that had been studied together than by two individually studied items that were re-combined (Giovanello et al., 2004), suggesting that it is more involved in binding elements together than in flexibly recombining them. That it is not required for flexibility is further supported by observations that both rats and humans with hippocampal damage perform normally in a novelty transfer task designed to test for representational flexibility (Driscoll et al., 2004; Bayley et al., 2005). Similarly, pigeons with hippocampal damage showed intact transitive responding in a TI task (Strasser et al., 2004). Finally, evidence for dopaminergic involvement in TI performance is suggested by differential patterns of learning in medicated and non-medicated Parkinson's patients, as predicted by our computational model of the striatal dopaminergic system (Frank, 2005; Frank et al., 2004).

A critical unresolved question concerns the contradictory findings with earlier reports that hippocampal lesions impaired transitive inference in rats (Dusek & Eichenbaum, 1997). One possible answer suggested by our computational model is that the hippocampus can make a measurable contribution in the relatively early stages of training (via interactions with the elemental learning system) (Frank et al., 2003). Perhaps the experiments differed in the effective amount of training? It is also possible that rats in these earlier studies somehow adopted a different, hippocampally-mediated strategy involving the use of pattern completion or relational memories in the hippocampus to perform a more explicit form of inference, as suggested by Eichenbaum and colleagues (Dusek & Eichenbaum, 1997; Eichenbaum, 2004), and in some of our earlier work (O'Reilly & Rudy, 2001).

In humans, where it is easier to manipulate and evaluate strategy use, very different patterns of behavior hold if one manipulates the extent to which people become explicitly aware of the hierarchical structure of the TI task (Frank et al., 2005a). When participants are explicitly aware, they behave qualitatively different from the implicit condition studied here, and the hippocampus and prefrontal cortex are likely critical for remembering and manipulating the individual premises to support rational decision making. Indeed, neuroimaging studies of humans performing explicit logical reasoning in TI tasks consistently implicate the hippocampus and prefrontal cortex (Nagode & Pardo, 2002; Acuna, Eliassen, Donoghue, & Sanes, 2002; Heckers, Zalesak, Weiss, Ditman, & Titone, 2004). Thus the hippocampus can be required for humans to quickly transfer newly learned associations to novel situations (e.g., Myers et al., 2003), but is not required for transfer when associations are ingrained habitually over multiple experiences (Bayley et al., 2005).

It is reasonable to question our assertion that midazolam preferentially deactivates the hippocampus, while sparing function in implicit associative areas (e.g., striatum). While we cannot discount the possibility that the drug affects multiple brain regions, we believe this simplification is valid. Midazolam is a benzodiazepene that increases the binding of $\gamma$-aminobutyric acid (GABA) to GABA-A receptors. Although GABA-A receptors are expressed throughout the brain, they are particularly densely expressed in the hippocampus, and far greater than in striatum (Montpied et al., 1988). Neurophysiologically, it has been shown that midazolam increases inhibitory currents in the CA1 and CA3 regions of the hippocampus (Rovira & Ben-Ari, 1993; Poncer et al., 1996; Kristiansen & Lambert, 1996; Kobayashi et al., 2004) and inhibits hippocampal long-term potentiation (Evans & Viola-McCabe, 1996). Psychologically, various lines of evidence suggest that midazolam impairs hippocampal-dependent explicit memory processes, while sparing other forms of memory (Hirshman et al., 2001; Arndt et al., 2004; Park et al., 2004; Thomas-Anterion et al., 1999; Hirshman et al., 2002). PET studies have shown that midazolam decreases blood flow to the hippocampus and left prefrontal cortex, which interact with each other in explicit memory and reasoning processes, with no effect on striatal areas (Reinsel et al., 2000; Bagary et al., 2000). Thus the most parsimonious explanation of our results is that by disengaging the hippocampus, midazolam induced explicit memory deficits and released the competitive dy-

namic with associative learning systems needed for implicit flexible behavior. Future research is needed to determine whether striatal / dopaminergic systems are increasingly engaged under midazolam administration.

In conclusion, it seems clear that there are multiple mechanisms for making inferences and decisions, with some made on the basis of explicit reasoning processes, and others on the basis of implicit reward associations. We suggest that the brain areas associated with implicit reward-association decisions are dissociable from those supporting the explicit forms. Future work will hopefully provide greater elaboration of the nature of these different systems, and the extent to which they operate across different species. Nevertheless, our findings suggest that it may be useful to rely on intuition to guide decisions, particularly when explicit memory fails.

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