

Research Article

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 researchers 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 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 through 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 infer that Zoey is older than Allison. Some researchers 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 have shown that even rats can make transitive judgments, but only if their hippocampal system is intact. Other researchers 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, Levy, & O'Reilly, 2005; Frank, Rudy, & O'Reilly, 2003; Frank, Seeberger, & O'Reilly, 2004). This explains why pigeons with hippocampal damage continue to respond transitively (Strasser, Ehrlinger, & Bingman, 2004), and why humans can respond transitively even when they are prevented from becoming explicitly aware of hierarchical relationships (and therefore from employing logical reasoning; Frank, Rudy, et al., 2005). In the study reported here, we investigated in humans the effects of the drug midazolam, which has potent amnesic properties and transiently deactivates the hippocampus (Hirshman, Passannante, & Arndt, 2001; Kobayashi, Fujito, Matsuyama, & Aoki, 2004; Kristiansen & Lambert, 1996; Poncer, Durr, Gahwiler, & Thompson, 1996; Rovira & Ben-Ari, 1993; Thomas-Anterion, Koenig, Navez, & Laurent, 1999). We show that midazolam-induced amnesia is accompanied by a marked enhancement in implicit transitive inference (TI) 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 is typically evaluated in the laboratory by first asking participants to select one of two stimuli in each of a series of “premise” pairs. The correct choices are learned via error feedback. More concretely, four pairs are presented: A+B−, B+C−, C+D−, and D+E− (the plus and minus signs indicate the reinforced and nonreinforced choice, respectively). After learning the correct choices, participants are presented with the novel test pairs AE and BD. Successful AE performance is trivial, because A was always reinforced during training, and E was never reinforced. In contrast, because B and D were reinforced equally often 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?

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Insight into this question comes from analysis of exactly what participants learn during the training procedure. In choosing between the members of a premise pair, participants can either explicitly memorize the correct choice or implicitly assign reinforcement value to each of the stimulus elements and choose the one with the higher value. Computational models of transitive responding suggest that these two processes occur in parallel and describe them formally 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 the event (Atallah, Frank, & O'Reilly, 2004; Davachi & Wagner, 2002; Frank et al., 2003; O'Reilly & Rudy, 2001). 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 versus negative reinforcement (Frank, 2005; Frank, Rudy, et al., 2005; Frank et al., 2004).

Correct performance on a novel test pair such as BD depends on the elemental learning system, because the conjunction is novel, but the elements are not. That is, although the B and D stimuli are associated with positive and negative reinforcement equally often during training, they may nevertheless develop asymmetrical associative strengths such that B has a net positive value and D has a negative value (Frank, Rudy, et al., 2005; Frank et al., 2003; Siemann & Delius, 1998; von Fersen, Wynne, Delius, & Staddon, 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 and D. As a result, B can take on a positive association to support BC performance, and D becomes negative to support CD performance. Therefore, participants may choose B over D simply because B has a higher dopamine reinforcement value; they do not have 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, Rudy, et al., 2005; Greene, Spellman, Dusek, Eichenbaum, & Levy, 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, this account suggests that successful choice of B over D in nonexplicit TI tasks depends not on the hippocampus, but on reinforcement learning systems that assign differential associative strengths to these stimuli (Frank, Rudy, et al., 2005).

This computational framework led us to the counterintuitive prediction that inactivating the hippocampal explicit memory

system would enhance implicit TI performance. This prediction stems from various observations that the basal ganglia and hippocampal memory systems interact competitively (Atallah et al., 2004; Packard & McGaugh, 1996; Poldrack et al., 2001; Poldrack & Packard, 2003; Seger & Cincotta, 2005), such that deactivating the 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 learn about individual stimulus reinforcement values, and therefore the worse they will perform on novel test pairs in TI tasks (Siemann & Delius, 1998). This prediction has been formalized in our models, in which 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 gamma-aminobutyric acid-A (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 administered by intravenous injection; order counterbalanced). To minimize potential learning effects across sessions, we used a different cognitive learning task 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 memorization of the stimulus pairs and encouraging greater implicit learning of reinforcement value. Finally, to verify that midazolam was effective in inducing amnesia, after each task we gave participants a list of names and told them to remember the names for a subsequent recall test.

METHOD

Participants

Our sample was 23 healthy participants, 15 females and 8 males between the ages of 18 and 28 ($M = 21$). Data for 1 participant in the PS task were lost because of a computer malfunction.

Stimuli

Stimulus items for the reinforcement learning tasks were characters selected from the Japanese hiragana script, as in Greene et al. (2001; Frank, Rudy, et al., 2005; Frank et al., 2004). The assignment of hiragana characters to hierarchical elements A through E was randomized across participants (Fig. 1 shows one example of a stimulus hierarchy). The characters were presented

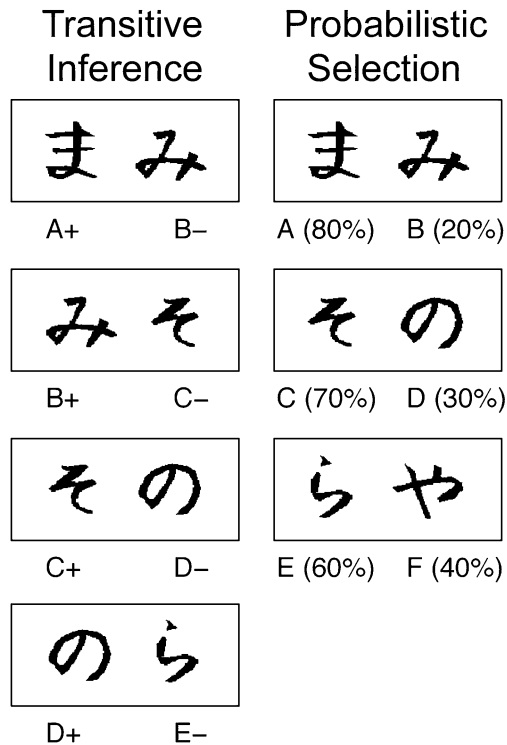


Fig. 1. Examples of the stimulus pairs used for training in the cognitive learning tasks. Hiragana characters were used in both tasks to minimize verbal encoding (in actuality, different characters were used across tasks to prevent transfer effects from one task or session to the next). The deterministic feedback in transitive inference training is indicated by the plus and minus signs. For probabilistic selection, the frequency of positive feedback for each choice is shown.

on a 19-in. color monitor in a 36-point font. Different hiragana characters were used across the two tasks.

Procedure

Procedures were approved by the Scientific Advisory Committee of the University of Colorado Health Sciences Center and by the University Human Research Committee. We used a within-subjects double-blind design. Participants reported to the Boulder General Clinical Research Center 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 to 2 weeks.

At each session, an intravenous catheter was inserted and the participant was administered an injection of either 0.03 mg/kg of body weight of midazolam diluted to a volume of 10 ml or 10 ml of saline. The injection was given over 2 min, with a maximum dose of 2.5 mg. Twenty minutes after drug administration, the cognitive learning test was administered. The study phase of the explicit name recall task began approximately 20 to 25 min later (45 min after drug administration).

TI Task

Prior to training in the TI task, participants were given the following instructions: “Two black figures will appear simultane-

ously on the computer screen. You are to select the ‘correct’ figure as quickly and accurately as possible.” Participants were given no instructions that would lead them to believe that the stimuli were ordered hierarchically.

For each stimulus pair, participants used the “z” and “m” keys to select the stimulus on the left or right, respectively. The position of each character was counterbalanced across trials. Feedback consisted of 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, Rudy, et al., 2005; Frank et al., 2004).

Training consisted of three phases of blocked trials, followed by a fourth phase of randomly interleaved trials (see Fig. 2). Each phase was terminated after the participant achieved criterion performance of at least 75% correct across all pairs and at least 60% correct 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 pairs from other blocks were inserted in the middle and end of each block. Such trials disrupt the descending order of hierarchical presentation, making the stimulus hierarchy less obvious and preventing participants from becoming explicitly aware of it (Frank, Rudy, et al., 2005). A similar procedure was used for Phase 3, except that there were 4 trials per block and a distractor pair only in the 4th trial, and 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 the 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. Each pair was presented six times.

PS Task

The PS task tests the extent to which people implicitly learn more from positive than from negative reinforcement (Frank et al., 2004; Frank, Woroeh, & Curran, 2005). During training, three different stimulus pairs (AB, CD, and EF) are presented in random order, and participants learn to choose one of the two stimuli in each pair through visual feedback. In 80% of AB trials, a choice of stimulus A leads to positive feedback and a choice of B leads to negative feedback (feedback is reversed for the remaining 20% of trials). Stimulus C is correct in 70% of CD trials, and 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 characters to hierarchical elements A through F was randomized across participants.

Phase	Block			
	1	2	3	4
1	AB	BC	CD	DE
	AB	BC	CD	DE
	AB	BC	CD	DE
	AB	BC	CD	DE
	AB	BC	CD	DE
2	AB	BC	CD	DE
	AB	BC	CD	DE
	CD	DE	AB	BC
	AB	BC	CD	DE
	AB	BC	CD	DE
3	AB	BC	CD	DE
	AB	BC	CD	DE
	AB	BC	CD	DE
	CD	DE	AB	BC
	CD	DE	AB	BC
4	CD			
	DE			
	BC			
	AB			
	CD			
				⋮
Test	DE			
	BD			
	CD			
	AB			
	AE			
	DE			
	BC			
	AE			
	BD			

(Items Randomly Interleaved)

Fig. 2. Illustration of the training and test phases of the transitive inference task. The first three phases of this task were blocked, with distractor trials inserted in the middle and end of each block in Phase 2 and at the end of each block in Phase 3 to prevent detection of the stimulus hierarchy (Frank, Rudy, Levy, & O'Reilly, 2005). A fourth phase consisted of one long block of randomly interleaved trials. Finally, in a test phase with no feedback, novel test pairs (in gray) were interleaved with training pairs.

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 the test segment. Because of the different probabilistic structures of the three stimulus pairs, we used a different criterion for each (65% A for AB, 60% C for CD, and 50% E for EF). Of the 11 participants on midazolam, 2 reached the criterion after two training phases, and of the 11 participants on saline, 3 reached the criterion after two training phases; the rest of the participants reached the criterion after three training phases. After reaching

the criterion, participants were tested with the training pairs, in addition to all novel combinations of the stimuli, in random sequence. They were instructed to use “gut instinct” if they did not know how to respond to these novel pairs. Each test pair was presented six times, and no feedback was provided.

Name Recall Task

In each session, the participant studied a series of 10 names presented sequentially in random order on a computer monitor. Each name was presented for 4 s, and different names were used in the two sessions. After a retention interval of 30 min, the participant wrote on an answer sheet as many names as he or she could recall within 2 min.

RESULTS

Midazolam profoundly impaired explicit memory processes (Fig. 3a). Relative to saline, midazolam was associated with a significant deficit in the number of names recalled in the recall test, $F(1, 22) = 13.8, p_{rep} = .99, \eta_p^2 = .38$, and these effects were similar regardless of the learning task performed in that session, $F(1, 22) = 0.25$ for the task-by-drug interaction. In contrast, there was a significant task-by-drug interaction for performance on novel test pairs in the reinforcement learning tasks, $F(1, 22) = 4.5, p_{rep} = .925, \eta_p^2 = .17$. Notably, midazolam was associated with strikingly enhanced TI performance on novel test pairs AE and BD combined, $F(1, 22) = 5.3, p_{rep} = .94, \eta^2 = .19$, as well as on pair BD alone, $F(1, 22) = 4.1, p_{rep} = .92, \eta_p^2 = .16$ (Fig. 3b). There was no effect of midazolam on test performance in the PS task (Fig. 3c), $F(1, 22) = 0.74$. These results are consistent with the proposals 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 critically involved in probabilistic learning.

Our hypothesis that the hippocampus is important for rapidly memorizing stimulus conjunctions leads to additional predictions for learning patterns during the training phases of both tasks. In the TI task, the 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 and 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 worse performance on the middle pairs than in the saline condition. In contrast, the tendency for participants to rely on reinforcement learning systems under midazolam was expected to lead to better performance on the anchor pairs than in the saline condition. We further hypothesized that these effects would be apparent very early in training, given the known role of the hippocampus in automatically and rapidly encoding stimulus conjunctions in very few

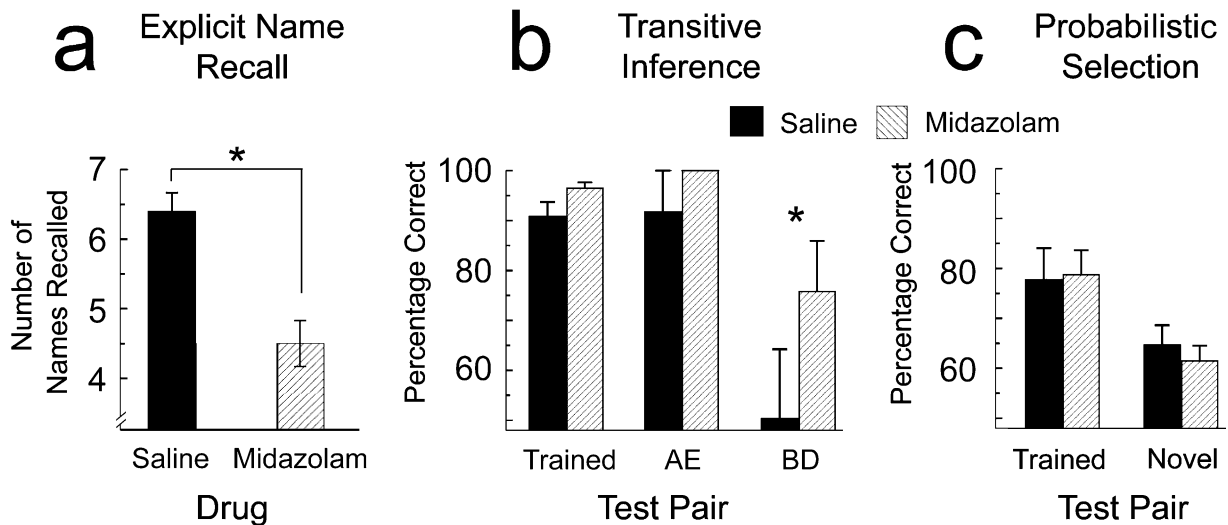


Fig. 3. Results for the three tests: (a) explicit name recall, (b) transitive inference, and (c) probabilistic selection. For each test, results are shown as a function of drug condition (saline vs. midazolam). For transitive inference, percentage correct is shown separately for the trained premise pairs (AB, BC, CD, and DE) and the two novel test pairs (AE and BD). For probabilistic selection, percentage correct is shown separately for the training pairs (AB, CD, and EF) and all novel combinations (AC, BC, DE, etc.). Error bars indicate 1 SEM. Asterisks indicate significant drug effects ($p < .05$).

trials (O'Reilly & Rudy, 2001). After multiple training trials, the differential reinforcement values learned for stimulus items A through E should be sufficient for good performance on all pairs.

To test these ideas, we performed a 2 (drug: midazolam vs. saline) \times 2 (training pair: anchor vs. middle) \times 2 (training phase: 1 vs. 2–4) repeated measures analysis of variance. As hypothesized, in the early stages of training midazolam was associated with better performance on anchor pairs (AB and DE) and worse performance on middle pairs (BC and CD) than the saline condition (Fig. 4a). Overall, performance was better for anchor pairs than for middle pairs (main effect of training pair), $F(1, 20) = 52.9$, $p_{\text{rep}} > .998$, $\eta^2 = .73$. Notably, the differentiation between performance on anchor pairs and performance on middle pairs was greater for midazolam than for saline (Drug \times Training Pair interaction), $F(1, 20) = 5.6$, $p_{\text{rep}} = .945$, $\eta_p^2 = .22$, and this differentiation depended on training phase (Drug \times Training Pair \times Training Phase interaction), $F(2, 20) = 9.2$, $p_{\text{rep}} = .99$, $\eta_p^2 = .48$. Planned contrasts confirmed that the Drug \times Training Pair interaction was significant in Phase 1, $F(1, 20) = 5.94$, $p_{\text{rep}} = .955$, $\eta_p^2 = .23$, but not in the remaining phases, $F(1, 20) = 0.1$. In particular, in Phase 1, performance on anchor pairs was better than performance on middle pairs under midazolam, $F(1, 20) = 7.8$, $p_{\text{rep}} = .97$, $\eta_p^2 = .28$, but not saline, $F(1, 20) = 0.58$, and performance on anchor pairs was marginally better under midazolam than under saline, $F(1, 20) = 3.15$, $p_{\text{rep}} = .885$, $\eta_p^2 = .14$. These particular interactions, which were predicted by our computational framework, were found despite the absence of a main effect of drug on overall training performance, $F(1, 20) = 0.1$, and of an interaction between drug and training phase, $F(1, 20) = 0.02$. Overall, these results support the hypothesis that midazolam administration leads to increased reliance on reinforcement learning about

individual stimuli (as evidenced by better anchor-pair performance than in the saline condition), together with reduced ability to rapidly bind 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, Quinlan, Thornton, & Reder, 2004).

Similar indications of a role for the hippocampus in rapid learning were found in the PS task (Fig. 4b), in which midazolam showed a trend toward impairing performance in the first training phase, $F(1, 20) = 2.8$, $p_{\text{rep}} = .877$, $\eta^2 = .12$, 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 with each training pair in the saline condition, $t(1, 10) = 3.4$, $p_{\text{rep}} = .98$, but not the midazolam condition, $t(1, 10) = 1.4$, n.s. These results are consistent with the notion that although probabilistic learning does not depend on the hippocampal explicit memory system, 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, 2005; Frank et al., 2003, 2004). Furthermore, midazolam's effects on training performance are consistent with the idea that the hippocampus

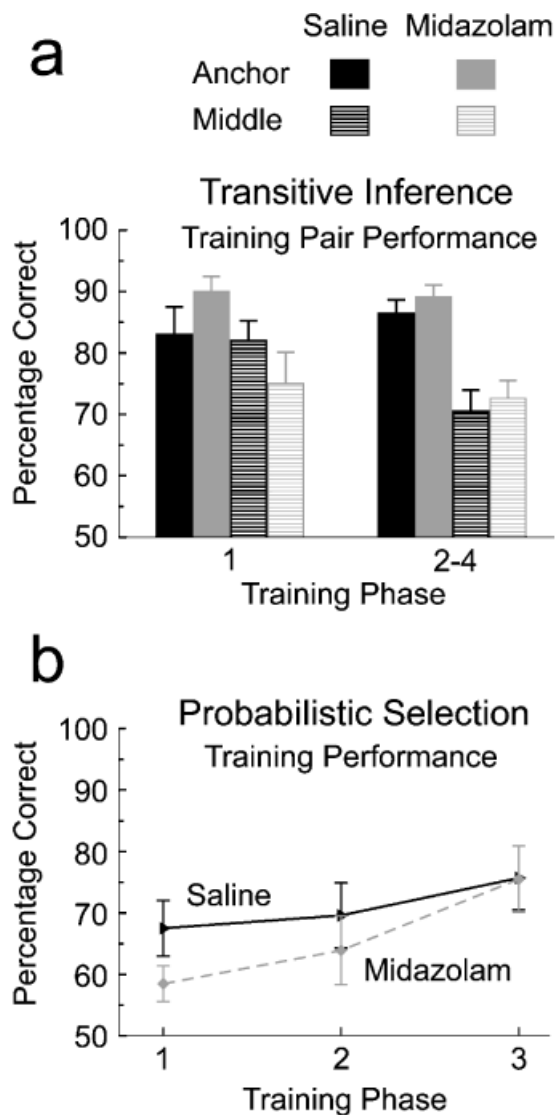


Fig. 4. Training performance in the saline and midazolam conditions of the cognitive learning tasks. For the transitive inference task (a), percentage correct is shown as a function of training phase (1 vs. 2–4) and training pair (anchor vs. middle). For the probabilistic selection task (b), percentage correct is shown as a function of training phase (1 vs. 2 vs. 3). Error bars indicate 1 SEM.

is critical for rapid learning of stimulus conjunctions (O'Reilly & Rudy, 2001). Overall, the results support the notion that the basal ganglia and hippocampus make distinct contributions to memory. Finally, our observation that midazolam actually enhanced TI performance suggests that disengagement of the hippocampal explicit memory system may lead to enhanced basal ganglia learning. This finding is consistent with previous demonstrations of competition among memory systems, whereby hippocampal lesions enhance performance in striatal tasks (Atallah et al., 2004; Packard, Hirsch, & White, 1989; Packard & McGaugh, 1996; Poldrack et al., 2001; Poldrack & Packard, 2003).

Our theoretical account is also consistent with several recent findings. First, neuroimaging studies show that the hippocampus is activated more by conjunctive items that have been studied together than by two individually studied items that are recombined (Giovanello, Schnyer, & Verfaellie, 2004), suggesting that it is more involved in binding elements together than in flexibly recombining them. That the hippocampus 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 (Bayley, Frascino, & Squire, 2005; Driscoll, Sutherland, Prusky, & Rudy, 2004). Similarly, pigeons with hippocampal damage showed intact transitive responding in a TI task (Strasser et al., 2004). Although hippocampal amnesics performed poorly in a recent human TI study, the patients failed to learn key training pairs, making the inference test moot (Smith & Squire, 2005). Finally, dopaminergic involvement in TI performance is suggested by differential patterns of learning in medicated and nonmedicated Parkinson's patients, and is predicted by our computational model of the striatal dopaminergic system (Frank, 2005; Frank et al., 2004).

A critical unresolved question concerns the earlier contradictory findings that hippocampal lesions impaired transitive inference in rats (Dusek & Eichenbaum, 1997). One possible explanation 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 seemingly contradictory results are due to differences in the effective amount of training. It is also possible that rats in these earlier studies somehow adopted a different, hippocampally mediated strategy involving pattern completion or relational memories in the hippocampus to perform a more explicit form of inference, as suggested by Eichenbaum and his colleagues (Dusek & Eichenbaum, 1997; Eichenbaum, 2004) and some of our earlier simulations (O'Reilly & Rudy, 2001). However, this pattern-completion account has difficulty explaining why rats trained in an extended (five-pair) TI task perform at chance levels on the BD test pair, but are better at novel pair BE; this pattern is predicted by associative models and is also seen in humans unaware of the transitive hierarchy (Frank et al., 2003; Frank, Rudy, et al., 2005).

In humans, it is easier to manipulate and evaluate strategy use, and very different patterns of behavior hold depending on the extent to which people become explicitly aware of the hierarchical structure of the TI task (Frank, Rudy, et al., 2005). When participants are explicitly aware of this structure, they behave qualitatively differently than they do in the implicit condition studied in the present experiment. The hippocampus and prefrontal cortex are likely critical for remembering and manipulating the individual premises to support rational decision making, and indeed, neuroimaging studies of humans performing explicit logical reasoning in TI tasks consistently

implicate the hippocampus and prefrontal cortex (Acuna, Eliassen, Donoghue, & Sanes, 2002; Heckers, Zalesak, Weiss, Ditman, & Titone, 2004; Nagode & Pardo, 2002). Thus, the hippocampus may be required for humans to quickly transfer newly learned associations to novel situations (e.g., Myers et al., 2003), but it is not required for transfer when associations are ingrained habitually over multiple experiences (Bayley et al., 2005).

Readers may question our assertion that midazolam preferentially deactivates the hippocampus, while sparing function in implicit associative areas (e.g., striatum). Although 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 GABA to GABA-A receptors. Although GABA-A receptors are expressed throughout the brain, the GABA-A/benzodiazepene receptors are particularly densely expressed in the hippocampus, in far greater numbers than in striatum (Montpied et al., 1988). It has been shown that midazolam increases inhibitory currents in the CA1 and CA3 regions of the hippocampus (Kobayashi et al., 2004; Kristiansen & Lambert, 1996; Poncer et al., 1996; Rovira & Ben-Ari, 1993) and inhibits hippocampal long-term potentiation (Evans & Viola-McCabe, 1996). In addition, various lines of evidence suggest that midazolam impairs hippocampal-dependent explicit memory processes, while sparing other forms of memory (Arndt, Passannante, & Hirshman, 2004; Hirshman, Fisher, Henthorn, Arndt, & Passannante, 2002; Hirshman et al., 2001; Park et al., 2004; Thomas-Anterion et al., 1999). Positron emission tomography 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, and that midazolam has no effect on striatal areas (Bagary et al., 2000; Reinsel et al., 2000). Thus, the most parsimonious explanation of our results is that by disengaging the hippocampus, midazolam induced explicit memory deficits and reduced the competitive dynamic with associative learning systems needed for implicit flexible behavior.

In conclusion, it seems clear that there are multiple mechanisms for making inferences and decisions—that some are 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 of decision making. Future work will 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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