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Diazepam and Memory: Evidence for Spared Memory Function

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FANG, J C , J V HINRICHS AND M M GHONEIM *Diazepam and memory Evidence for spared memory function* PHARMACOL BIOCHEM BEHAV **28**(3) 347–352, 1987 —The effects of diazepam on several tests of memory were investigated in a double-blind study of 24 healthy young adults Following a single oral administration of 0 3 mg/kg diazepam or placebo, subjects in the diazepam group showed marked impairment in immediate free recall of words as compared to placebo control subjects However, diazepam-treated subjects demonstrated performance benefits from prior exposure to the same words on tests of memory priming using word completion and category-generation tasks The two types of memory tests differ in their demand for conscious recollection Tests of free recall have explicit (declarative) memory demands whereas the priming test places only implicit (procedural) demands upon memory The results demonstrate that diazepam spares some forms of memory as does amnesia induced by neurological impairment

Diazepam Memory Free recall Declarative/Procedural Word completion Category generation Priming Implicit memory

THE profound effect of diazepam (Valium) on explicit memory functions has been established by many experimental investigations (e.g., [11, 14, 15]) Several studies of specific memory deficits demonstrate that diazepam disrupts acquisition of new information [11] and impairs long-term memory [11,15]. However, it is uncertain whether diazepam affects other, more implicit or indirect memory functions.

Recent investigations of human memory in special populations have produced evidence of multiple memory systems [4]· Despite severe impairments evident in amnesic patients when standard memory tests are used, these same patients often revealed intact memory function on special memory tests, such as skill learning tasks and tests sensitive to "priming" that do not emphasize conscious, verbal, factual memory The contrast between profound reductions in verbal, factual recollection and spared memory capacities serves as the primary basis for a proposed distinction between implicit, indirect, covert or procedural memory on the one hand and explicit, direct, overt or declarative memory on the other [4] The proposed distinction between explicit and implicit memory systems would be enhanced by a demonstration of spared implicit memory in subjects with temporary reversible deficits in explicit memory such as those induced by treatment with diazepam.

Some of the earliest observations of intact memory performance in an amnesic are reports on the extensively studied global amnnesic, H M. [7, 8, 16]. While displaying profound retrograde and anterograde memory deficits, H M. was nonetheless able to learn and retain many perceptual-motor skills Acquisition and retention of rotary pursuit skill have been demonstrated in amnesics of varying etiologies including Korsakoff syndrome patients [3], post-encephalitic patients [2], depressive patients undergoing bilateral electroconvulsive therapy, and an amnesic with a diencephalic lesion [4]. A test of mirror-reading found similar pattern analyzing skills in amnesics and normal controls [6] Despite their lack of verbal recollection of having had prior exposure to the "Tower of Hanoi" puzzle, amnesics acquired skills in solving the complex puzzle through repeated exposure [5]

All of the above tasks on which amnesics have demonstrated spared capacities can be described as tasks involving perceptual-motor skill learning, but there is evidence of a separate category of preserved memory capacities unrelated to skill learning For example, amnesic patients' ability to complete fragmented words and drawings is facilitated by prior exposure ("priming") to the stimulus materials [19,20] Facilitation occurs in spite of the amnesics' inability to recall prior exposure to the stimulus materials and impaired performance on tests of recognition and recall of these materials For example, consider a study in which subjects were exposed to a printed list of words containing the less frequent semantic representation of a number of homonyms Later when asked to spell lists of words presented aurally, amnesic patients responded more often with the primed spellings of the homonyms [13] In another series of studies [10,18], recall and recognition were impaired in amnesics when compared to normals, despite prior priming. However, in a word completion task requiring completion of three-letter word stems, each of which had several possible completions, normal controls and amnesics were equally biased toward completions using primed words. An additional study [9] demonstrated similar priming effects in a cued category

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TABLE 1
SCHEDULE OF TASKS

Relative Time	Tasks
−30	General Introduction, Informed Consent Instructions and Practice
+0	Drug Administration
+45	Digit Symbol Substitution 1 Symbol Cancellation 1 Number Learning 1, Tapping 1 Mood Evaluation 1
+55	Word Completion Task 1 Presentation List Priming Test Free Recall Test
+70	Category Completion Task Presentation List Priming Test Free Recall Test
+85	Word Completion Task 2 Presentation List Priming Test Free Recall Test
+95	Mood Evaluation 2 Filler Task
+125	Rest
+130	Tapping 2, Number Learning 2 Digit Symbol Substitution 2 Symbol Cancellation 2 Mood Evaluation 3
+140	Filler Task
+155	Rest
+180	Mood Evaluation 4

generation task: when presented with category labels, amnesics were able to produce primed category exemplars at a rate similar to normal controls while failing to produce the primed items in tests of free recall

The present study compares priming effects in diazepam-treated and placebo control subjects tested on free recall, cued category generation, and word completion tasks. A demonstration of disjunction between ability on tests of free recall and tests of memory priming would lend added support to the distinction between explicit and implicit memory systems

METHOD

Subjects

Twenty-four healthy, paid volunteers (12 males and 12 females) ranging in age from 18–26 (mean age 21.8) were recruited through a newspaper advertisement and paid for their participation Individuals were excluded from participation if they were currently taking any medications, if they had a history of drug abuse, if their medical history contraindicated the use of diazepam, or if they were not within 20% of their ideal body weight

Treatments

Diazepam or placebo were administered orally in identical gelatin capsules. Diazepam capsules containing 2, 5, or 10 mg were administered to yield an approximate dosage of 0 3 mg/kg Subjects were not informed which treatment they received until they had completed all experimental procedures The experimenter was blind to the subjects' treatment condition until all data had been coded and tabulated

Procedure

Subjects were tested in groups of four to eight individuals in the same room. All subjects were instructed not to eat or drink caffeinated beverages for at least 4 hr prior to the start of the experimental session and to abstain from alcohol and marijuana for 24 hr prior to the start of the session In addition, subjects were advised to sleep at least 8 hr on the night before their test session. Prior to drug administration, subjects practiced an abbreviated version of each of the tasks Instructions and practice of the tasks required approximately 30 min after which the drug or placebo capsules were administered The schedule of tasks is presented in Table 1

To test implicit (priming) and explicit (recall) memory, subjects were exposed to three word lists, each followed by a priming task, two using word completion and one using a category generation procedure, and a free recall test. The subjects were not informed about the type of test to follow the presentation of each word list. Subjects were presented with a list of 26 words consisting of primed words (the term primed words will be used to denote those words that are a possible correct response for a later task) and filler words (words unrelated to later task responses). The words were presented one at a time on a slide screen in block letters Each word was presented for 5 sec In order to insure the subjects' attention to each presentation, subjects were instructed to rate each word on how well they liked the word on a 5-point scale (ranging from "Dislike Very Much" to "Like Very Much") Following the presentation of the word list, subjects were given either the word completion task or the category generation task After the priming test, subjects were asked to recall and write down as many of the presented words as possible on a blank piece of paper

In addition to the three memory tasks of primary interest, subjects completed a number of reference tasks to establish that their performance was comparable to that of previous subjects in this laboratory These reference tasks were also used to establish the presence of a diazepam-induced deficit, the tasks were subjective mood evaluation, tapping, number learning, symbol cancellation, and digit symbol substitution Finally, an audiotape consisting of music, voices, and environmental sounds was used as a filler task after the memory tasks as the subjects recovered from the effects of diazepam.

Tasks and Materials

Word completion In the test phase of the two word completion tasks, subjects were requested to complete a list of randomly ordered word stems Subjects were told: "Each of the following three-letter word stems is the beginning of an English word Complete each of the stems to form the first word that comes to mind, excluding proper names or proper nouns." No time limitation was specified on the task, but subjects were instructed to work as quickly as possible The presentation list for the two word completion tasks consisted

of 20 primed words and six filler words (two preceding and four following the primed words)

On the test list, 44 word stems were presented, 20 corresponded to the beginnings of words presented in the word list just before the test. These items were used to establish the rate for primed word completion Another 20 word stems consisted of stems that did not appear in the presented list, but corresponded to a list of words that was not seen. These word stem completions were used to establish a baseline for nonprimed word completion, that is, the rate at which word stems might spontaneously be completed with the target word regardless of whether the word had been previously presented (primed) Four filler items were included at the beginning of each test.

Seventy-two of the words for the word completion task were a subset of those used in previous research [9], six more filler words were added using the same selection criteria. Each word was selected from Webster's Pocket Dictionary and was four to eight letters long The initial three letters (the "stem" of each word) appeared only once in the selected set of words used in this study The dictionary listed at least ten common words that could be used to complete each stem Sixty words were divided into three lists of 20 words each The remaining twelve words and the additional six words were used as filler items at both ends of presentation lists Two lists were used either as primed or nonprimed words for the first word completion task and counterbalanced across sessions so that each list was used equally often as the primed or nonprimed words The third list was used as the primed word completion list for all subjects on the second word completion task The primary purpose of the second word completion test was to determine whether prior experience with the task would change implicit memory performance

Category completion The presentation list for the category generation task was composed of 15 primed words and 11 filler words (5 fillers before and 6 fillers after the primed words) On the category test, subjects were given the names of seven randomly ordered categories one at a time Subjects were instructed to list the first eight items that they thought of that belonged in each category Three of the categories were categories to which all words (excluding filler words) in the preceding list presentation belonged These categories were used to establish a baseline for primed category completion Three other categories were categories to which all items on the alternative list that was not seen by the group belonged, establishing a baseline for nonprimed category completion

Forty words were selected for use in category completion presentation lists. The Battig and Montague norms [1] were used to create eight category lists of five words each In accordance with prior methodology [9], the category exemplars had the following characteristics (a) each word was not ranked among the 10 most frequently produced exemplars for its category, (b) each word was listed as an exemplar by at least 10 subjects in Battig and Montague's normative sample of 442 college students, (c) average rank of category exemplars was 20.03 (range 11–33) in the Battig and Montague norms.

The six categories were divided into two lists of three categories each, i e , 15 words. Each list of words was randomly ordered The two lists of words were counterbalanced across sessions so that each set of words was used equally often as primed and nonprimed words The remaining two additional categories were used as filler words at both ends of the category completion presentation and as filler words at the start of the category completion task.

Free recall After each of the three priming tasks, subjects were instructed to recall, in any order, as many of the words that appeared in the most recent list as they could Subjects were allowed 4 min to complete each trial Specifically, they attempted to recall the 26 words presented before the two word completion tasks (20 primed items and 6 fillers) and they attempted the 26 words used in the category completion task (five instances of each of the three primed and two filler categories, plus one additional filler)

Reference tasks Five other tasks were administered prior to and following the free recall and primed memory tasks

The mood evaluation consisted of subjective ratings on ten 7-point scales [17]. The scales were marked by adjectives representing the extremes of the dimension being rated. Subjects circled one point along each scale that best represented their feeling along the particular dimension The sum of the ten mood scores was used as a composite mood score

In the tapping task subjects were required to use the index finger of their dominant hand to press a button on a mechanical counter as quickly as possible Subjects tapped for two 30-sec trials with a 30-sec rest interval between trials. The dependent measure was the total number of taps executed in both trials

The number learning task required subjects to listen to a series of 15 digits presented aurally Immediately after the presentation, subjects were instructed to write down as many of the numbers as they could recall in order of their presentation on a sheet of paper containing 15 boxes The numbers in each list were generated randomly Each sequence of numbers was presented six times at a rate of two digits per sec. The number of correct digits recalled in the correct order was the dependent measure.

In the symbol cancellation task a string of 60 letters appeared immediately to the right of two target letters The 60 letter strings and target letters were generated randomly using random letter configurations [12]. Subjects were instructed to cross out every instance of the two target letters on each line The dependent measure was the number of correct targets identified in 1 min.

Digit symbol substitution, a subtest from the Wechsler Adult Intelligence Scale, required subjects to complete substitution of a symbol for each of a set of 100 randomly ordered digits as quickly as possible. In the digit symbol substitution task each of nine digits (1–9) is assigned a unique symbol. The dependent measure was the number of correct substitutions made in 90 sec

Statistical Analysis

Analysis of variance was used to compared performance in the priming and recall tasks. The main factor analyzed for each dependent measure was treatment (diazepam or placebo), with list (1 or 2) included as a factor when relevant. The reference tasks, administered to establish the drug effect with tasks similar to those used in previous investigations from this laboratory [11,14], were analyzed using t-tests for independent samples

A strict criterion was used in scoring all three protocols free recall, nonprimed completions, and primed completions Words were scored as correct only if they appeared on the presentation list (or on the baseline nonprimed list) in exactly the same form (no plurals, distortions, changes in tense, etc.) All effects with significance levels of 0.05 are

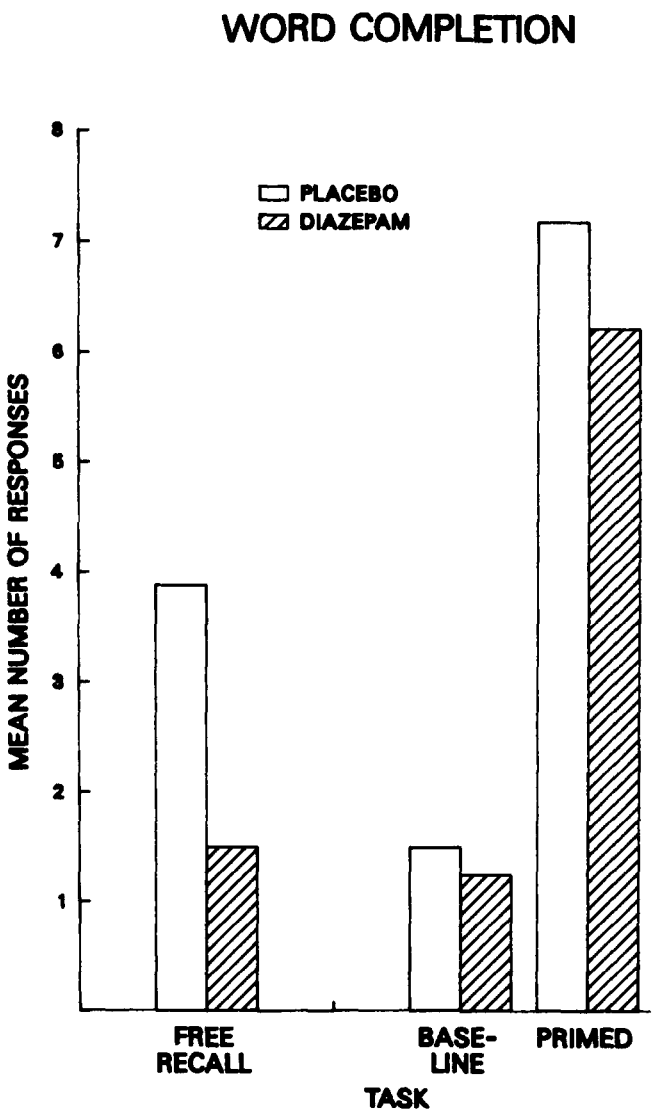

FIG 1 Mean performance on the two word completion tasks after priming of test words, compared to free recall of the same words and completion rate for nonprimed words (baseline) Maximum possible score is 20

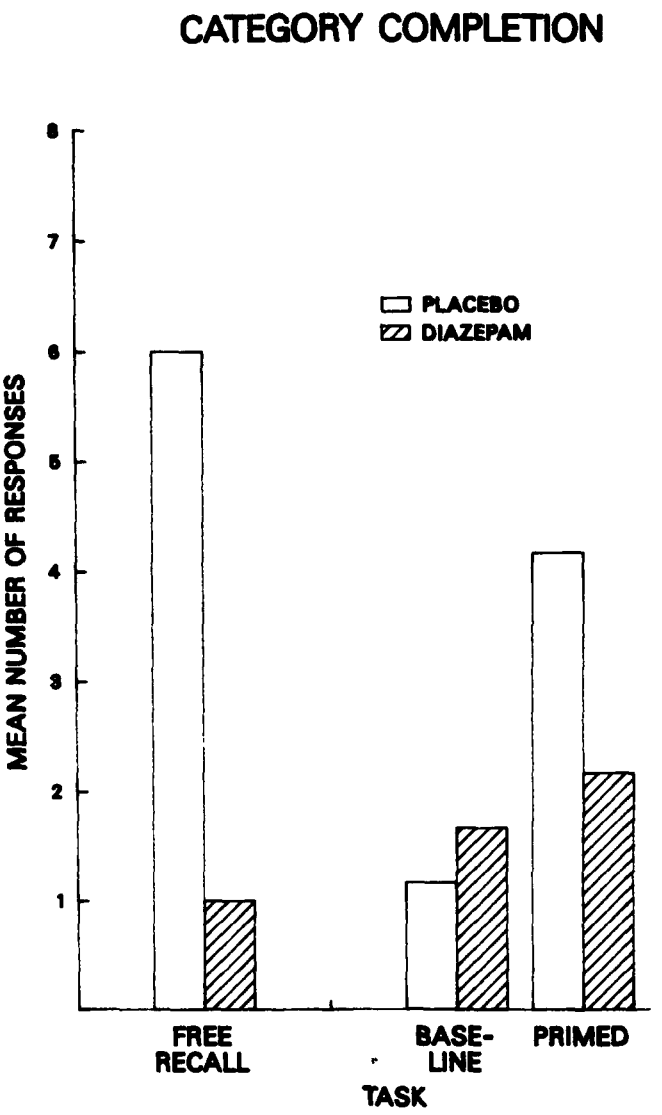

FIG 2 Mean performance on the category completion task after priming of test words, compared to free recall of the same words and baseline completion rate for nonprimed words Maximum possible score is 15

reported. Unless otherwise stated, the level of significance was at the 0.01 level or beyond

RESULTS

Word Completion Task

Because no main effects or interactions with list were found, all reported results are collapsed over list.

Free recall The left-hand panel of Fig 1 illustrates the well-established decrement in recall produced by diazepam, averaged over the first and second word completion lists, $F(1,20)=11.94$. There was an interaction between trial and drug group, $F(1,20)=4.74$, $p<0.05$, such that the difference between diazepam and placebo groups was greater on the first task (1.08 vs. 4.33) than on the second (1 92 vs. 3.42)

Priming. Comparison of the number of word stems completed on the first word completion task demonstrated a significant priming effect, $F(1,20)=64.79$. Word stems were completed with target words at a higher rate if those words were presented in a prior list, i.e., primed, than if they were not, 5.71 words versus 1.38. Diazepam and placebo groups did not differ in their production of target words in response to nonprimed word stem cues (1.25 versus 1.50), $F(1,20)<1$. Nor did the diazepam and placebo groups differ in their rate of completion of word stems with target words in the primed condition on either first task (5.00 versus 6.42) or second task (7.42 versus 7.92), $p>0$ 10 in both cases. The right-hand panel of Fig. 1 shows the performance level for the baseline (nonprimed) condition and primed word completion averaged over both word completion tasks

Category Completion Task

Free recall Once again diazepam and placebo groups dif-

TABLE 2
RESULTS AND STATISTICS FOR REFERENCE TASKS

	Diazepam		Placebo			
Task*	Mean	SD	Mean	SD	t	p
ME-0	48 00	6 99	51 25	8 63	−1 01	NS
DSS-1	59 00	13 01	75 08	8 85	−3 54	0 01
SC-1	6 33	2 96	8 75	1 71	−2 45	0 01
NL-1	47 00	13 14	63 25	13 53	−2 98	0 01
TAP-1	314 42	51 46	369 58	37 10	−3 01	0 01
ME-1	32 25	6 41	45 92	7 29	−4 88	0 01
ME-2	29 75	5 82	42 25	10 30	−3 66	0 01
TAP-2	324 75	50 70	361 92	35 26	−2 08	0 05
NL-2	55 00	13 24	66 83	12 96	−2 21	0 05
DSS-2	66 92	13 27	77 75	11 10	−2 17	0 05
SC-2	8 08	2 23	10 17	2 59	−2 11	0 05
ME-3	30 58	6 60	43 58	7 31	−4 57	0 01
ME-4	34 17	8 09	46 00	5 12	−4 28	0 01

*Abbreviations for each task are DSS—Digit symbol substitution task, SC—Symbol cancellation task, NL—Number learning task, TAP—Tapping task, ME—Mood evaluation
Note Compare with Table 1 for time of each task

fered significantly on free recall for category completion words, $F(1,20)=27\ 61$, as shown in the left panel of Fig 2. Additionally, there was a significant Drug × List interaction, $F(1,20)=7\ 85$, $p<0.05$. The diazepam group experienced less difficulty on one list while the placebo group performed better on the other. However, there were no differences in overall free recall means on the two lists.

Priming Overall, there was a significant difference between completion of primed versus nonprimed (baseline) category cues, $F(1,20)=13\ 16$ There also was a significant interaction between primed versus nonprimed category completion and drug group, $F(1,20)=6\ 72$, $p<0.05$

Diazepam and placebo groups did not vary significantly on production of nonprimed targets in baseline category completion, $F(1,20)<1$ However, unlike the word completion task, the two groups differed significantly in their category production of primed words, $F(1,20)=6\ 61$, $p<0\ 05$ The diazepam group produced fewer primed exemplars than did control subjects (right panel of Fig 2)

Reference Tasks

Forty-five min following drug administration diazepam and placebo groups varied significantly on mood evaluation, digit symbol substitution, symbol cancellation, number learning, and tapping tasks. Diazepam subjects' performances on all these tasks were impaired compared to placebo controls. Mean scores on all reference tasks are comparable to results from prior investigations (e.g., [14]) Diazepam and placebo groups also differed significantly at 130 min post-drug administration These results are taken as an indication that the effects of diazepam were evident both prior to and after all tasks of primary interest to this investigation had been completed. Results and statistical comparisons are presented in Table 2

DISCUSSION

The results indicate that diazepam-treated subjects, like patients with permanent amnesia, exhibit a profound deficit in performance on tests of free recall in agreement with many past studes [11, 14, 15]. Tests of free recall place explicit demands on memory, require conscious verbal recollection, and may require more elaborate or complex processing involving construction of new data structures and integration of new and old data structures and processes. According to the view esposued by Cohen [4], the demands of free recall tests fall under the domain of explicit, declarative memory Thus, the evidence supports the claim that diazepam-treated subjects suffer a disruption to the declarative memory system.

The rate of primed word completion for both groups exceeded baseline completion (nonprimed or chance levels of completion), indicating that both placebo and diazepam-treated subjects benefitted from prior exposure to verbal stimulus material. Despite a reduction in their ability to recall previously presented lists of words, diazepam-impaired subjects performed as well as placebo control subjects on the cued word completion priming task Priming tasks such as cued word completion tasks make use of processes that operate upon existing structures, require no conscious verbal recollection, and have been described as falling under the domain of implicit or procedural memory [4] The dissociation between free recall and word completion for primed material lends support to the distinction between implicit and explicit memory systems and extends the range of the dissociation between the two memory systems to impairments induced by temporary drug states

On the category completion task, diazepam subjects produced a greater number of primed words than nonprimed category words, but generated significantly fewer primed words than placebo controls. This result failed to replicate results of a study of category completion in amnesics that demonstrated priming effects in patients with poor free recall for the same material [9] However, in that prior study [9], the size of the category-priming effect was smaller than the priming effect on word completion tests, suggesting that priming effects for category generation may be weaker.

Several explanations for failure to replicate, or for a weaker priming effect in category completion as compared to word completion, seem plausible Category completion may differ from word completion in the processing and memory demands it makes Category completion may require greater amounts of complex processing and integration of new and existing data structures and processes For example, category completion may involve clustering items (category exemplars) into new categories (category labels). Such processing demands might place the task under the explicit (declarative) memory system A slight variation of this interpretation is that category exemplar generation may implicate the declarative memory system due to its demand for conscious recollection of category exemplars in a given existing data structure Another possible interpretation is that the nature of the category labels used in this study may have been general enough to bias completion toward specific clusters of common exemplars Such a bias may have superseded the priming effect

Results of the present investigation lend support to the implicit/explicit distinction in the theory of multiple memory systems The disruption to memory processes, involving conscious verbal recollection and explicit memory demands along with the spared ability to benefit from prior exposure on tasks requiring implicit demands for memory in diazepam-impaired subjects, provides an example of speci-

ficity in memory impairment produced by drug effects. This drug-induced memory loss, though reversible, parallels the pattern of cognitive dysfunction seen in permanent neurological syndromes.

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