

Selective Effects of Triazolam on Memory for Emotional, Relative to Neutral, Stimuli: Differential Effects on Gist Versus Detail

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Benzodiazepines are known to reduce learning and memory performance, presumably through their facilitation of GABAergic neurotransmission, but the effects of these drugs specifically on memory for emotional material has not been addressed in humans. The effects of a benzodiazepine (triazolam, 0.25 mg) on nonincidental memory for emotional stimuli were assessed in 20 healthy volunteers (10 female). Triazolam reduced the normally facilitative effect of emotion on memory. The drug specifically affected memory for the gist of stimuli while leaving detail memory relatively unaffected. This pattern of performance is similar to that seen in patients with amygdala damage. Results suggest an effect of GABAergic neurotransmission at the level of the amygdala on memory modulation.

Considerable research has shown that benzodiazepines (BZDs) have deleterious effects on memory function (Curran, 2000; Tomaz et al., 1993), in addition to their well-known anxiolytic effects. BZDs do not, however, exert uniform effects on all types of memory. The effects of this class of drugs are limited to the anterograde phase of memory: These drugs impair the acquisition of new information while leaving existing memories intact. This impairment seems limited to declarative memories, as nondeclarative learning such as priming is unaffected by BZDs (although see Brown, Brown, & Bowes, 1989 and Curran, 2000, for a discussion of an exception). More specifically, cognitive research in humans has shown that BZDs impair the learning of episodic declarative memories while leaving semantic declarative memories intact (Curran, Gardiner, Java, & Allen, 1993).

Studies in animals have shown that this BZD-induced memory impairment is also present in emotional learning and memory, an effect that depends on the basolateral amygdala (Salinas, Dickinson-Anson, & McGaugh, 1994; Tomaz, Dickinson-Anson, & McGaugh, 1991, 1992). Enhanced memory for emotional events is thought to be the result of an interaction between stress hormones and amygdala activity. Specifically, it is postulated that both epinephrine and glucocorticoids act at the amygdala to enhance the encoding and consolidation of stimuli that produce an emotional response (McGaugh & Cahill, 1997). Separate research

endeavors with lesion subjects (Buchanan, Denburg, Tranel, & Adolphs, 2001; LaBar & Phelps, 1998); functional neuroimaging (Cahill et al., 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000); and pharmacological probes, including adrenergic agents (Cahill, Prins, Weber, & McGaugh, 1994) and glucocorticoids (Buchanan & Lovallo, 2001), have borne out this relationship in humans. BZDs exert their effect on memory through facilitation of the activity of GABA_A receptors at sites throughout the brain including the amygdala, hippocampus, septum, and entorhinal cortex (Izquierdo et al., 1992). The amnesic effects of other compounds, such as alcohol and barbiturates, are also believed to result from their actions at this receptor complex.

The relationship between memory for emotional stimuli and GABAergic neurotransmission has not been addressed in humans. This study set out to examine this relationship. In a double blind, placebo-controlled design, 20 healthy volunteers were administered either triazolam (0.25 mg) or placebo 1 hr before they were presented with emotionally neutral, pleasant, and unpleasant pictures. In addition, and in light of previous work showing a differential pattern of memory for the gist and detail of emotional stimuli in patients with amygdala damage (Adolphs, Denburg, & Tranel, 2001), we assessed memory for both the gist and detail of these stimuli. This previous work has shown that damage to the amygdala results in disproportionately poorer memory for gist and relatively spared memory for detail of emotional stimuli (Adolphs et al., 2001). We predicted (a) that triazolam would result in an overall reduction in the enhancement of memory for emotional stimuli and (b) that if BZDs produce their amnesic effect by modulating GABAergic activity within the amygdala, then the administration of triazolam to healthy volunteers should result in a pattern of memory performance similar to that previously reported for patients with amygdala damage: reduced gist memory for emotional stimuli and less effect on memory for the detail of these stimuli.

Method

Participants

Twenty healthy volunteers (10 female, 10 male) between the ages of 20 and 28 ($M = 22.7$, $SD = 2.27$), who had been screened to exclude

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psychiatric and neurological conditions, were recruited from the university community. None of the participants were taking any chronic medication, except oral contraceptives, which were taken by 8 of the 10 women. All participants had abstained from drinking caffeinated beverages for at least 12 hr prior to testing and refrained from drinking alcoholic beverages for at least 48 hr prior to and following drug administration. The Institutional Review Board of the University of Iowa approved this study; written informed consent was obtained from all participants.

Tasks

All participants were tested individually on 2 days, separated by 48 hr. We used a double blind, placebo-controlled, between-subject design. Ten participants (5 men, 5 women) were randomly assigned to receive triazolam (0.25 mg, Upjohn Pharmaceuticals), and the other 10 participants were assigned to receive placebo (identically appearing caplets). Drug and placebo were given in oral form 1 hr before stimulus presentation. This drug and dose were chosen because of previous use in memory studies (Weingartner, Hommer, Lister, Thompson, & Wolkowitz, 1992), safety, fast onset of activity, and short half-life (2.9 ± 1.0 hr; Hardman, Limbird, & Gilman, 2001).

The stimuli consisted of 15 color photographs; 5 pleasant, 5 unpleasant, and 5 neutral, as classified by a priori ratings from participants in previous studies (Adolphs et al., 2001; Buchanan et al., 2001). Several of the pictures were chosen from the International Affective Picture System (Lang, Bradley, & Cuthbert, 1999), and the rest were drawn from print media sources. All stimuli included depictions of people and were chosen to be of equal visual complexity (see Adolphs et al., 2001 for description of complexity ratings) and equal mean luminance. Participants were seated in a laboratory room while watching the stimuli. During stimulus presentation, skin conductance responses (SCRs) were recorded from silver chloride electrodes on the palms of the hands. SCRs were later analyzed for peak amplitude during a 7-s period following each picture onset. Each stimulus was presented for 20 s on a computer monitor and was accompanied by a simple, single-sentence narrative description read by one of the experimenters. An example of the narrative description for a photograph of a dead man and a dog lying in a road read as follows: "An old man and his dog had been brutally gunned down on a street in Northern Ireland." Each narrative sentence contained information that could not have been obtained from the picture. For example in the picture of the man and the dog, the location and cause of death were given only in the narrative. Participants were told to watch the stimuli and listen to the spoken narrative and to "feel whatever emotion came naturally in response to the pictures." Participants were told that upon their return visit they would be asked questions about the stimuli; encoding of the stimuli was therefore not incidental. Stimuli were shown in three blocks of five stimuli each, with stimuli in each block presented in a randomized, counterbalanced order for each subject. Between each stimulus within a block, there was a 20-s interstimulus interval, during which the screen was blank.

Forty-eight hours after the encoding session, participants returned to the laboratory and participated in three memory tests in the following order: a free-recall test, a multiple-choice test, and a four-alternative forced-choice recognition test. During the free-recall test, participants were told to write down as much information as they could recall about each picture and each narrative. A trained technician who was unaware of each subject's group membership then scored participants' written responses according to standardized criteria. Responses were coded as 0 if there was no information linking the response to any of the stimuli, 1 if a response could be unambiguously linked to a particular narrative or picture but omitted or was in error about some of the information, and 2 if a response could definitely be linked to a specific narrative or picture and stated correct details. This scoring scheme results in a total possible score of 30 on the free-recall test.

Ninety multiple choice questions (6 per picture–narrative) were used to assess gist versus detail memory. Four independent judges categorized each multiple-choice question as assessing either gist or detail information. *Gist* was defined as salient, general information about the stimulus that "could not be changed or excluded without changing the basic story line" (Heuer & Reisberg, 1990). An example gist question for the picture of the dead man and dog is: "What had the man and dog died from? a) poison, b) shooting, c) gases, or d) a bomb blast". An example detail question from this picture is: "Choose the *exact wording* of the narrative that accompanied the picture." Detail choices were taken from a list that included three foil statements that were different in wording only (e.g., from the aforementioned picture, the narrative read "An old man and his dog had been brutally gunned down on a street in Northern Ireland," whereas a foil states "In Northern Ireland, an old man and his dog had been brutally gunned down"). Any questions agreed on as gist by three out of the four judges were coded as gist, and any questions agreed on as detail by three out of four judges were coded as detail. Questions that produced a split decision among the judges were not included in the analyses. Of the remaining 84 questions, 69 produced unanimous agreement among the four judges. From the total of 90 questions, 47 were coded as gist, 37 were coded as detail, and 6 were discarded. There was a differential breakdown in gist versus detail questions for each valence category (pleasant: 16 gist, 13 detail, 1 discarded; unpleasant: 18 gist, 9 detail, 3 discarded; neutral: 13 gist, 15 detail, 2 discarded). Results are reported as proportion correct within each valence and question type.

The four-alternative forced-choice visual recognition task was designed to assess memory for visual detail. This test consisted of showing the original scene and three foils that had been computer manipulated to differ in detail but not in gist (e.g., from the picture of the dead man and dog, one foil picture shows no grass, whereas the original shows grass visible on the side of the road). We took great care so that none of the tasks should interfere with each other: The information given and queried in the multiple choice questionnaire was not the information that was manipulated in the visual recognition foils, and the identification of the stimuli given for the gist questionnaire did not give away the answer to the verbal detail question.

Following memory testing, participants were shown the original pictures again and were asked to rate them on separate scales of valence (pleasantness), arousal, complexity of the visual image, and unusualness of the depicted scene. Valence and arousal were rated on a 9-point Likert scale, and unusualness and complexity were rated on 4-point Likert scales. In each case, the extremes of the rating scale corresponded to the extremes of the dimension being rated.

Results

Analysis by Gender

Recent work has demonstrated gender differences in emotional memory performance as well as in the neurobiological underpinnings of enhanced memory for emotion (Cahill et al., 2001; Kilpatrick & Cahill, 2001). Preliminary analyses assessing the effects of gender showed no differences between men and women in any dependent measure ($ps > .10$). Data were thus collapsed over the gender variable for all subsequent analyses.

SCRs

SCR data are missing from 4 subjects (2 from placebo group, 2 from triazolam group) as a result of computer error. Using square-root transformed SCR as the dependent measure, we conducted a 2×3 repeated measures multivariate analysis of variance

(MANOVA) with group as a between-subjects variable and picture valence as a within-subjects variable. This analysis revealed no overall effect of valence, $F(2, 13) = 1.9, p = .18, \eta^2 = 0.23$, no effect of group, $F(1, 14) = 0.9, p = .35, \eta^2 = 0.06$, nor was there a Drug Group \times Valence interaction, $F(2, 13) = 1.1, p = .36, \eta^2 = 0.15$. Inspection of the mean differences in SCR responses between groups illustrates that the triazolam group did not show the degree of enhanced SCR response to the unpleasant stimuli shown by the placebo group (unpleasant mean difference = 0.23, effect size = 0.76, 95% confidence interval [CI] = -0.3 to 1.73; pleasant mean difference = 0.07, effect size = 0.25, CI = -0.75 to 1.22; neutral mean difference = 0.11, effect size = 0.27, CI = -0.73 to 1.24). These data suggest, in spite of the low statistical power, that the dose of triazolam used in this investigation reduced sympathetic nervous system arousal, although not at a statistically significant level.

Ratings of the Stimuli

Ratings of the picture stimuli by both drug groups confirmed the a priori categorizations of neutral, pleasant, and unpleasant. We conducted 2×3 repeated measures MANOVAs with a between-subjects variable of group and a within-subjects variable of valence for the ratings of valence, arousal, complexity, and unusualness. There were main effects of emotion category for valence, arousal, and unusualness, $F_s(2, 17) > 43.0, p_s < .01$. Unpleasant stimuli were rated as more unpleasant, arousing, and unusual than the other two categories ($p_s < .01$). The pleasant pictures were rated as more pleasant than the other two categories and more unusual than the neutral pictures ($p_s < .0001$). Arousal was the only rating scale in which there was a difference between drug groups, $F(1, 18) = 6.4, p < .02, \eta^2 = 0.28$. Follow-up contrasts revealed that the triazolam group rated both the pleasant and neutral stimuli as less arousing than did the placebo group, but only on the neutral slides was there a significant group difference ($p = .018$, Bonferroni corrected). The groups did not differ in arousal ratings of the unpleasant stimuli, possibly because of a ceiling effect on ratings of these stimuli (see Figure 1).

Free-Recall

For free-recall and all subsequent memory measures, data were first analyzed with a 2 Drug (placebo vs. triazolam) \times 3 Valence (pleasant, neutral, unpleasant) MANOVA with valence as a within-subjects variable and drug as a between-subjects variable. Planned follow-up Bonferroni-adjusted contrasts along with effect sizes (Cohen's d) and 95% confidence intervals for each between-group comparison are reported in Table 1.

The triazolam group recalled significantly less information compared with the placebo group, $F(1, 18) = 20.4, p < .01, \eta^2 = 0.53$. While both groups showed enhanced memory for the pleasant and unpleasant stimuli compared with neutral stimuli, $F(2, 17) = 26.6, p < .01, \eta^2 = 0.76$ (main effect of valence), the placebo group showed a greater facilitation of memory by emotion than the triazolam group, as shown by a significant interaction between drug and emotion category, $F(2, 17) = 3.77, p < .05, \eta^2 = 0.31$. Follow-up contrasts show that although the placebo group had significantly better recall of both pleasant and unpleasant stimuli

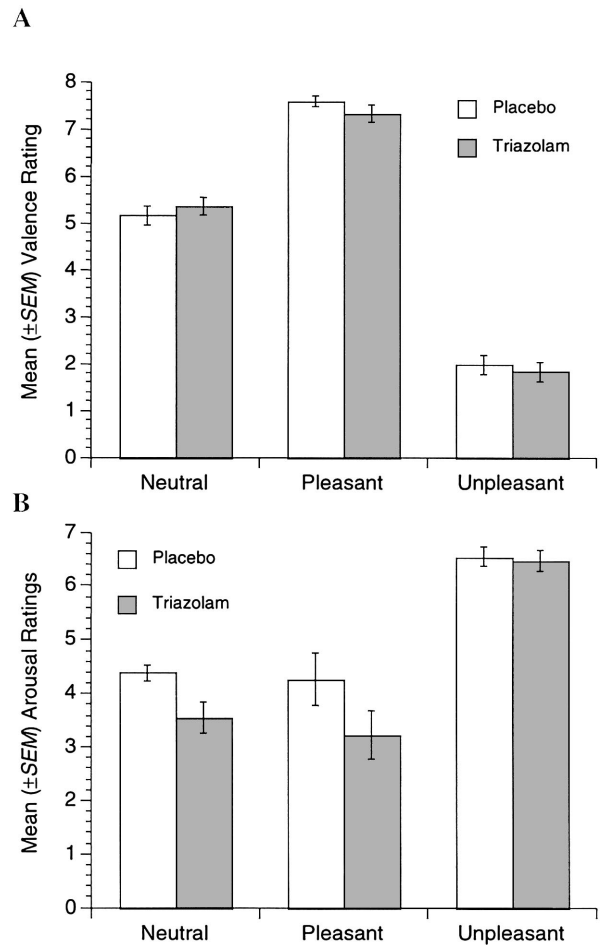


Figure 1. A: Ratings of picture valence and arousal. Mean (\pm SEM) ratings of valence (pleasantness) are shown from all subjects across the three emotion categories. The scale represents maximum pleasantness at 9 and maximum unpleasantness at 0. B: Mean (\pm SEM) ratings of arousal from all subjects across the three emotion categories. The scale represents maximum arousal at 9 and minimum arousal at 0.

than the triazolam group, this group difference was much less pronounced for neutral stimuli (see Figure 2). There exists the possibility that this interaction effect is driven by a floor effect of recall for neutral stimuli by the triazolam group. This issue was addressed in two ways: First, an analysis of covariance (ANCOVA) was conducted on the mean recall of emotional stimuli (both pleasant and unpleasant) as the dependent measure, drug group as the independent measure, and recall of the neutral stimuli as a covariate. Results from this analysis show that there remained a significant effect of drug on emotional recall even when recall of neutral material was controlled for, $F(1, 17) = 12.7, p = .01, \eta^2 = 0.43$. Second, a proportion analysis was conducted to test whether the effect of triazolam on neutral recall was as great as its effects on emotional recall. The ratio of neutral to emotional recall was computed as a percentage of increased recall of emotional compared with neutral stimuli for each group. The placebo group remembered 164% more from the emotional category than from

Table 1
Mean Performance on Free-Recall, Multiple-Choice, and Recognition Tests for Unpleasant, Pleasant, and Neutral Stimulus Materials

Test	Placebo	Triazolam	Effect size (95% CI)	<i>p</i>
Free-recall				
Unpleasant	8.30 ± 3.90	3.50 ± 2.80	1.42 (0.38–2.33)	.004*
Pleasant	6.20 ± 3.40	2.20 ± 1.70	1.48 (0.44–2.40)	.005*
Neutral	2.20 ± 2.40	0.50 ± 0.97	0.95 (0.01–1.83)	.049
Multiple-choice				
Gist				
Unpleasant	0.78 ± 0.14	0.54 ± 0.18	1.53 (0.47–2.45)	.003*
Pleasant	0.69 ± 0.17	0.58 ± 0.16	0.68 (0.25–1.55)	.05
Neutral	0.76 ± 0.12	0.62 ± 0.17	0.94 (0.02–1.82)	.15
Detail				
Unpleasant	0.44 ± 0.14	0.44 ± 0.12	0.00 (–0.88–0.88)	1.00
Pleasant	0.47 ± 0.09	0.40 ± 0.14	0.59 (0.32–1.46)	.20
Neutral	0.58 ± 0.19	0.47 ± 0.09	0.74 (0.19–1.61)	.11
Recognition				
Unpleasant	2.70 ± 1.25	2.11 ± 1.69	0.40 (–0.53–1.29)	.40
Pleasant	3.50 ± 1.08	2.67 ± 1.80	0.57 (–0.38–1.46)	.23
Neutral	3.30 ± 0.82	2.67 ± 1.12	0.65 (–0.30–1.54)	.18

Note. Data are mean (\pm SD) values for memory performance across drug groups. Effect sizes are represented by Cohen's *d* statistic. *p* values are derived from independent-samples *t* tests comparing the mean values from each group. CI = confidence interval. Asterisks indicate significance at the Bonferroni-adjusted alpha level of $.05/3 = .017$ (corrected for three comparisons within each memory test).

the neutral category, whereas the triazolam group recalled 80% more emotional stimuli than neutral stimuli. Although this difference is not statistically significant, $t(18) = 1.2$, $p > .20$, the effect size for this difference is of moderate size (0.6, 95% CI: –0.36 to 1.42).

Taken together, these analyses lend partial support to our first hypothesis: Triazolam reduces overall memory performance and disproportionately reduces the enhancement of memory by emotion (as shown by the steeper slope of memory modulation in the placebo group compared with the triazolam group shown in Figure 2). Although this effect occurs on top of the normally depressing effect of triazolam on general memory function, the degree to

which emotional recall is affected is larger than the effect on recall of neutral material.

Memory for Gist

The triazolam group showed significantly worse memory for gist than did the placebo group, $F(1, 18) = 9.92$, $p = .01$, $\eta^2 = 0.36$. Although there was no Drug Group \times Emotion Category interaction, $F(2, 17) = 0.63$, $p = .54$, $\eta^2 = 0.15$, contrasts showed that the groups showed different patterns of memory across the valence categories. The largest group difference was for gist memory of the unpleasant pictures, whereas gist memory for the other valence categories was less pronounced (see Figure 3 and Table 1). Unlike the results of the free-recall test, there was no overall effect of valence on gist memory, $F(2, 17) = 0.99$, $p = .39$, $\eta^2 = 0.1$. These data provide support for Hypothesis 2, in that the triazolam group shows reduced memory for the gist of all categories, but the greatest difference between drug groups is in the memory for unpleasant stimuli. This is analogous to the memory performance of patients with amygdala damage who show reduced gist memory for unpleasant stimuli in a similar task (Adolphs et al., 2001).

Memory for Detail

Because detail memory was assessed with two ostensibly different tasks (multiple choice and forced-choice recognition), results for each task are reported separately.

There was no group difference in memory for detail as assessed with the multiple-choice test, $F(1, 18) = 2.42$, $p = .14$, $\eta^2 = 0.12$. However, contrasts illustrated that the groups showed different patterns of performance by stimulus category, such that although the groups did not differ on detail memory for the unpleasant

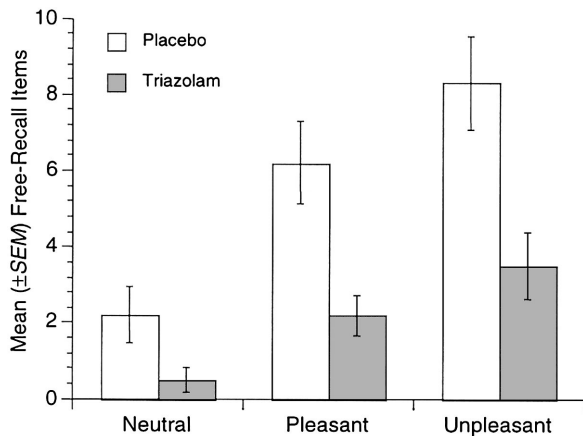


Figure 2. Free-recall performance. Mean (\pm SEM) of correctly recalled information in the free-recall test across both drug groups and across all three emotion categories.

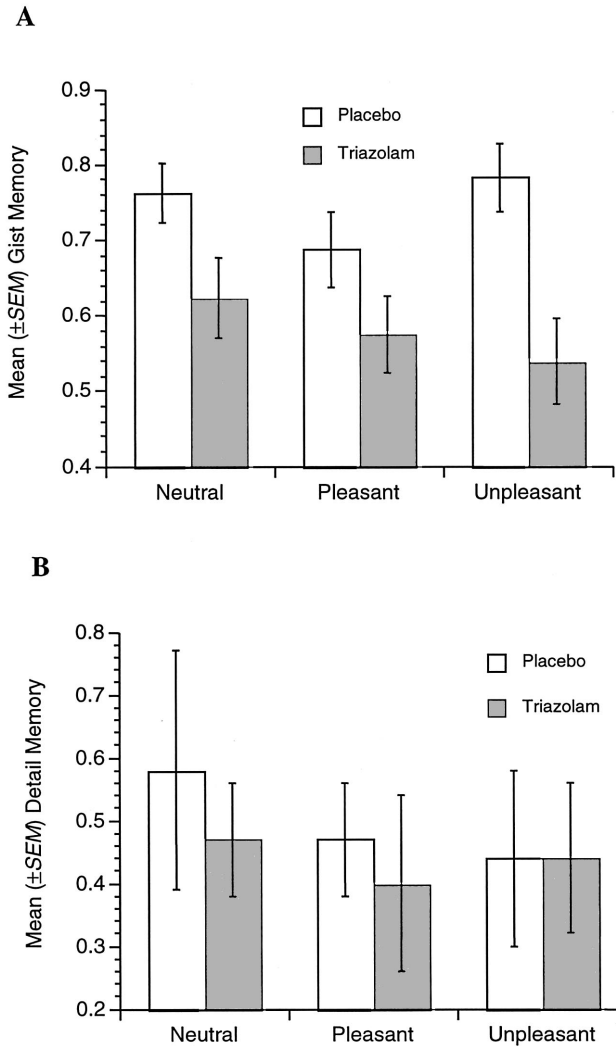


Figure 3. Memory from multiple-choice test. A: Mean (\pm SEM) number of gist questions answered correctly per emotion category. B: Mean (\pm SEM) number of detail questions answered correctly per emotion category.

stimuli (mean difference = 0), the placebo group remembered the neutral (mean difference = 0.113) and pleasant (mean difference = 0.069) stimuli better than the triazolam group (see Table 1 and Figure 4). There was no overall effect of valence on detail memory, $F(1, 18) = 2.27, p = .13, \eta^2 = 0.21$. These results illustrate a pattern of performance in which memory for the details of unpleasant stimuli are not affected by triazolam, but memory for the less arousing pleasant and neutral stimuli is reduced by the drug.

Performance on the forced-choice recognition task illustrates a slight advantage for the placebo group compared with the triazolam group, $F(1, 17) = 3.07, p < .10, \eta^2 = 0.15$. Contrasts show that although the placebo group showed slightly better performance across all categories, these effects were quite small (effect sizes ranging from 0.40 to 0.65) in comparison with the large differences between groups on free-recall and gist memory (see

Table 1). Across both groups, recognition of unpleasant pictures was lower than for the other two categories.

Effects of Arousal on Memory

Arousal ratings from this group of participants were used to assess differences in memory performance by rated arousal of these stimuli. A median split was performed to classify pictures as either low or high in arousal, and a 2 Drug Group \times 2 Arousal Level MANOVA was conducted for free-recall, gist, and detail. In free-recall, more high-arousal pictures than low-arousal pictures were recalled across both groups, but this effect did not reach statistical significance, $F(1, 18) = 3.4, p < .09, \eta^2 = 0.16$. There was no arousal-induced difference in performance for gist memory, but contrasts showed that the placebo group remembered more high-arousal stimuli than did the triazolam group. There was not, however, any difference in the pattern of memory for arousing stimuli between the drug groups (no significant Drug Group \times Arousal interactions, $F_s < 1$).

The effects of arousal on memory for these stimuli were further examined with correlation analyses. The stimuli were rank ordered according to the mean arousal rating that they received and then correlated with memory performance for each individual picture. Free-recall was positively correlated with arousal for both groups. Pearson's correlations were .57 for the placebo group and .55 for the triazolam group ($p_s < .05$). Memory for gist was not strongly associated with the arousal ratings of the pictures (placebo group: $r = .33$; triazolam group: $r = .14$). Detail memory, on the other hand, was negatively associated with rated arousal in both the placebo ($r = -.44, p < .05$) and the triazolam group ($r = -.32, p = .13$). These data suggest that as arousal increases, memory for detail decreases.

Discussion

Results from this study replicate and extend previous reports on the effects of BZDs on memory. Following triazolam administration, healthy participants recalled significantly less information

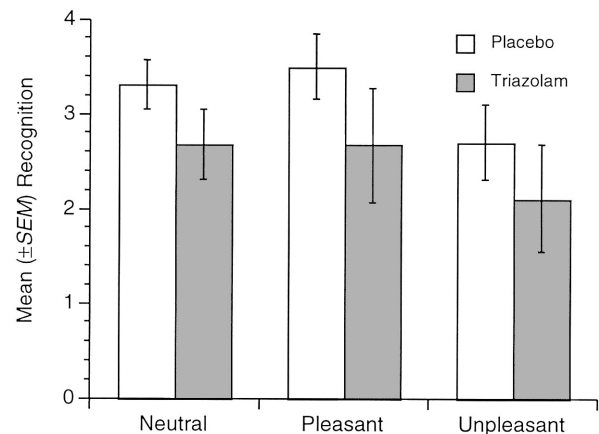


Figure 4. Detail memory from visual recognition test. Mean (\pm SEM) number of questions answered correctly per emotion category on the visual four-alternative forced-choice recognition memory task.

about pleasant, unpleasant, and neutral stimuli compared with a placebo group. The drug additionally resulted in a reduction of the normally robust enhancement of recall for emotionally arousing stimuli that was shown in the placebo group. Further analysis of memory performance using multiple-choice and recognition testing revealed that those receiving triazolam were impaired on memory for the gist of the unpleasant stimuli but showed no impairment in recollection of the details of these stimuli. These findings, therefore, lend support to our first hypothesis, that triazolam would reduce the normally enhancing effect of emotion on memory. Partial support is provided for our second hypothesis, which predicted that gist memory for emotionally arousing stimuli would be impaired but that detail memory for emotional stimuli would not be impaired.

The results showed that only the gist memory for the unpleasant stimuli was impaired following triazolam administration, and that detail memory for the unpleasant stimuli was unaffected by the drug. This pattern of results is similar to that seen in patients with amygdala damage and corroborates previous animal research that suggests a relation between the effects of BZDs and the amygdala in memory modulation. One explanation for the restriction of the effect to only unpleasant stimuli, rather than to both pleasant and unpleasant stimuli, could be that unpleasant stimuli are of substantially higher emotional arousal value than are the pleasant stimuli. Future studies, in which pleasant stimuli of high emotional arousal value are used, would be needed to address this possibility.

The BZD used in this experiment, triazolam, was chosen because of its previous use in memory studies (Weingartner et al., 1992), its safety, fast onset of activity, and short half-life (Hardman et al., 2001). Weingartner and colleagues showed that the same dose of triazolam (0.25 mg) as used in the current study reduced free-recall performance while leaving a measure of attention/vigilance unaffected. Several studies have shown that BZDs reduce declarative memory performance in humans (Curran, 2000; Weingartner et al., 1992). The current results, however, extend these findings by showing that this modulatory effect extends to memory for emotional stimuli. Specifically, the effect of triazolam on free-recall performance was not merely an overall reduction in performance, but recall for pleasant and unpleasant stimuli were affected more than was recall for neutral stimuli, as evidenced by the Drug Group \times Emotion interaction. Although there was not a statistically significant group difference in free-recall for neutral stimuli, the possibility exists that there was a floor effect for recall of these stimuli, resulting in less variability in this measure and no differences between groups. Future studies in which floor effects are circumvented would be required in order to definitively establish the interaction of emotion with drug condition that we have reported here. The pattern of a differential memory impairment for emotional stimuli following triazolam administration is similar to previously reported effects of propranolol and other β -adrenergic antagonists on memory for emotionally arousing stimuli (Cahill et al., 1994; van Stegeren, Everaerd, Cahill, McGaugh, & Gooren, 1998). In these studies, central, but not peripheral, β -adrenergic blockade resulted in a specific impairment of memory for unpleasant stimuli compared with neutral stimuli. The current findings extend this pattern to BZDs and further implicate the GABAergic system as playing a modulatory role in the enhancement of memory by emotion.

Psychophysiological data from this study suggest that the triazolam group experienced the stimuli in a manner similar to that of the placebo group, albeit with reduced magnitude of response. More specifically, the greatest mean difference between the groups was in response to the unpleasant stimuli, with the placebo group showing higher SCRs to those stimuli than the triazolam group. This finding brings up the possibility that the effects of triazolam on memory are secondary to effects on emotional reactions more generally. Although it is impossible to disentangle these effects on the basis of the current findings, such indirect action of BZDs on memory for emotion would be interesting in and of itself. The role of bodily response in emotional processing is well documented (Adolphs & Damasio, 2000; Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Critchley, Mathias, & Dolan, 2001), and it would be expected that reducing this bodily response to emotional situations would reduce the normal enhancement of memory for these stimuli. These data suggest that some level of sympathetic nervous system activity is necessary for the enhancement of gist memory for emotionally arousing stimuli but is unrelated to detail memory. Similar psychophysiological results were reported by Cahill and colleagues (1994): Following the administration of propranolol, two measures of autonomic nervous system activity (heart rate and blood pressure) were reduced, as was subsequent memory for emotional stimuli. The triazolam group showed reduced sympathetic activity in response to the unpleasant pictures, and so were less able to remember the gist of those pictures 2 days later. Also, this lack of sympathetic response may have resulted in their altered arousal ratings following retrieval. Follow-up studies could more closely examine the links between psychophysiological responses and subsequent memory performance for emotional stimuli.

Similarly, subjective ratings of these stimuli by the two groups were not conducted under the influence of the drug and so it is impossible to get a true picture of each group's emotional responses to the stimuli at the time of encoding. Subjective ratings conducted following retrieval illustrate that both groups showed identical valence ratings for all the stimuli. The arousal ratings by the triazolam group were lower for the pleasant and neutral stimuli compared to placebo, but the arousal ratings for unpleasant stimuli were the same between groups. Perhaps these reduced arousal ratings are related to the reduced sympathetic nervous system response during encoding. The relations among subjective emotional response, autonomic activity, and memory performance is a topic that should be addressed in follow-up research.

Previous work with rodents has documented an effect of BZDs on emotional memory and has shown this effect to be dependent on the amygdala. In a series of experiments using both systemic administration (Tomaz et al., 1991), as well as microinjections directly into several amygdaloid nuclei (Tomaz et al., 1992), Tomaz and colleagues have shown that these manipulations impair performance on an inhibitory avoidance task. Specifically, this work has narrowed down the locus of this effect to the basolateral amygdala (Tomaz et al., 1993). Although a recapitulation of these results in humans is not surprising, the current results are, to our knowledge, the first demonstration of altered emotional memory following BZD administration in a human sample.

Those participants who received triazolam showed impaired memory for the gist or central information from the stimuli (specifically the unpleasant stimuli), while showing much less impair-

ment of memory for the details of these stimuli, and in fact no impairment on memory for the details of the unpleasant pictures. Assessment of gist was accomplished by asking several multiple-choice questions focusing on the central information contained in the narrative and picture of each stimulus. Detail memory for the narrative was assessed with multiple-choice questions and, for the picture, with a forced-choice recognition test. BZDs are known to have differential effects on numerous types of memory. For example, "remember," but not "know," responses are reduced by BZDs in a remember/know (R/K) recognition paradigm (Bishop & Curran, 1995; Curran et al., 1993). In the R/K paradigm, participants are asked to decide, once they have indicated recognition of an item, whether they remember that item or just know that it was seen previously. Remember responses correspond to a specific recollection of an event, or episodic memory, whereas know responses are more related to a sense of familiarity, and thus semantic memory (Tulving, 1985). The differential effects of BZDs on remember/know responses suggests that episodic, but not semantic, memory is affected by these drugs (see Curran, 2000). Although the current experiment was not designed to assess effects along the episodic-semantic dichotomy, the differential memory for gist versus detail suggests another instance of a pharmacological dissociation of memory.

Results from the current investigation illustrate another example of a memory dissociation engendered by BZD administration. Memory for gist versus peripheral details has been a major topic in the study of the effects of emotion on memory (Christianson & Loftus, 1991; Heuer & Reisberg, 1990). Although findings are somewhat equivocal, several studies have shown that emotional arousal enhances memory for gist, whereas memory for detail is less well remembered (Burke, Heuer, & Reisberg, 1992; Reisberg & Heuer, 1992). Correlation analysis from this study suggests that the arousing nature of the pictures was positively associated with gist memory and negatively associated with detail memory. These associations were small, however, and should be replicated in a study designed to address the issue more definitively.

An important issue concerns possible gender differences in emotional memory. Emotional memory disproportionately activates the left or the right amygdala in women or in men, respectively (Cahill et al., 2001; Canli, Desmond, Zhao, & Gabrieli, 2002), and a recent pharmacological study (Cahill & van Stegeren, 2003) has provided suggestive evidence that these differential activations may correspond to differences in encoding gist or detail. Specifically, there is preliminary evidence to suggest that emotional arousal results in a three-way interaction between gist/detail memory, subject gender, and laterality of amygdala activation: it increases memory for gist in males via the right amygdala, whereas it enhances memory for detail in females via the left amygdala (Cahill & van Stegeren, 2003). Although we did not find any gender differences in the present study, likely because of the small sample sizes, this will be an important issue to pursue in future studies.

Two caveats should be mentioned in relation to these reported disproportionate effects of triazolam on memory for emotional materials. First, in the free-recall data, there may be a floor effect for the neutral stimuli in the triazolam group. This would make it difficult to interpret the Drug Group \times Emotion Category interaction found in these data. We have further examined this effect

with follow-up analyses, which support our hypothesis of a selective effect of triazolam on emotional memory. In the future, tasks designed to avoid the possibility of a floor effect for such analyses should be used in order to further test this hypothesis. Second, in the multiple-choice gist data, there is an unexpected pattern such that the placebo group does not show enhanced memory for the unpleasant stimuli compared with the neutral stimuli. In the strictest form of our hypothesis, we would expect a decreased enhancement of gist memory for the unpleasant pictures caused by triazolam, with the placebo group showing the greatest memory facilitation for these stimuli. Regardless of the form of the pattern, however, the greatest difference in gist memory performance between groups is for the unpleasant stimuli. This result, along with the lack of a group difference in detail memory for these unpleasant stimuli, supports our hypothesis of a differential effect of triazolam on memory for emotional stimuli (large difference in gist memory for unpleasant stimuli, no difference in detail memory for unpleasant stimuli). These data certainly raise other questions that should be addressed using different groups and methodologies in order to carefully address the questions raised by the current investigation.

In light of the relationship between BZDs and the amygdala in memory enhancement previously noted in animal research, we note the similarity of the pattern of results from those receiving triazolam in the current investigation and the performance of patients with amygdala damage tested previously in our laboratory. The pattern of memory performance shown by the triazolam group in the current investigation is quite similar to the pattern observed from a patient with bilateral amygdala damage (Adolphs et al., 2001). Specifically, the triazolam group and the patient with bilateral amygdala damage (Patient SM046) were both impaired on memory for the gist of unpleasant stimuli, while showing no impairment for memories of the detail of these stimuli (in fact, Patient SM046 showed increased detail memory compared with controls). The memory pattern of Patient SM046 is consistent with the view that the amygdala serves as a filtering system for incoming information, guiding attention to the central, salient details of stimuli (Anderson & Phelps, 2001). Results from the triazolam group, along with previous animal research, suggest an interaction between BZDs and the amygdala in the amnesic effects of these drugs.

Similar to the BZD effects on memory, there has been a report of altered processing of facial expressions of emotion following BZD administration (Blair & Curran, 1999). Specifically, participants who received diazepam were found to be impaired in the recognition of anger from facial expressions. This report illustrates another example of the separable behavioral effects of BZDs. Although a hypothesis about the specific effect of this drug on the amygdala would have predicted an impairment in the recognition of fear (on the basis of lesion and neuroimaging results, see Adolphs, Tranel, Damasio, & Damasio, 1994; Morris et al., 1996), there have been reports of amygdala damage affecting anger recognition (Calder, Young, Rowland, & Perrett, 1996; Scott et al., 1997). In a similar vein, those receiving triazolam in the current investigation rated the pleasant and neutral pictures as being less arousing than did those who received placebo. It is important to note that this rating took place 2 days after drug administration and initial picture encoding. This finding is certainly unexpected, but it suggests that the ratings of these pictures 2 days postdrug were influenced by the participant's initial experience with the picture

under the influence of triazolam. However, there was no drug effect on ratings of the unpleasant pictures.

This correspondence between the effects of BZD administration and amygdala damage is congruent with the view that there are overlapping neural substrates in the amnesic and anxiolytic actions of these drugs (McGaugh & Izquierdo, 2000; Tomaz et al., 1993). Lesion of the amygdala attenuates both the anti-anxiety (Shibata, Yamashita, Yamamoto, Ozaki, & Ueki, 1989) and amnesic effects of BZDs (Tomaz et al., 1991) in rodents. Triazolam, like all BZDs, is believed to exert its effects, both on anxiety behaviors and memory, through enhancing the activity of GABA_A receptors at the level of the amygdala, as well as the hippocampus, septum, and entorhinal cortex (Izquierdo et al., 1992). Perhaps in the current investigation, triazolam exerted inhibitory effects at the level of the amygdala, resulting in a pattern of memory performance similar to that of Patient SM046, circumventing the normal function of the amygdala in memory processing. Future work could further examine the commonalities in memory and anxiety behaviors in individuals following BZD administration compared to patients with bilateral and unilateral damage to the amygdala.

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