Psychopharmacology (1998) 138:311–317 © Springer-Verlag 1998

ORIGINAL INVESTIGATION

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Triazolam-induced changes in alcoholic thought processes

Received: 7 July 1997 / Final version: 22 September 1997

Abstract This study was designed to examine and contrast cognitive effects (explicit memory and access to semantic knowledge) of the benzodiazepine Halcion (triazolam) in ten normal volunteers and ten cognitively unimpaired detoxified alcoholics. The two groups were indistinguishable from one another under placebo conditions on all measures of cognitive functioning. Under Halcion test conditions (0.375 mg PO), both groups were about equally impaired in their recall of to-be-remembered information. However, alcoholics, were more likely to recall information that they were not asked to remember (intrusion errors) on all measures of explicit remembering. Alcoholics also generated relatively uncommon (low frequency) responses from semantic memory, rather than common, categorically related associations in response to stimuli such as types of vegetables, flowers, and fruit following the administration of Halcion, but were not different from normal volunteers in the types of responses generated under placebo conditions. These findings suggest that a drug challenge that simulates many of the effects of acute alcohol administration induces alcoholics to think and remember differently (qualitatively) from normal volunteers.

Key words Triazolam · Cognitive effect · Alcohol

Introduction

This study was designed to examine the cognitive effects of the benzodiazepine Halcion (triazolam) in normal volunteers and cognitively unimpaired detoxified alcoholics. This class of drugs mimics many of the acute effects of alcohol and therefore was used as a pharmacological manipulation in order to express underlying cognitive differences between alcoholics and normal volunteers that might not be apparent under placebo conditions.

The use of challenge paradigms for uncovering pathology has been one of the diagnostic strategies used in clinical medicine. The specific use of pharmacological challenges in behavioral-cognitive research has only recently begun to be used (Weingartner 1985; Weingartner et al. 1992a). For example, the acute administration of drugs with selective cognitive effects has been proposed as an experimental means of both uncovering impaired cognitive processes that ordinarily are undetected and modeling cognitive impairments associated with different types of cognitive dysfunctions associated with neuropsychiatric disorders (Molchan et al. 1992b; Weingartner et al. 1992a, 1993a). Three examples of this strategy are: 1) acute administration of benzodiazepines, such as triazolam, has been shown to result in selective memory difficulties, independent of sedative or motor effects, that resemble those in amnestic disorders; 2) administration of anticholinergics to elderly normal volunteers results in performance that resembles the cognitive profile found in Alzheimer's disease (Curran and Birch 1991; Molchan et al. 1992b; Hommer et al. 1993; Weingartner et al. 1993a); 3) individuals with histories of post-traumatic stress disorder (PTSD) are much more likely to respond with anxiety to a single administration of yohimbine [β_2-antagonist that stimulates norepinephrine release in the brain, a neurotransmitter postulated to be particularly important in defining the stress response (Bremmer et al. 1997)].

A great deal of research has documented that the acute administration of benzodiazepines, much like alcohol, impairs a variety of cognitive functions, particularly memory and learning (Ghoneim and Mewalt 1990; Curran 1991; Weingartner et al. 1992b, 1993a; Gorissen et al. 1995). The drug challenge chosen to alter state in alcoholics and normal volunteers was the benzodiazepine triazolam, a drug that produces behavioral, cognitive and

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neurobiological effects that resemble the effects of acute alcohol administration. While we anticipated that alcoholics would be less memory impaired than normal volunteers in response to the same challenge dose of a benzodiazepine (based on cross-tolerance of alcohol and benzodiazepine), we predicted that, based upon previously published findings (Weingartner et al. 1994, 1996a), alcoholics would be less able to inhibit commission errors in remembering (intrusions in recall) than normal volunteers.

Cognitive effects of triazolam were contrasted with those of placebo in these two groups, utilizing memory paradigms previously used to evaluate differences between detoxified alcoholics and normal volunteers as well as cognitive deficits associated with other classes of drugs and clinical conditions (Weingartner et al. 1983a,b, 1993b, 1996; Molchan et al. 1992a) These procedures produced various measures of explicit remembering (categorically related words) as well as access to semantic knowledge.

Two sets of hypotheses were tested in this study. Firstly, we predicted that alcoholics are more likely to demonstrate differences in how they think about (respond to) standard stimuli compared to normal volunteers under drug conditions that simulate many of the effects of alcohol but not under placebo conditions. That is, we wanted to examine whether an alcohol-like drug might qualitatively alter how alcoholics think about standard events in ways that differentiate them from normal volunteers.

In addition, we postulated that under these same drug-challenge conditions, alcoholics would demonstrate a failure in inhibitory cognitive functions that would be present in normal volunteers.

Materials and methods

Subjects

Two groups (normal volunteers and detoxified alcoholics) of ten subjects each participated in the study. One group was made up of normal volunteers (paid college student volunteers: mean years of education 14.9±0.4 years; mean age 22.0±0.3; eight males and two females). They were judged to be in good physical health on the basis of extensive history and physical examination, and urine drug screens were negative; no-one reported use of benzodiazepines during the previous year. On the basis of the Structured Clinical Interview (SCID) for DSM-III-R (Spitzer et al. 1990), no current neuropsychiatric disorder or mental illness was detected. Two of the normal volunteers were cigarette smokers. All subjects were recruited only after the Institutional Review Board had reviewed and approved the protocol along with all informed consent documentation. All subjects were provided with detailed information about the protocol before agreeing to participate in the study.

Detoxified alcoholics were studied while on an intramural NIAAA inpatient research unit. Seven of the alcoholics had an early onset form of their disease (abuse prior to age 25; three were late onset patients, after 25 years of age). Their mean age was 35.1±3.0, and they had 12.0±0.6 years of education. The alcoholic sample consisted of seven males and three females. They did not have any other neuropsychiatric diagnosis apart from that of alcohol dependence on the basis of the SCID. Furthermore, aside from their alcoholism, these patients were in good physical health with no additional major health problems. The alcohol consumption history was as follows. Their MAST scores (Selzer 1971) were 42±11. They consumed an average of 160±58 g alcohol per day during the 6 months prior to their admission to the NIAAA research unit. Their lifetime estimated alcohol consumption was 513±520 kg alcohol. Eight of the patients were cigarette smokers, smoking from 15 to 50 cigarettes per day (mean=33±12). Alcoholics had not consumed alcohol for at least 3 weeks prior to participation in the study and had not required benzodiazepines for detoxification. Furthermore, none reported using a benzodiazepine during the last year.

Experimental design

Subjects were orally administered placebo or 0.375 mg triazolam, in a within-subjects double-blind crossover design. This dose of triazolam has been shown previously to produce an acute, reliable, and robust amnesia (failure in explicit but not implicit memory) in normal volunteers (Weingartner et al. 1991, 1992b). One hour after administration, subjects (1) listened to a list of categorically related words (e.g., types of vegetables), (2) self-generated exemplars of another category, and (3) listened to words and generated additional exemplars of a third category. These tests are described in detail below. Two days later, subjects were administered the same compound, and 1 h later, their memory for previously presented and self-generated categorically related words was tested. Subjects also judged their level of sedation [using a standard, validated rating scale (Norris 1971)] at 0, 60, 90, and 120 min after administration. After at least 1 week, the other compound was administered twice, and an identical procedure was followed.

Cognitive methods

All memory tasks used in this study have been validated and standardized in studies of normal volunteers and cognitively impaired patients and in studies of the effects of various classes of psychoactive drugs, including benzodiazepines, glutamatergic receptor antagonists, stimulants such as amphetamine, and cholinergics (Weingartner et al. 1983a,b, 1992a,b, 1993b, 1996; Sunderland et al. 1987; Lister et al. 1991; Molchan et al. 1992b). The time to complete the entire battery of memory tasks was 30 min.

Explicit recall of structured (categorically related) words (task 1)

This task assessed the ability of subjects explicitly to recall (free recall and recognition memory) categorically related stimuli. Subjects were read a list of 12 categorically related words at a 2-s rate. These words are typical exemplars of categories such as vegetables, fruit, and four-legged animals. Six of the 12 words were read once, and six of the words were repeated after the presentation of at least two other words. Subjects were instructed to listen to the words and identify when a word was repeated by raising their hand. To accomplish this task, subjects had to be able to attend to the words as they were read and also hold them in working memory for as long as 34 s. Two days later, subjects freely recalled these categorically related words and then were evaluated on ability to recognize previously presented words from an equal number of new equivalent category exemplars (distractor items). There was no time limit on recalling or recognizing words.

Recall of self-generated and experimenter-provided categorically related words (task 2)

The second task was used as a measure of explicit memory (equivalent words to the ones used in task 1) as well as source memory (identifying source of remembered knowledge). To identify the source of remembered knowledge requires that subjects be able to evaluate, track, and monitor both acquisition and retrieval of information from memory. Subjects were read a list of six categorically

related words at a 2-s rate. These words were typical exemplars of categories such as vegetables, fruit, and four-legged animals but always came from a different category than the one used in task 1. After hearing all of the words, subjects generated six additional category exemplars from the same category that had been read to them. Two days later, subjects freely recalled all categorically related words, both self-generated words and words that were read by the experimenter. They were also asked to identify the source of remembered information (whether the word was presented as a stimulus or self-generated by the subject).

Accessing semantic memory (category fluency) (task 3)

Subjects were also tested on a task that is commonly used to assess verbal fluency and the ability of subjects to access and make use of semantic knowledge. Subjects were asked to generate 12 categorically related words that belong to two closed categories of information, such as fruit and vegetables. The order in which subjects were asked to generate exemplars to the common categories of information such as fruits and vegetables was randomized across subjects. Each word generated in response to the category name fruits or vegetables was classified as either a common or high frequency exemplar (H), one of medium strength or moderately frequent occurrence (M), or an uncommon, low frequency response (L). The category norms of Battig and Montague 1969) were used to classify these responses. A common category exemplar was defined as a word that occurs as a response in 20–250 out of 500 subjects who produce a single word association to these category names. Typical common category exemplars include words like apple, orange in response to fruit and carrot, potato in response to vegetables. A medium strength association (M) is one that is generated by 2–10 of 500 college students who responded to these category names with a single word response. Fruits such as blackberry, honeydew and vegetables such as mushroom and, sweet potato are medium-strength responses. An uncommon, low frequency category exemplar was used to designate words that were appropriate category exemplars but were generated by no more than one of the 500 subjects that were tested in compiling the category norms of Battig and Montague. Words categorized as uncommon responses included kiwi and starfruit as types of fruit and snow peas as a vegetable. This same classification scheme has been previously used to track changes in semantic memory in early-stage Alzheimer's disease patients (Weingartner et al. 1993c).

Results

Statistical analysis of results

Two- and three-factor repeated measures analyses of variance (ANOVA) were used to evaluate differences between normal volunteers and alcoholics in their response to triazolam and placebo for all of the measures of cognitive functioning assessed in this study. Findings are presented in the following order; (1) comparison of alcoholics and normal volunteers on all cognitive measures; (2) comparison of groups in terms of triazolam effects on explicit remembering and sedation; (3) group differences with respect to the types of category exemplars self-generated under triazolam compared to placebo conditions.

Comparison of alcoholics and normal volunteers under placebo test conditions on tests of explicit remembering

Alcoholics and normal volunteers were indistinguishable from one another on the three measures of explicit memory obtained using the procedures described above (see Table 1 below). This was the case for both the number of categorically related words (1) freely recalled, (2) correctly recognized and (3) the number of presented and self-generated related words recalled as well identified as to source (self-generated versus provided as a stimulus by the experimenter). Furthermore, the groups were not different in term of the number of intrusions generated at the time of remembering (see Fig. 1 below for a summary of these results). Likewise, the two groups of subjects were also not different from one another in the types of category exemplars that they generated from semantic memory under placebo conditions (see Fig. 2 below). In fact, alcoholics were somewhat more likely to generate a greater proportion of common rather than uncommon responses under placebo conditions.

Drug effects on explicit remembering and sedation

All subjects reported feeling sedated after triazolam ($F_{1,18}$=84.6; P<0.00001), and this effect was somewhat less pronounced in the alcoholics, ($F_{1,18}$=4.05; 0.1>P>0.05). It has been shown previously that the sedative effects of triazolam do not account for its memory-impairing effects (Curran and Birch 1991; Hommer et al. 1993). Judged sedative effects of triazolam were similarly not significantly correlated for any of the cognitive measures outlined below.

Table 1 Memory performance of detoxified alcoholics and normal volunteers after acute administration of placebo or triazolam

Task	Detoxified alcoholics (n=10)		Normal volunteers (n=10)	
	Placebo	Triazolam	Placebo	Triazolam
Recall of 12 categorically related words	10.4 +0.4	6.9 +0.9	10.0 +0.3	7.3 +0.6
Recognition of 12 categorically related words0	10.4 +0.4	6.9 +.8	10.0+0.4	7.3 +0.6
Recall of six categorically related words presented as stimuli and six self-generated words belonging to the same category	5.2 +0.2	3.2 +0.7	4.9 +0.5	3.4 +0.8

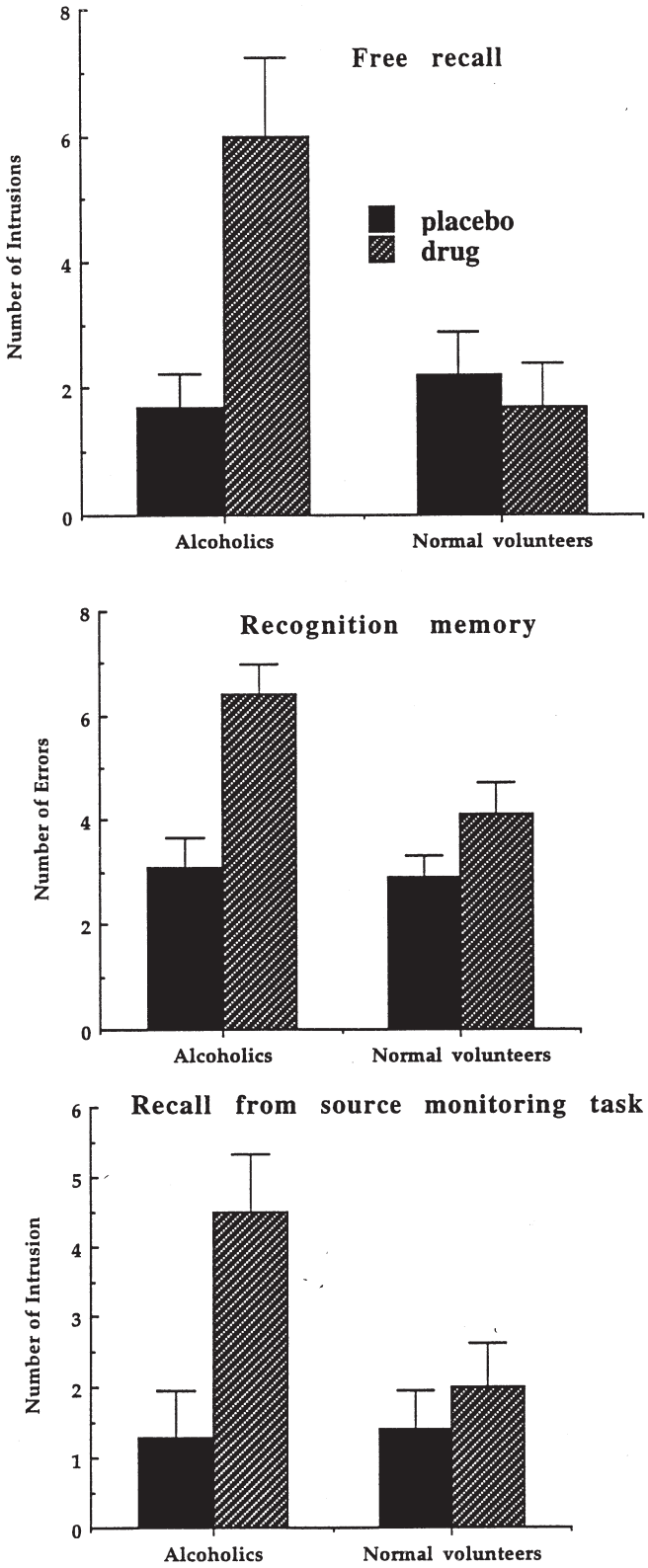

Fig. 1 Intrusions in remembering in alcoholics and normal volunteers under placebo and triazolam test conditions. *Top panel*: triazolam-dependent intrusions in free recall of experimenter-presented words. *Middle panel*: triazolam-dependent intrusions in recognition memory (false positives) of experimenter-presented words. *Lower panel*: triazolam-dependent intrusions in free recall of both self-generated and experimenter-presented words

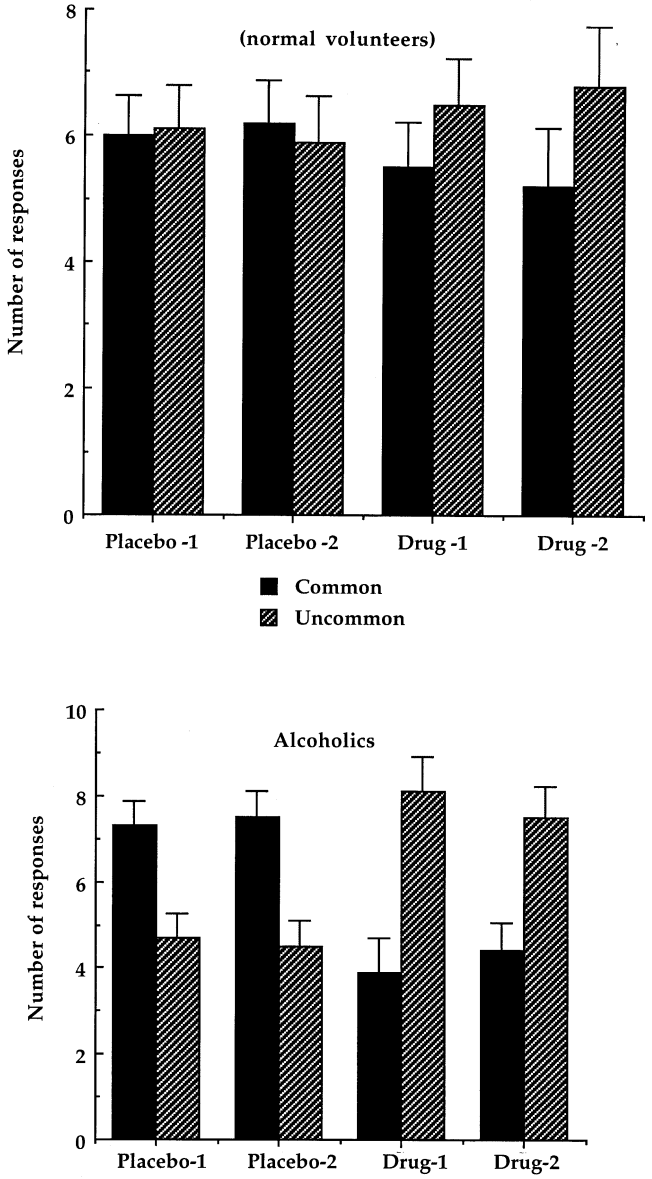

Fig. 2 Types of associations (exemplars) that were generated in response to superordinate category names in alcoholics and normal volunteers under placebo and triazolam test conditions. *Top panel*: number of common and uncommon category associations generated by normal volunteers after administration of triazolam and placebo. *Bottom panel*: number of common and uncommon category associations generated by alcoholics after administration of triazolam and placebo

Detoxified alcoholics and normal volunteers recalled fewer words in a free recall task following the administration of triazolam, particularly for twice-presented words ($F_{1,18}$=7.85; P<0.01): after placebo, normal volunteers recalled 2.3±0.4 and alcoholics 3.1±0.6 words, while following triazolam, normal volunteers remembered 0.6±0.3 and alcoholics 1.3±0.5 words; there was no significant group effect or group by drug effect. Following triazolam treatment, both groups demonstrated an impairment in the accuracy of their recognition performance as measured by a d^1 signal-detection analysis $F_{1,}$

$_{18}$=36.8; P<0.0001). There were no statistical reliable group differences or group by drug interactions. Subjects were less able to recognize previously presented words correctly ($F_{1,18}$=59.04; P<0.0001): after placebo, normal volunteers recognized 10.0±0.3 and alcoholics 10.4±0.4 of previously presented words, but following triazolam, this was reduced to 7.3±0.6 in normal volunteers and 6.9±0.9 in alcoholics, with no group effect or group by drug effect. However, false alarm rates in the two groups following triazolam administration were quite different as described in the section below. Free recall of words presented or self-generated in the source-monitoring task was equally impaired in both groups after triazolam ($F_{1,18}$=16.28; P<0.0001), with no group by drug effect. Both groups recalled more self-generated words than similar words presented by the experimenter ($F_{1,18}$=195.77; P<0.0001): normal volunteers recalled 1.6±0.4 experimenter-presented words and 4.9±0.5 self-generated words after placebo and 0.4±0.2 experimenter-presented words and 3.4±0.8 self-generated words following triazolam; alcoholics recalled 1.5±0.4 experimenter-presented words and 5.2±0.2 self-generated words after placebo and 1.2±0.4 experimenter-presented words and 3.2±0.7 self-generated words following triazolam.

In summary, both groups freely recalled fewer categorically-related words following the administration of triazolam (Table 1). Similarly, when subjects were asked if they recognized previously presented words, they remembered fewer of them following the administration of triazolam, and the size of this effect was similar in the two groups. Both groups recalled more self-generated words than those belonging to the same category that were presented by the experimenter, and there was a reduction in recall of both sets of words after triazolam. In addition, both groups were also equivalently impaired in identifying the source of remembered information, i.e., whether a remembered word was self-generated or provided by the experimenter. The proportion of words that were correctly identified as to source for normal volunteers was 0.94±0.05 after placebo conditions and 0.63±0.14 after triazolam, while alcoholics identified the source correctly 0.87±0.04 after placebo and 0.54±0.11 after triazolam.

Intrusion errors in remembering under drug conditions

Alcoholics made more errors than normal volunteers in remembering following the administration of triazolam. This was apparent in the number of intrusions generated in free recall of categorically related words ($F_{1,18}$=16.51; P<0.001); in recognition memory (false positives) of categorically related words ($F_{1,18}$=12.86; P<0.001); and the number of intrusions in free recall of both self-generated and experimenter-presented words ($F_{1,18}$=4.23 P<0.05). That is, although alcoholics recalled and recognized as many words as normal volunteers after placebo, they were more likely to generate intrusion errors (remembering words not heard previously) in free recall and were also more likely to say that a word that had never been presented before was a previously presented stimulus in tests of recognition memory after triazolam (see Fig. 1 above).

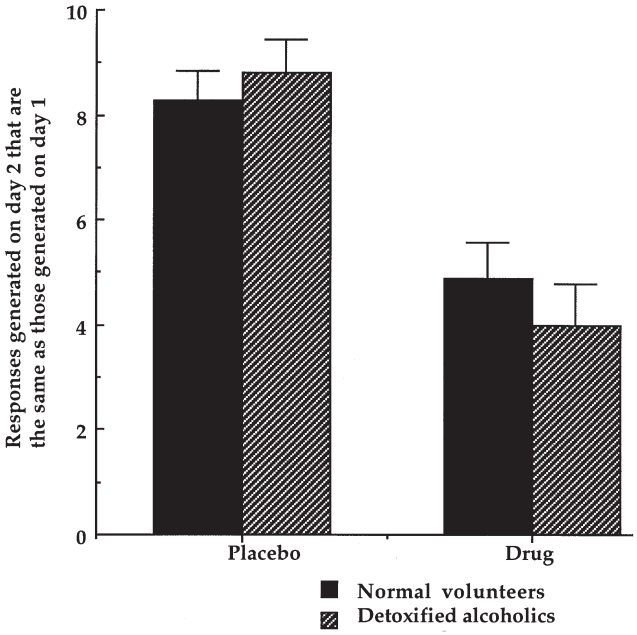

Fig. 3 Number of associative responses generated on day 2 that are the same as those that were generated on day 1 in normal volunteers and alcoholics under placebo and drug (triazolam) conditions

Accessing semantic memory

Alcoholics generated proportionally more uncommon words to an experimenter defined category than normal volunteers after an acute administration of triazolam, (group by drug treatment interaction ($F_{1,18}$=4.55; P<0.05), and this effect was equally apparent on both day 1 and day 2 ($F_{1,18}$=0.62; P>0.1). A parallel analysis of the number of common words generated following the administration of triazolam, supported this same interpretation ($F_{1,18}$=4.88; P<0.05). Under placebo conditions, alcoholics were not different from normal volunteers in the number of uncommon responses generated, with a trend towards producing more rather than less common responses. That is, alcoholics, unlike normal volunteers, thought differently about categories of knowledge after the administration of triazolam, compared to placebo, as demonstrated by an increase in the number of uncommon word associations that were generated in response to category names (Fig. 2a and b). Both groups were far less likely to generate the same associations on day 2 compared to day 1 under triazolam, compared to placebo conditions ($F_{1,18}$=38.30; P<0.0001 with no group by treatment effect ($F_{1,18}$=1.12; P>0.1; and these findings are summarized in Fig. 3 above).

Discussion

The findings described above, in general, confirm the hypotheses that were to be tested in this study. Following the administration of triazolam, subjects in both groups reported being sedated and demonstrated impairments in explicit remembering. However, unlike normal volunteers, detoxified alcoholics were consistently more likely to generate intrusions in both free recall and in recognition memory. Furthermore, the kinds of categorically related responses to category names generated by alcoholics under triazolam conditions were qualitatively different those generated under placebo conditions. These findings are particularly meaningful, since alcoholics were indistinguishable from controls in terms of all aspects of their cognitive performance under placebo conditions. This was the case despite the fact that the alcoholics were somewhat older than the normal controls. It should also be pointed out that, based upon normative validation studies, this age difference and age range is not associated with alterations in cognitive performance with the battery of tests used in this study. They were neither different on measures of explicit remembering nor on how they responded associatively, in terms of what they could retrieve from their knowledge base, in response to stimuli in the form of category names. This is consistent with other findings demonstrating that while alcoholics often demonstrate broadly defined and substantial cognitive deficits in the early phases of alcohol withdrawal those deficits are dramatically attenuated weeks later although subtle deficits may remain (Eckardt et al. 1980). The findings also demonstrate the potential value of pharmacological challenges in uncovering and elucidating the cognitive features of alcohol-related deficits.

It was not surprising that triazolam impaired many facets of learning and remembering. In addition, as expected, alcoholics demonstrated a blunted drug-induced memory deficit. Despite the fact that alcoholics were somewhat less sensitive to the memory-impairing effects of triazolam, they nevertheless produced far more intrusions in recalling to-be-remembered information and were also more likely to think of more unusual, low probability, word responses in accessing semantic knowledge. These findings are meaningful in several ways. First, it is often of value to examine cognitive as well as other deficits in a clinical population under conditions that potentially exacerbate symptoms. For example, the use of pharmacological challenges paradigms in the study of neuropsychiatric disorders has proven useful in normal aging in contrast to early-stage Alzheimer's disease, PTSD, and individuals at risk for developing alcoholism**.** In the present study, it is only under the triazolam-challenge condition that it is possible to observe alterations in two facets of the cognitive functioning of alcoholics (the ability to inhibit intrusions and the types of exemplars that are generated from superordinate categories of knowledge) that are indices of cognitive functioning. In the presence of triazolam, whose acute effects resemble alcohol, otherwise healthy detoxified alcoholics demonstrate substantial changes in how they think about commonplace types of stimuli. Access to what is in knowledge memory is triazolam state-dependent, but not in normal volunteers. Change in the types of associations that come to mind in accessing what we know is likely to be reflected in how subjects, i.e., alcoholics, think about and respond to events around them. The observed effects are not secondary to a generalized impairment in cognitive effectiveness, i.e., alterations in learning, memory and attention. In addition, these alcoholics were less able to inhibit intrusions (a reflective cognitive function) after triazolam administration. This latter finding substantiates those obtained in a previous study wherein impairments in reflective cognitive operations were observed in untreated detoxified alcoholics who also expressed associated impairments in memory source monitoring. These specific impairments were associated with decreased glucose utilization in left prefrontal and left anterior temporal lobes (Weingartner et al. 1994, 1996). The functional and neurobiological mechanisms that define reflective functions has begun to be characterized in normal volunteers as well as in cognitively impaired patients (Shallice 1982; Stuss and Benson 1986; Moscovitch 1989; Petrides 1989; Cummings 1993; Patterson and Newman 1993) and may play an important role in maintaining patterns of alcohol abuse. Impairments in reflective functions and related cognitive functions have also been postulated to be particularly important as a risk factor for the development of alcoholism (Cloninger 1987; Giancola et al. 1993, 1996; Begleiter and Porjesz 1990; Moss and Kirisci 1995).

The findings presented here are obviously quite limited in their scope. It is therefore appropriate to limit the theoretical and practical implications and interpretations that can be drawn from a few findings from relatively few subjects. Nevertheless, we would point out the value of exploring not merely how well subject learn, remember, attend under differing conditions but also alterations in "cognitive styles" such as their ability to reflect on performance and inhibit errors in remembering, and the kinds of idea units to come to mind in responding to their immediate environment (as captured here in the types of associations generated to category names). Differences in cognitive performance and cognitive styles (Sternberg and Grigorenko 1997) between normal volunteers and some patient populations can be of value in furthering our understanding of underlying mechanisms that important in the development and maintenance of psychopathology. Drug challenges can be useful in unmasking the features of that cognitive picture.

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