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Acute effects of triazolam on false recognition

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Neuropsychological, neuroimaging, and electrophysiological techniques have been applied to the study of false recognition; however, psychopharmacological techniques have not been applied. Benzodiazepine sedative/anxiolytic drugs produce memory deficits similar to those observed in organic amnesia and may be useful tools for studying normal and abnormal memory mechanisms. The present double-blind, placebo-controlled repeated measures study examined the acute effects of orally administered triazolam (Halcion; 0.125 and 0.25 mg/70 kg), a benzodiazepine hypnotic, on performance in the Deese (1959)/Roediger-McDermott (1995) false recognition paradigm in 24 healthy volunteers. Paralleling previous demonstrations in amnesic patients, triazolam produced significant dose-related reductions in false recognition rates to nonstudied words associatively related to studied words, suggesting that false recognition relies on normal memory mechanisms impaired in benzodiazepine-induced amnesia. The results also suggested that relative to placebo, triazolam reduced participants' reliance on memory for item-specific versus list-common semantic information and reduced participants' use of remember versus know responses.

False recognition refers to the phenomenon of mistakenly claiming that one has been exposed previously to a novel item. Although experimental studies of false recognition have been reported since the 1960s (e.g., Anisfeld & Knapp, 1968; Underwood, 1965), recently there has been a dramatic rise in research interest in the phenomenon, stimulated in part by Roediger and McDermott's (1995) demonstration of exceptionally high levels of false recognition within the context of a simple list-learning paradigm (originally introduced by Deese, 1959) (see also Read, 1996). In the Deese/Roediger-McDermott paradigm (DRM), after studying lists of words (associates; e.g., *bed*, *rest*, *awake*, *tired*, *dream*, *wake*, *snooze*, *blanket*, *doze*, *slumber*, *snore*, *nap*, *peace*, *yawn*, *drowsy*) that are all associatively related to a word that is not presented (referred to here as the *theme* but referred to elsewhere as the *critical nonstudied lure*, the *prototype*, or the *false target*; e.g., *sleep*), participants are given a standard recognition memory test in which they are asked to discriminate between words that had been presented during the study phase (old) and words that had not been presented (new). The standard finding in this paradigm, which has been replicated in numerous studies, is that participants claim at high rates (approximately 70%–80% of responses) and with high confidence that the nonpresented theme words had been presented during the study phase (for reviews see Payne, Neuschatz, Lampinen, & Lynn, 1997; Roediger, McDermott, & Robinson, 1998). Furthermore, when asked to make remember/know judgments indicating whether they have a specific recollection of the word's presentation during the study phase ("remember"; recollection-based recognition) or responded "old" because the word seemed familiar ("know"; familiarity-based recognition) (Tulving, 1985), participants tend to provide remember responses more frequently than know responses to the nonpresented theme words (see, e.g., Roediger & McDermott, 1995; Schacter, Verfaellie, & Pradere, 1996). The exceptionally high rates of false recognition observed in this paradigm and the vividness of participants' memories for the nonpresented items are striking and suggest that false recognition arises from normal memory mechanisms and must be accounted for by basic theories of recognition memory.

False recognition in the DRM paradigm has been studied in a variety of different populations, including healthy older adults (e.g., Norman & Schacter, 1997; Schacter, Israel, & Racine, 1999), Korsakoff and non-Korsakoff amnesic patients (e.g., Schacter, Verfaellie, & Anes, 1997; Schacter, Verfaellie, Anes, & Racine, 1998; Schacter, Verfaellie, & Pradere, 1996), and individuals with dementia of the Alzheimer's type (e.g., Balota et al., 1999). Functional neuroimaging (e.g., Schacter, Buckner, Koutstaal, Dale, & Rosen, 1997; Schacter, Reiman, et al., 1996) and event-related potential (e.g., Johnson et al., 1997) techniques also have been applied to the study of false recognition. The results of these neuropsychological, neuroimaging, and electrophysiological studies are beginning to provide insights into the cognitive and brain mechanisms underlying false recognition (for a review see Schacter, Norman, & Koutstaal, 1998).

Despite a growing interest in the cognitive and brain mechanisms underlying false recognition, to our knowl-

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edge, no studies have examined the effects of psychoactive drugs on false recognition. Benzodiazepine drugs such as diazepam (Valium) and triazolam (Halcion) are prescribed commonly for the treatment of anxiety and sleep disorders. Pharmacologically, they act as specific receptor sites in the brain by facilitating the action of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter (Hobbs, Rall, & Verdoorn, 1996). Benzodiazepine receptor sites are found throughout the cerebral cortex, but are particularly abundant in areas thought to be involved in learning and memory such as the hippocampus and other regions of the limbic system. It is well established that in addition to having anxiolytic and sedative properties, benzodiazepines also have memory- and cognitive-impairing effects (for reviews see Curran, 1991; Duka, Curran, Rusted, & Weingartner, 1996; Woods, Katz, & Winger, 1992). Several researchers (e.g., Curran, 1991; Duka et al., 1996; Hirshman, Passannante, & Arndt, 1999; Polster, 1993) have argued that, like neuropsychological studies of brain-damaged patients, which have played a critical role in advancing the theoretical understanding of normal and abnormal memory mechanisms, investigation of the amnesia induced by drugs such as the benzodiazepines can also be a useful tool for elucidating memory mechanisms. In fact, investigation of drug-induced amnesia has certain advantages over traditional studies of amnesic patients; most importantly, unlike the memory deficits found in amnesic patients, effects of drugs on memory processes are reversible and can be empirically manipulated in a dose-related fashion in tightly controlled repeated measures laboratory experiments with healthy volunteers.

The purpose of the present study was to examine the acute dose effects of the benzodiazepine hypnotic triazolam on false recognition in the DRM paradigm using a repeated measures placebo-controlled double-blind design with healthy volunteers. Previous recognition memory studies have demonstrated that triazolam produces a decrease in the proportion of hits made to studied items and an increase in false alarms to nonstudied items (e.g., Mintzer & Griffiths, 1999; Weingartner, Hommer, Lister, Thompson, & Wolkowitz, 1992). Signal detection analyses suggest that triazolam-induced amnesia is associated with a decrease in sensitivity and possibly also with the adoption of a more liberal response bias (e.g., Mintzer & Griffiths, 1999). However, to our knowledge, the effects of triazolam on false recognition within the DRM paradigm have not been investigated previously. Results of previous studies suggest that the pattern of memory deficits induced by acute administration of a single dose of triazolam is similar to that observed in amnesic patients. For example, like the performance of amnesic patients, participants' performance following triazolam administration is impaired relative to their performance following placebo administration on explicit (e.g., recognition memory) but not implicit (e.g., fragment completion) memory tests (e.g., Weingartner et al., 1992). In several recent studies (e.g., Schacter, Verfaellie, & Anes, 1997; Schacter, Verfaillie, et al., 1998; Schacter, Verfaellie, & Pradere, 1996), Schacter and his colleagues have demonstrated that in addition to exhibiting reduced rates of true recognition of studied words, amnesic patients also exhibit reduced rates of false recognition of nonstudied related theme words relative to matched controls, despite exhibiting increased rates of false alarms to unrelated nonstudied words. On the basis of these results, they have argued that false recognition of related theme words relies on normal memory mechanisms that are impaired in amnesia. In particular, they have suggested that true recognition relies on memory for distinctive features of individual items (item-specific information), whereas false recognition relies on memory for general semantic features that are shared by items in a list, and that memory for both types of information is impaired in amnesia. On the basis of these results with amnesic patients, we hypothesized that triazolam-induced amnesia also would be associated with reduced false recognition rates to nonstudied related theme words, despite increased rates of false alarms to unrelated nonstudied words.

METHOD

Participants

Twenty-six adult volunteers (9 male) completed this study. The data of 2 female participants were incomplete due to technical errors; data are presented for the remaining 24 participants. These 24 participants ranged in age from 19 to 48 years (M = 31) and in weight from 46 to 108 kg (M = 74) and reported having completed 9 to 20 years of education (M = 14). Ten participants reported consuming 1 to 2 alcoholic beverages/week (M = 1.6), while the other 14 participants reported not drinking any alcoholic beverages. Six participants reported smoking tobacco cigarettes. No participants reported significant histories of using psychoactive drugs.

All participants were in good health (as determined by medical history and personal interview) with no contraindications to hypnotic drugs. Individuals with current or past histories of psychiatric disorders, except nicotine dependence, were excluded. In the female participants, urine pregnancy tests before, and periodically during, study participation were negative. This study was approved by the Institutional Review Board of the Johns Hopkins Bayview Medical Center. Participants gave their written informed consent before beginning the study and were paid for their participation.

Participants were requested to refrain from using all psychoactive drugs (with the exception of tobacco and caffeinated products) during the time they were participants in the study. Each session, before drug administration, participants were tested for the presence of various drugs in urine (benzodiazepines, barbiturates, opioids, amphetamines, and cocaine) using an EMIT system (Syva Co., Palo Alto, CA) and the presence of alcohol in expired air using a breathalyzer test.

General Procedures

Participants completed a total of three sessions as outpatients at the Behavioral Pharmacology Research Unit. Successive sessions were separated by a minimum of 48 h (e.g., Monday, Wednesday, Friday). Participants were informed that during their participation in the study, they would receive various drugs, and that these could include placebo, various sedatives, anxiolytics, stimulants, and weight loss medications. Other than receiving this general informa-

tion, participants were blind to the type of drug administered. Participants were told that the purpose of the study was to see how different drugs affect performance. Participants attended sessions in groups of up to 3 at a time, but each participant was tested individually. The primary dependent measures involved the DRM paradigm. In order to evaluate the overall magnitude and time course of effects at different doses, psychomotor/cognitive performance and self-ratings of subjective state also were assessed using a battery of measures that was administered repeatedly during each session (i.e., predrug; .5, 1.0, 1.5, 2.5, 3.5 h postdrug). All experimental measures (except balance and circular lights) were administered on an Apple Macintosh microcomputer.

Drug Administration

The three drug conditions were placebo, 0.125 mg/70 kg, and 0.25 mg/70 kg triazolam. Single oral doses were administered in a double-blind, cross-over design. The order of drug conditions was determined by two Latin squares using the Williams (1949) method to achieve balance in presentation order and in the order of drug conditions relative to one another. Triazolam doses were prepared from commercially available .125-mg tablets (Halcion; UpJohn Company, Kalamazoo, MI). Capsules were crushed and doses were adjusted by participant body weight. All doses were dispensed in a size 0 capsule. Lactose was used to fill the remainder of all the capsules. Placebo capsules contained only lactose. Capsules were taken orally with approximately 150 ml of water.

Primary Experimental Measure

Apparatus and Materials. The materials consisted of 60 lists of 16 words each. The lists include modified versions of lists used by other researchers (i.e., Arndt & Hirshman, 1998; Roediger & McDermott, 1995), and additional lists that we developed from Russell and Jenkins's (1954) association norms using criteria similar to those used by other researchers. Each list includes 15 words (associates) that are all highly associated to one target word (theme). The 60 lists were divided into three 20-list sets, each used during one of the three sessions. The 20-list set used in each session was divided into two 10-list subsets; one subset was assigned to the studied condition and one was assigned to the nonstudied condition. The subsets assigned to the two conditions were counterbalanced so that within each drug order condition, each list appeared equally often in the studied and nonstudied conditions.

Procedure. The study phase was conducted 1.5 h after drug administration to coincide with the anticipated time of triazolam's peak effect based on previous studies in our laboratory (e.g., Mintzer, Frey, Yingling, & Griffiths, 1997; Mintzer & Griffiths, 1999). During the study phase, participants were presented with 10 lists of 15 words, each of which appeared on the computer screen one at a time. The words in each list (associates) were presented in the order of their association to the theme on the basis of the association norms, with the strongest associate presented first. Successive lists were separated by a 1-sec "Next List" message. Each word was displayed for 4 sec. Encoding task was manipulated as a between-participants variable so that half of the participants (12) were randomly assigned to the encoding-task condition and half (12) were randomly assigned to the no-encoding-task condition. For participants in the encoding-task condition, seven buttons labeled "1-lo" through "7-hi," respectively, appeared at the bottom of the screen. Participants were instructed to rate the pleasantness of the concept represented by each word on a scale of 1 to 7 (1 = *least pleasant*; 7 = *most pleasant*) and to make their response by clicking on the appropriately numbered button using the computer mouse. They were informed that their memory for these words would be tested later in the session. In order to register their responses, participants clicked on a button labeled "next," which appeared below the seven response buttons. Participants in the no-encoding-task condition simply were instructed to try to remember as many words as possible for a subsequent memory test; they also were instructed to click on a "next" button between successive items. In both encoding conditions, each word was displayed for 4 sec regardless of when the participant made his/her response.

During the test phase, which was conducted 2.5 h after drug administration, participants were presented with a list of 100 words that appeared on the computer screen one at a time in random order. The list included the words presented in Positions 1, 6, 8, and 10 of each of the 10 studied lists (total of 40 "studied" associates), the theme word from each of the 10 studied lists (total of 10 "studied" themes), the words presented in Positions 1, 6, 8, and 10 of each of the 10 nonstudied lists (total of 40 "nonstudied" associates), and the theme word from each of the 10 nonstudied lists (total of 10 "nonstudied" themes). Each test word remained on the screen until the participant responded. Participants were instructed to click on the button labeled "old" if they recognized the word from the study lists and to click on the button labeled "new" if they did not recognize the word from the study lists. If the participant responded "old," he/she was asked to make a remember (R) versus know (K) judgment by clicking on the appropriately labeled button. Participants received detailed instructions for the R/K judgment that were modeled after those given by Rajaram (1993). In these instructions, participants essentially were told to respond R if they had a specific conscious recollection of the word's presentation during the study phase and to respond K if they were confident that the word had been presented during the study phase, but had no specific recollection of its presentation. During the initial screening interview, participants received training on the R/K judgment until it was ascertained that they understood the distinction.

Other Experimental Measures

These measures have been used extensively in our laboratory and have been described in detail previously (e.g., Kirk, Roache, & Griffiths, 1990; McLeod, Griffiths, Bigelow, & Yingling, 1982; Mintzer et al., 1997). The psychomotor/cognitive performance tasks included a balance task, a psychomotor task in which participants pressed a series of 16 buttons as rapidly as possible in response to the randomly sequenced illumination of their associated lights (circular lights), a computerized version of the digit symbol substitution test (DSST), and a short-term number recall task. The participant ratings included ratings of the strength and liking/disliking of the drug effect and of 34 items about their physical (e.g., "Do you feel queasy or sick to your stomach?") and mental (e.g., "Do you feel mentally slowed down?") state; these ratings were made on the computer on a scale with five response options, coded numerically from 0 to 4.

Data Analysis

The analyzed data from the DRM paradigm included the raw proportions of R and K responses and overall old responses (collapsed over R/K) as a function of stimulus type (associate vs. theme) and list type (studied vs. nonstudied). As in previous studies, the signal detection measures of sensitivity, d', and response bias, C, also were calculated for R/K and overall old responses by comparing performance for associates and themes from studied lists to performance for the corresponding control items from nonstudied lists. The recommended correction for computing d' (Snodgrass & Corwin, 1988) was applied to all hit and false alarm rates.

Yonelinas, Kroll, Dobbins, Lazzara, and Knight (1998) have pointed out that traditional analyses of R/K responses may be unreliable when comparisons are made between experimental conditions that differ in level of performance. Therefore, as in recent studies with amnesic patients and older adults (e.g., Schacter et al., 1999; Yonelinas et al., 1998), R/K responses also were analyzed using the Yonelinas et al. dual process signal detection model, in which recollection (the construct presumed to underlie R responses)

Table 1
Mean Proportions of Overall Old, R, and K Responses as a Function of Drug Condition, Stimulus Type, and List Type

	Placebo			0.125 mg/70 kg Trz			0.25 mg/70 kg Trz		
Stimulus	Old	R	K	Old	R	K	Old	R	K
Associate									
Studied	.85	.67	.18	.70	.48	.22	.69	.43	.26
Nonstudied	.09	.04	.05	.18	.09	.09	.29	.14	.15
Theme									
Studied	.78	.54	.24	.71	.45	.26	.63	.35	.28
Nonstudied	.10	.05	.05	.20	.10	.10	.33	.14	.19

Note—Trz, Triazolam.

is modeled as a high-threshold process and familiarity (the construct presumed to underlie K responses) is modeled independently as a signal detection process. However, because the analyses conducted on recollection/familiarity estimates yielded a pattern of effects similar to those conducted on R/K responses, they are not reported here.

Data from the DRM paradigm initially were analyzed by mixed design analyses of variance (ANOVAs), with encoding-task condition (present vs. absent) as the between-participants factor. However, because encoding-task condition did not produce any significant main effects or interactions, data were reanalyzed by repeated measures ANOVAs collapsed over encoding-task condition, and only collapsed data are presented. The raw proportions of responses were analyzed by a 3 × 2 × 2 repeated measures ANOVA with drug condition (placebo .125 mg/70 kg, and .25 mg/70 kg triazolam), stimulus type (associate vs. theme), and list type (studied vs. nonstudied) as factors. C and d' were analyzed by a 3 × 2 repeated measures ANOVA with drug condition and stimulus type as factors. Data from the psychomotor/cognitive performance and participant-rated measures were analyzed by a 3 × 6 repeated measures ANOVA with drug condition and time as factors. For all statistical tests, $p \leq .05$ was considered significant. Pairwise comparisons were conducted using Tukey's HSD tests.

RESULTS

DRM Paradigm

Raw proportions of responses. Table 1 shows the mean proportions of overall old, R, and K responses as a function of drug condition, stimulus type, and list type. The pattern of statistical results was similar for overall old and R responses and will be described first, followed by the results for K responses. Of primary interest, the 3 × 2 × 2 ANOVA revealed a significant interaction between drug condition and list type [for old responses, $F(2,46) = 25.70$, $p = .000$; for R responses, $F(2,46) = 22.72$, $p = .000$], such that triazolam produced orderly dose-related *decreases* relative to placebo in the mean proportions of responses to associates (i.e., true recognition) and themes (i.e., false recognition) from studied lists, but dose-related *increases* in the mean proportions of responses to the corresponding control items from nonstudied lists. Tukey's comparisons revealed that for items from studied lists, the difference between triazolam and placebo was significant in both the low and high triazolam dose conditions for associates, but only in the high-dose condition for themes; this result suggests that true recognition is more sensitive to a triazolam-induced deficit than false recognition. For R responses, Tukey's comparisons also revealed that under placebo, but not triazolam conditions, the proportions of responses to items from studied lists were higher to associates than to themes; this result suggests that under placebo, but not triazolam conditions, participants remembered information about studied associates above and beyond the information that supported false recognition of themes. For items from nonstudied lists, there were no significant differences between the proportions of responses to associates and themes in any drug condition. The ANOVA also revealed a significant main effect of list type [for old responses, $F(1,23) = 407.10$, $p = .000$; for R responses, $F(1,23) = 171.80$, $p = .000$] such that the mean proportions of responses were significantly higher to associates and themes from studied lists than to the corresponding items from nonstudied lists under both placebo and triazolam conditions.

The ANOVA on K responses revealed a significant main effect of drug condition [$F(2,46) = 5.27$, $p = .015$] such that triazolam produced overall dose-related increases in the mean proportions of K responses, a significant main effect of stimulus type [$F(1,23) = 4.61$, $p = .043$], such that the mean proportions of K responses were higher to themes than to associates, and a significant main effect of list type [$F(1,23) = 19.24$, $p = .000$], such that the mean proportions of K responses were higher to associates and themes from studied lists than to the corresponding items from nonstudied lists under both placebo and triazolam conditions. There were no significant interactions.

d'. Figure 1 shows the mean d' values for overall old and R/K responses as a function of drug condition and stimulus type. Again, the pattern of statistical results was similar for old and R responses. The 3 × 2 ANOVA revealed a significant main effect of drug condition [for old responses, $F(2,46) = 28.20$, $p = .000$; for R responses, $F(2,46) = 20.90$, $p = .000$], such that triazolam produced significant dose-related decreases in d' relative to placebo, and a significant main effect of stimulus type [for old responses, $F(1,23) = 4.63$, $p = .042$; for R responses, $F(1,23) = 10.57$, $p = .004$], such that d' was significantly higher for associates than for themes. The interaction between drug condition and stimulus type on d' was signif-

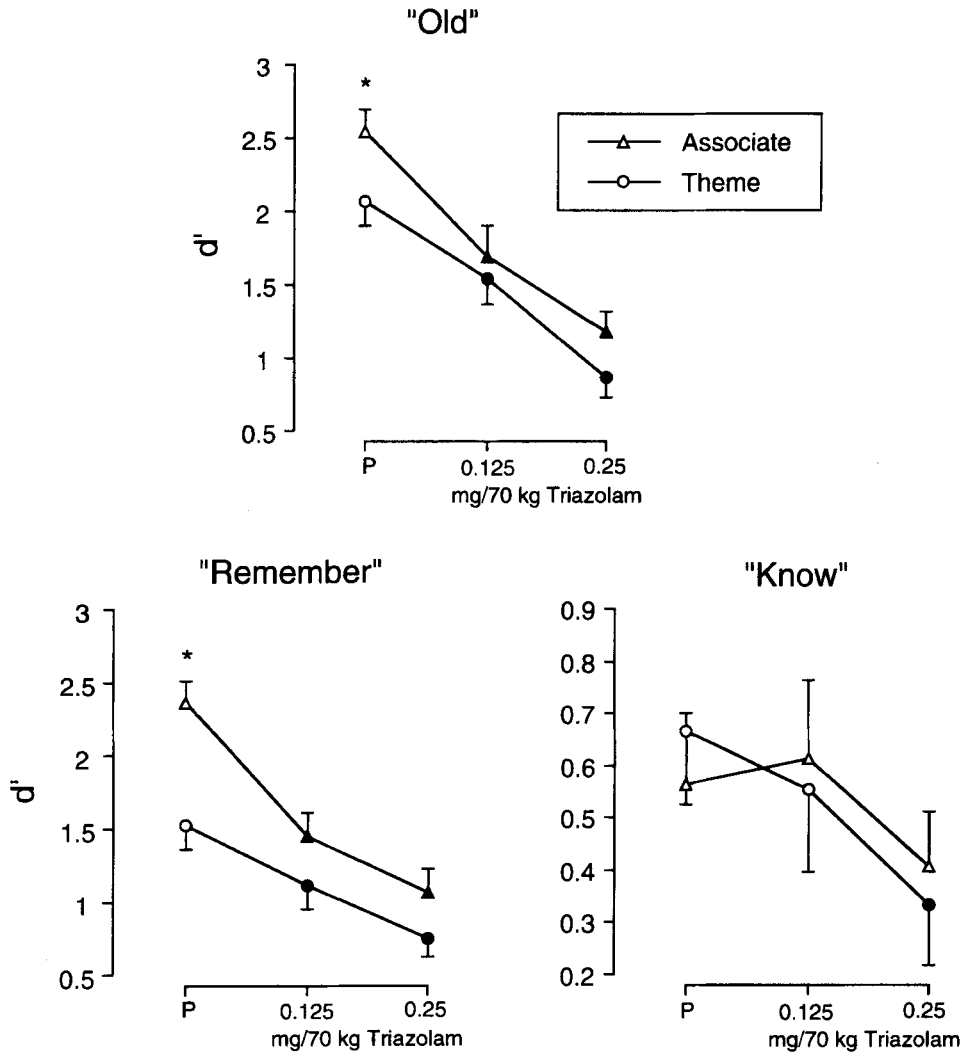

Figure 1. *d'* in the Deese/Roediger-McDermott paradigm as a function of drug condition and stimulus type (i.e., associate vs. theme) for overall "old" and R/K responses. *x*-axis: dose in mg/70 kg; data points at P designate placebo values. Data points show means of 24 participants; brackets show ± 1 *SEM*. Filled symbols indicate triazolam values that are significantly different from placebo; *significant difference between associate and theme values in that drug condition ($p \leq .05$, Tukey's HSD tests).

icant for R responses [$F(2,46) = 4.85$, $p = .015$] but not for overall old responses [$F(2,46) = 1.84$, $p = .176$]. However, Tukey's comparisons revealed for both old and R responses that under placebo, but not triazolam conditions, d' was significantly higher for associates than for themes; again, this result suggests that under placebo, but not triazolam conditions, participants remembered information about studied associates above and beyond the information that supported false recognition of themes. The difference between triazolam and placebo was significant in both the low and high triazolam dose conditions both for associates and themes. The ANOVA for K responses revealed only a marginally significant main effect of drug condition on d' [$F(2,46) = 2.71$, $p = .077$] and no other significant effects.

C. The 3 × 2 ANOVA revealed no significant effects on *C* for overall old or R responses. However, the ANOVA for K responses revealed a significant main effect of drug condition [$F(2,46) = 6.40$, $p = .006$] such that triazolam produced significant dose-related decreases in *C* relative to placebo. The mean *C* values for K responses are shown in Figure 2 as a function of drug condition and stimulus type. Since a positive *C* score reflects a conservative response bias (i.e., reduced tendency to respond "old"), this finding suggests that participants adopted a less conservative response bias for K responses under

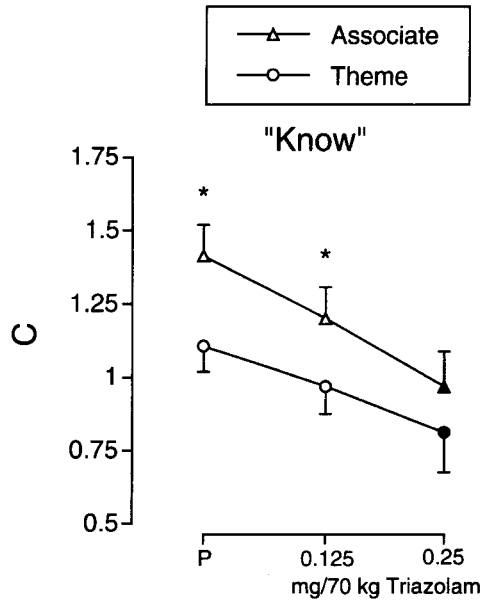

Figure 2. *C* in the Deese/Roediger-McDermott paradigm as a function of drug condition and stimulus type (i.e., associate vs. theme) for K responses. Other details are similar to those for Figure 1.

triazolam than under placebo conditions. There was also a significant main effect of stimulus type on *C* for K responses [$F(1,23) = 31.64$, $p = .000$] such that *C* was lower (i.e., less conservative response bias) for themes than for associates.

Psychomotor/Cognitive Performance and Participant-Rated Measures

Triazolam produced orderly dose- and time-related decrements in psychomotor/cognitive performance and increases in several participant-rated measures (e.g., strength of drug effect, sleepy, lightheaded). Figure 3 shows the triazolam time course functions for two representative measures: participant-rated strength of drug effect and DSST. As predicted, the effects of triazolam generally peaked approximately 1.5 h after drug administration.

DISCUSSION

The present study was designed to examine the acute dose effects of the benzodiazepine hypnotic triazolam on false recognition in the Deese/Roediger-McDermott paradigm using a repeated measures placebo-controlled double-blind design with healthy volunteers. Replicating the results of previous studies with this paradigm, participants made more false alarms to nonstudied words that were associatively related to studied words (themes from studied lists) than to unrelated nonstudied words (themes from nonstudied lists) under both placebo and triazolam conditions. The rates of false recognition observed in the placebo condition were comparable to those reported in previous studies with healthy volunteers (e.g., Roediger & McDermott, 1995; Seamon, Luo, & Gallo, 1998). Of primary interest, triazolam produced dose-related reductions in the proportions of recognition responses made both to studied associates (true recognition) and to nonstudied related themes (false recognition), despite producing increased rates of false alarms to unrelated nonstudied words. The findings of triazolam-induced reductions in true recognition and increases in false alarms to unrelated nonstudied words replicate the results of previous studies demonstrating impaired recognition memory performance with triazolam and other benzodiazepines (e.g., Mintzer & Griffiths, 1999; Weingartner et al., 1992). However, to our knowledge, this is the first study to examine the effects of a benzodiazepine on false recognition in the DRM paradigm. The finding of reduced false recognition rates with triazolam is consistent with our a priori prediction based on previous reports of reduced false recognition rates in patients with organic amnesic syndromes (e.g., Schacter, Verfaelli, & Anes, 1997; Schacter, Verfaellie, & Pradere, 1996). As Schacter and his colleagues have argued, these results suggest that false recognition of related theme words relies on normal memory mechanisms that are impaired in amnesia. In addition, the results of the present study provide further evidence suggesting that the pattern of memory deficits induced by benzodiazepine drugs is similar to that found in amnesic patients.

The present results are also similar to those reported with amnesic patients in another respect. Schacter, Verfaellie, and Pradere (1996) reported that in control but not amnesic participants, recognition responses were higher to associates than to themes. Likewise, several analyses revealed that under placebo, but not triazolam conditions, recognition responses were higher to associates than to themes. Although both true and false recognition are supported by normal memory mechanisms that are impaired in amnesia, these results are consistent with the notion that the mechanisms supporting true versus false recognition are different, and suggest that under nondrug (placebo) versus drug conditions, participants may vary in the degree of their reliance on each of these mechanisms. True recognition has been characterized as being driven primarily by memory for distinctive features of individual items (e.g., Schacter, Norman, & Koutstaal, 1998) (or the verbatim trace [e.g., Brainerd, Reyna, & Kneer, 1995], or the high degree of similarity between the test item and a single memory trace [see Arndt & Hirshman, 1998, for an application of Hintzman's, 1988, MINERVA2 model to false recognition]), whereas false recognition has been characterized as being driven by memory for general semantic features that are shared by items in a list (e.g., Schacter, Norman, & Koutstaal, 1998) (or the gist trace [e.g., Brainerd et al., 1995], or the summing of small amounts of similarity between the test item and multiple memory traces [see Arndt & Hirshman, 1998]). The observation of triazolam-induced deficits in both true and false recognition suggests that triazolam impairs both item-specific memory and memory for list-common semantic information. Furthermore, the observation of

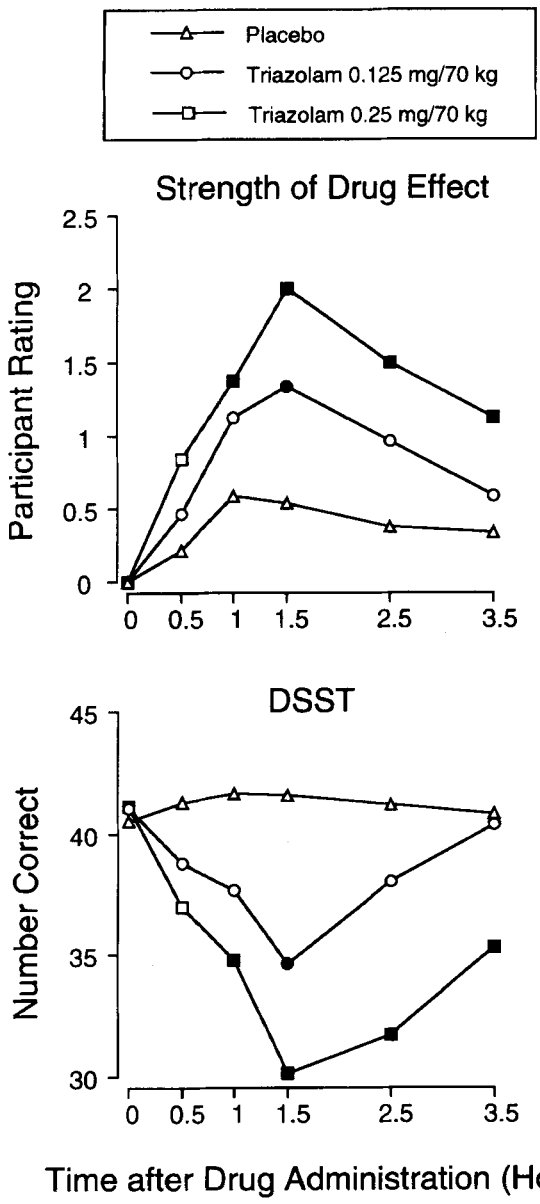

Figure 3. Triazolam time-course functions for participant ratings of drug strength and performance on the DSST. *x*-axis: time in hours after drug administration; 0 indicates predrug. Data points show means of 24 participants. Filled symbols indicate triazolam values that are significantly different from the corresponding placebo value at the same time point ($p \leq .05$, Tukey's HSD tests).

higher recognition responses to associates than to themes under placebo but not triazolam conditions suggests that under placebo, but not triazolam, conditions, participants remembered distinctive item-specific information about studied associates above and beyond the shared semantic information that supports false recognition of themes. Thus, this analysis suggests that triazolam produces a particularly strong deficit in the ability to remember distinctive information about individual items, and that under triazolam conditions, participants rely on (impaired) memory for list-common semantic information for recognition of both themes and associates.

The notion that triazolam produces a particularly strong deficit in memory for item-specific information also is supported by the finding that for the raw proportions of responses, the triazolam-induced deficit in true recognition was significant even at the lowest dose, whereas the deficit in false recognition was significant only at the highest dose. As a methodological note, we point out that the ability to demonstrate graded deficits through the manipulation of dose level is one of the advantages of studying drug-induced amnesia over studying patient populations; although it is possible to classify patients by level of amnesia (e.g, mild, moderate, severe), defining criteria for each level and recruiting a sufficient number of patients to conduct meaningful comparisons among levels may be cumbersome.

Although we have provided a possible account of triazolam's differential effects on true versus false recognition, it should be noted that the conclusions that can be drawn from the present results may be somewhat limited by the fact that in some cases the observed differences in responses to associates versus themes in the triazolam conditions (although not significant) were in the same direction as those in the placebo condition. Thus, further studies are necessary to confirm the robustness of the placebo–triazolam difference.

As in previous studies with the DRM paradigm, the remember/know procedure was used in the present study to investigate the qualitative nature of participants' recognition responses. The observed pattern of R and K responses in both the placebo and triazolam conditions replicates the pattern reported in previous studies. In particular, participants provided higher proportions of R than K responses to both associates and themes, and higher proportions of both R and K responses to items from studied lists than to items from nonstudied lists. Analyses of R/K responses also yielded the following results, which provide insights into the differential operation in true versus false recognition of the processes underlying R/K responses, as well as into the effects of triazolam on these processes. First, under placebo conditions, R, but not K, responses were higher to associates than to themes; this result suggests that it is primarily the process of recollection (the construct presumed to underlie R responses) that confers the recognition advantage to associates (true recognition) over themes (false recognition), and that the process of familiarity (the construct presumed to underlie K responses) contributes to a similar degree to both true and false recognition. Given the foregoing discussion about the different processes underlying true versus false recognition, it may be speculated that recognition based on item-specific memory reflects the operation of recollection, whereas recognition based on memory for list-common semantic information reflects the operation of familiarity. However, the notion that false recognition is based exclusively on a familiarity-based processes is difficult to reconcile with the high proportions of R responses provided to themes in this

and in previous studies, and with the vividness of participants' memory for the themes (see Roediger et al., 1998, for a similar argument regarding difficulties with global memory model and fuzzy trace theory accounts of true versus false recognition). Second, the finding of a robust triazolam-induced deficit in true recognition (i.e., of associates) for R but not K responses suggests that triazolam produces a greater deficit in recollection than in familiarity. This result is consistent with previous reports that triazolam and other benzodiazepines produce greater deficits on explicit than on implicit memory tests (e.g., Schifano & Curran, 1994; Weingartner et al., 1992). It should be noted, however, that although triazolam was not associated with a significant decrease in sensitivity (i.e., d') for K responses relative to placebo, it was associated with the adoption of a less conservative response bias (i.e., C) for K responses. This finding is consistent with the results of a previous study in which participants exhibited a less conservative response bias in responding to words in a recognition memory test under triazolam than under placebo conditions (Mintzer & Griffiths, 1999).

In calculating signal detection measures for themes by comparing performance for themes from studied lists to performance for themes from nonstudied lists, we have followed the lead of other investigators in this area (e.g., Arndt & Hirshman, 1998; Schacter et al., 1999). However, it should be noted that the conclusions drawn from these signal detection analyses should be regarded cautiously. As Miller and Wolford (1999) have pointed out, signal detection measures traditionally are calculated by comparing the proportion of old responses made to each item type when the item *is* presented to the proportion of old responses made to the item type when the item is *not* presented; thus, most false recognition studies lack a condition that is typically required for signal detection analyses—a condition in which the theme word is actually presented during study. The results of future studies in which this additional condition is included will allow firm conclusions to be drawn about whether the effects observed in the present study reflect changes in sensitivity or response bias.

To our knowledge, the DRM paradigm has not been used previously in a repeated measures design. Thus, it is possible that participants may have developed strategies for performing the task across the three sessions, and that this learning process may have varied depending on the order in which participants received the drug conditions. However, we believe it is unlikely that the use of a repeated measures design contributed significantly to the effects reported above for the following reasons. First, to achieve balance in presentation order and in the order of drug conditions relative to one another, we determined the order of drug conditions using the Williams (1949) method. Four participants were assigned to each of the six order conditions derived from the Williams method; thus, any effects of drug order would have been counterbalanced across participants. Second, we included the drug condition that was administered during the first session (i.e., placebo, triazolam 0.125 mg/70 kg, or triazolam 0.25 mg/70 kg) as a between-participants factor (8 participants in each of the three conditions) in the original ANOVAs conducted on the data. These analyses revealed no significant main effects of the drug order variable on any of the dependent variables. There was one significant interaction—that between the drug order variable and stimulus type (i.e., associate vs. theme) on d' for K responses; however, Tukey's post hoc tests revealed no significant differences among conditions for this variable. Third, in order to minimize any differences in learning effects between the first and final two experimental sessions, participants were exposed to the DRM paradigm prior to the first session, at the initial screening interview, in which they completed an abbreviated version of the task (with a stimulus set different from that used for the three experimental sessions). Finally, the results of previous studies suggest that the use of strategies does not, in fact, substantially affect performance in the DRM paradigm; robust false recognition effects have been demonstrated even under conditions when participants are fully instructed about the nature of the effect and warned not to make errors (e.g., Gallo, Roberts, & Seamon, 1997; McDermott & Roediger, 1998).

The results of previous studies with triazolam and other benzodiazepines suggest that benzodiazepines act primarily to impair encoding processes, and do not impair retrieval processes (e.g., Ghoneim, Hinrichs, & Mewaldt, 1984; Weingartner, Sirocco, Curran, & Wolkowitz, 1995); therefore, the study phase of the DRM paradigm in the present study was timed to coincide with the anticipated period of triazolam's peak effect. However, by varying the timing of the study and test phases relative to drug administration, future studies could systematically test the effects of triazolam on encoding versus retrieval in the DRM paradigm. The ability to examine different stages of memory processing by manipulating drug administration time is another advantage of studying drug-induced amnesia over studying amnesic patients whose deficits are irreversible.

In summary, the primary result of the present study is that the benzodiazepine hypnotic triazolam produced significant dose-related reductions in false recognition rates relative to placebo in the DRM paradigm. The results also suggested that under drug versus nondrug conditions, participants varied in the degree of their reliance on item-specific memory versus memory for list-common semantic information, and in their use of R versus K responses. In addition to providing novel information about triazolam's memory-impairing effects, this study demonstrates the usefulness of drug-induced amnesia as a tool to model the deficits found in patients with organic amnesic syndromes and to elucidate normal memory mechanisms.

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