Br. J. clin. Pharmac. (1979), 7, 479–483

DRUGS AND HUMAN MEMORY: EFFECTS OF LOW DOSES OF NITRAZEPAM AND HYOSCINE ON RETENTION

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1 The effects of diazepam (5 mg) and hyoscine hydrobromide (0.3 mg) were assessed in two memory tasks: short-term retention of digit strings and the free recall of items from categorizable lists.

2 One hundred and two healthy subjects were tested in an independent-groups design. Subjects were assigned randomly to either placebo, diazepam or hyoscine groups. Treatments were administered orally under double-blind conditions.

3 The short-term retention of digits was impaired to an equivalent degree and locus for both drugs ($P < 0.05$). This effect was ascribed to the action on primary memory.

4 The drugs produced no significant effects on the recall of categorizable lists either in terms of the number of words recalled or the cohesiveness of categorical recall.

5 These results demonstrate that drugs of different pharmacological actions produce isomorphic psychological deficits in memory and that 'anti-memory' effects on one task should not be extrapolated to all aspects of memory.

Introduction

Both hyoscine and nitrazepam have been shown to produce anti-memory effects (Ghoneim & Mewaldt, 1977; Jones, Lewis & Spriggs, 1978). Recent evidence indicates that these effects may arise from different pharmacological actions. Hyoscine appears to act centrally as a cholinergic antagonist. The anticholinesterase physostigmine acts in an antagonistic fashion to the effects of hyoscine upon memory, but has no such antagonistic effect on a diazepam-induced memory deficit (Ghoneim & Mewaldt, 1977). On the other hand it has been suggested that the action of diazepam may be GABA-ergic (Costa, Guidotti, Mao & Suria, 1975).

The present study explores the possibility that the differences between these two drugs may be manifested in qualitative and quantitative differences in recall. Two tasks were chosen to represent a wide range of memory function. First, an auditory digit span task requiring the retention and recall in serial order of nine-digit strings after a relatively short interval. Second, a task which represented higher-order aspects of memory involving the free recall of long lists of categorizable words. This latter task offered indices of both quantitative (in terms of the number of words recalled) and qualitative (the tendency to recall members of the same category together) aspects of retention.

The study is concerned with effects of these drugs on memory, given in a typical therapeutic dosage. As with previous work from our laboratories this experiment employs an independent-groups design and a group administration of tasks (Jones *et al.*, 1978).

Methods

Subjects

One hundred and two students, males and females, took part in the study. Subjects were randomly assigned to either a placebo, hyoscine or nitrazepam group ($n = 34$ in each group).

Drugs

All groups were given identical gelatin capsules. Those administered to the nitrazepam group contained 5 mg nitrazepam. The hyoscine group were given 0.3 mg hyoscine hydrobromide. The placebo group were given lactose filled dummy capsules. All capsules were administered at 12.30 h on the day of the experiment. Treatments were administered under double-blind conditions.

0306–5251/79/050479–05$01.00

Physical arrangements

Subjects were seated some 1 m apart and lateral vision was restricted by using screens. All subjects were able to observe a projection screen at the front of the room. 'White' noise at 70 dB was played during the presentation of visual material in order to mask out any auditory cues which could have been heard by adjacent subjects.

Design

Each subject completed two memory tasks, viz. digit span and category clustering. A group of forty-eight subjects performed the experiment on day 1 whilst the remaining fifty-four subjects performed the experiment on day 2 a week later. The order of presentation was balanced between days, i.e. on day 1 subjects undertook the tasks in the order digit span–category clustering, on day 2 this order was reversed. On each day subjects were given a standard light lunch at noon. At 12.30 h the tablets were administered. Testing began at 14.00 h.

Tasks

(i) *Digit span.* Subjects were asked to listen to 9-digit sequences. Digits were presented at a rate of 1/s. After the termination of each sequence subjects were required to write down the digits from memory in their order of presentation on a response blank provided. Twelve seconds was allowed for response. Subjects heard sixty nine-digit sequences in all.

(ii) *Category clustering.* Subjects saw five lists. Each list contained thirty nouns composed of five categories drawn from the Battig & Montague (1969) norms. Lists were presented at a rate of 1 word/2 s Lists were assembled such that category members were distributed evenly throughout a list and that members of the same category were not presented successively. After the end of each list subjects were required to write down as many words as they could in the order in which they remembered them. That is, subjects engaged in free recall, rather than ordered recall which was required for the digit span test. Typically, subjects have found to recall the words in category clusters (Bousfield, 1953).

The classes of words employed in each list are given in Table 1. The lists were presented in a fixed order to all subjects.

Results

Digit span

Errors were scored for each serial position, thus performance could be studied for each point in an archetypal list. Mean errors are given in Table 2.

Error data were cast into a mixed model analysis of variance (Winer, 1962) with drugs serving as an independent factor and serial position as a repeated-measure factor. There was a robust effect of serial position ($F=83.49$; d.f. $=8/784$; $P<0.01$) which took the form of a rise in errors toward the seventh serial position followed by a precipitous fall toward the end of the list. This pattern of errors is typical of auditory lists at this rate of presentation (Crowder & Morton, 1969).

There was no main effect of drug treatment ($F=0.91$; d.f. $=2/98$; $P>0.05$). However there was a significant interaction between drug treatment and serial position ($F=1.88$; d.f. $=16/784$; $P<0.05$). An examination of Table 2 shows that both drug treatments had deleterious effects in the early serial positions.

Table 1 Composition of lists in the category clustering task. Classes of nouns from the Battig & Montague (1969) norms having a frequency of production greater than 10 in 442 responses in the norms

List 1	*List 2*	*List 3*	*List 4*	*List 5*
Alcoholic beverage	Kitchen utensil	Unit of distance	Relative	Sport
Tool	Part of the body	Metal	Stone	Weather phenomenon
Food flavouring	Fruit	Rank	Reading material	Clothing
Fuel	Weapon	Colour	Animal	Part of house
Geographical feature	Dwelling	Cloth	Unit of time	Musical instrument

Table 2 Digit span: mean errors per serial position for the three treatments

Treatment	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Placebo	6.88	11.29	12.09	15.50	19.44	18.21	21.97	19.74	7.94
Nitrazepam	8.88	15.09	17.50	20.53	23.76	24.47	23.91	20.82	5.15
Hyoscine	9.30	14.67	15.67	16.78	21.00	22.39	23.76	19.12	7.36

Category clustering

(i) *Number of words recalled.* Errors of omission were pooled over successive ten serial positions. Table 3 shows the mean values of errors for blocks of few items in each of the five lists. Three factors were combined in an analysis of variance: drug treatments, lists, and blocks. There were no significant terms involving drugs: neither as a main effect ($F=1.07$; d.f.$=2/99$; $P>0.05$) nor as an interaction (Drugs × lists: $F=1.26$; d.f.$=8/396$; $P>0.05$. Drugs × blocks: $F=0.51$; d.f.$=4/198$; $P>0.05$. Drugs × lists × blocks: $F=0.62$; d.f.$=16/792$; $P>0.05$).

(ii) *Indices of clustering.* Two measures of clustering were employed: the C-score (after Dalrymple-Alford, 1970) and the BDD-score (after Bousfield & Bousfield, 1966).

The C-score is calculated from R (the number of times a category item follows an item from the same category) and max R (the maximum possible number of category repetitions in a list) where C = R/max R in the present case. The C scores they were arc-sin transformed in order to satisfy the conditions of normality required by the analysis of variance model (Winer, 1962). Means for non-transformed scores are given in Table 4.

An analysis of variance employing drugs as a independent factor and lists as a related factor gave no significant main effect ($F=0.54$; d.f.$=2/99$; $P>0.05$) nor interaction (Drug × lists; $F=0.69$; d.f.$=8/396$; $P>0.05$).

Due to the restricted range of scores given by the C-score measure, data using the BDD-score was also calculated. This index of clustering is calculated from R − E(R) where R is as above, and

$$E(R)=\frac{\sum_i n_i^2}{N}-1$$

(where n_i is the number of items recalled from category i and N is the total number of items recalled). Means are given in Table 5

An analysis of variance using untransformed data again gave no significant effects of drug (Drugs $F=0.35$; d.f.$=2/99$; $P>0.05$. Drug × lists, $F=0.53$; d.f.$=8/396$; $P>0.05$).

Table 3 Drug effects on category clustering. Mean error for successive blocks of ten items in each of five lists

		Placebo	*Nitrazepam*	*Hyoscine*
List 1	Block 1	2.97	3.65	2.44
	Block 2	2.26	3.62	1.82
	Block 3	2.56	3.35	2.09
List 2	Block 1	2.47	2.47	2.26
	Block 2	3.29	3.41	2.03
	Block 3	3.26	3.91	3.21
List 3	Block 1	2.82	3.88	2.03
	Block 2	2.91	3.47	2.18
	Block 3	2.71	3.24	3.00
List 4	Block 1	3.00	3.94	1.97
	Block 2	2.62	3.15	2.59
	Block 3	2.53	3.79	1.91
List 5	Block 1	2.79	3.47	2.35
	Block 2	2.76	2.94	2.71
	Block 3	2.85	3.29	2.38

Table 4 Category clustering. Mean C – scores for clustering in each drug treatment and each of five lists. Means based on untransformed data

	List				
Treatment	*1*	*2*	*3*	*4*	*5*
Placebo	0.75	0.80	0.82	0.84	0.81
Nitrazepam	0.79	0.88	0.87	0.94	0.90
Hyoscine	0.77	0.86	0.89	0.91	0.88

Table 5 Category clustering. Mean BDD – scores for clustering in each drug treatment and each of five lists

	List				
Treatment	*1*	*2*	*3*	*4*	*5*
Placebo	9.63	10.42	10.73	11.65	10.63
Nitrazepam	8.97	10.98	11.16	12.16	11.12
Hyoscine	9.38	11.39	11.81	12.60	11.16

Discussion

The data for digit span show no differential effect of the type of drug employed. The psychological action of these drugs does not reflect the putative pharmacological distinction between them. The locus of the effects within the list is identical as is the extent of the effect. Performance on early items in serial lists of this sort is generally considered to be result of the action of Primary Memory and it appears from these data that the drugs influence the action of this store. The later items of the list are thought to be under the aegis of the Precategorical Acoustic Storage (PAS). Crowder & Morton (1969) envisage that PAS is an acoustic buffer store containing information in its raw and unelaborated state. Due to the short-lived span of this store it only encompasses the last presented items whilst the first items in the list have passed on to the Primary Memory with its larger capacity and higher order coding mechanisms. The present data indicate that the action of PAS is not influenced by either hyoscine or nitrazepam.

We cannot conceal our disappointment in the absence of a drug effect on category clustering. This is in part due to the substantial evidence showing that the retrieval of different classes of material is easily disrupted by such factors as noise (Hörrmann & Osterkamp, 1966; Smith, Jones & Broadbent, in preparation) and alcohol (Eich, Weingartner, Stillman & Gillin, 1975). At the outset the apparent sensitivity of category clustering led us to believe that this task would be disrupted by relatively small doses of the drugs employed in this study. Despite an extremely lengthy and sophisticated analysis this promise was unfulfilled. Nevertheless the differential effect of drugs on the tasks employed might provide insights into the *modus operandi* of drug effects on retention and lead to the formulation of a tentative hypothesis worthy of further study.

The main difference between the digit span and category clustering task was the demands placed on serial recall: in the former task a small set of overlearned items had to be produced in the correct order whereas in the clustering task the original order of items required rearrangement for successful clustered recall. It seems reasonable to suppose, on the basis of the present data, that the drug effects are restricted to material requiring ordered recall. That is, the effect of these drugs is to interfere with cues for order such that recall of digit strings is impaired. At the same time clustering is not impaired since order cues are not required for recall. This notion tacitly assumes that, in normal circumstances, order cues do not hinder recall. Any formulation which posits that centrally depressant drugs reduce the impediment offered by order cues would naturally predict that clustering would improve rather than show no effect as in the present case. Despite these uncertainties the effect of drugs on differences between ordered and non-ordered recall would seem to merit systematic study. In an analagous approach Hamilton, Hockey & Quinn (1972) found that noise produced its effect only when recall was required in fixed rather than random order.

The present study highlights the danger of regarding memory as a single cohesive corpus. In our introduction we referred to 'anti-memory effects', but the present study exemplifies the fact that some memory tasks are more sensitive than others to the action of drugs. Moreover, the data for digit span sustain an interest in establishing the critical differences between various aspects of drug-induced memory deficit.

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(Received August 14, 1978)