THE EFFECTS OF DIAZEPAM AND OXPRENOLOL ON SHORT TERM MEMORY IN INDIVIDUALS OF HIGH AND LOW STATE ANXIETY

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- 1 The effect of oral doses of diazepam (5 mg) and oxprenolol (80 mg) on short term memory of normal individuals stratified for 'state' anxiety levels has been investigated.
- 2 Normal student volunteers were stratified into high and low anxiety groups on the basis of responses to the Spielberger 'A-state' scale. Subjects were then randomly administered active drug or placebo and given a form of running memory test performed under a variety of conditions in which variable rate of item presentation and articulatory suppression were used.
- 3 Diazepam significantly reduced the errors of recall in the running memory test in the high anxiety group and produced a distinct separation of response from the low anxiety group under the test conditions of slow item presentation with articulatory suppression. Oxprenolol had no effect on the short term memory test in either high or low anxiety groups in any experimental test situation.
- 4 These results are compared to previous work in which generally a deleterious effect of diazepam on short term memory in normal volunteers has been reported. The implications of these findings are further discussed in relationship to possible models of memory function.

Introduction

The detrimental effects of high anxiety on memory have been well documented (Eysenck, 1977). Although the concept of anxiety has always been difficult to define, a useful method of categorisation is the division into 'state' anxiety (i.e. a transitory emotional state or condition) and 'trait' anxiety (i.e. a relatively stable and continuous individual difference) (Spielberger, 1966). Experimental evidence suggests that stress and high levels of state anxiety may have a detrimental effect on short term memory, whereas trait anxiety has negligible effects (Hodges & Durham, 1972; Knox & Grippalid, 1970; Mueller, 1976). In spite of this, centrally acting anxiolytics like diazepam, have shown an overall deleterious effect on formal testing of short term memory (Klienknecht & Donaldson, 1975), when a facilitative effect of the drug might have been expected in anxious subjects. This possibility has not been previously investigated in a subgroup of 'anxious' normal individuals.

Generally, symptoms of anxiety have both psychological (e.g. tension, fear etc.) and physiological (tachycardia, sweating etc.) manifestations. The latter acting both as a response to the central nervous

state of anxiety and as a reinforcement of further anxiety (Breggin, 1964). It is possible that peripherally acting drugs which influence the physiological component of anxiety (e.g. β -adrenoceptor blocking drugs) may decrease the number of somatic stimuli and by reducing transient 'feelings' of anxiety mimic the effects of diazepam. Behavioural symptoms of anxiety have been alleviated by small doses of β -adrenoceptor blockers (Siltanen & Janne, 1976; Liden & Gottfries, 1974), but the possibility of indirectly produced central effects has not been previously studied.

We have, therefore, investigated the effects of diazepam and the β -adrenoceptor blocker oxprenolol on short term memory in two groups of normal volunteers stratified into low and high anxiety groups using the A-state form of the Spielberger state/trait anxiety inventory (Spielberger *et al.*, 1969). Using a form of running memory test (Hamilton *et al.*, 1977), we introduced into the study variable conditions of different rate of item presentation and articulatory suppression to assess the possible drug effects on underlying mechanisms in short term memory. We

have attempted to highlight any particular task conditions which may have induced more stress and thus have been more susceptible to drug effects.

Methods

Two identical experiments were carried out to ensure that placebo groups were closely comparable to their corresponding drug groups.

Subjects

Volunteers (both male and female) were recruited from the general body of university students (age range 18–24 years). Subjects were assigned to either a 'high anxiety' or 'low anxiety' group on the basis of scores obtained on the Spielberger A-state scale. State anxiety is assessed on the basis of responses to a series of 20 statements such as 'I feel calm' or 'I feel anxious' etc. Subjects were required to rate each statement on a four point scale according to how they felt at that particular moment. Responses indicating high anxiety scored highest. Thus, individuals' degree of state anxiety was directly proportional to their overall score. The median score was calculated for each experimental group at the end of the whole test procedure, but before the randomisation code for drug or placebo allocation had been broken (see later). Those subjects that scored above and below the median score for that experiment were assigned to the high and low anxiety groups respectively (Table 1).

Drugs

All subjects were given either active drug or identical placebo. In experiment 1, twenty-four subjects were randomly allocated 5 mg diazepam or placebo. Similarly, in experiment 2, twenty subjects were

randomly allocated either 80 mg oxprenolol (2×40 mg tablets) or identical placebo (Table 1). The drug or placebo was administered after the subjects had completed the A-state form and 1 h prior to the running memory test. To ensure, as far as possible, identical procedures, all subjects were told that there was a 50% chance that they would receive the active drug which might have mild tranquillising or soporific effects. Subjects were not fasted but all testing was performed at least 1–2 h after a light meal (breakfast or midday). Subjects were, however, instructed to refrain from smoking and not to drink any coffee, tea or alcohol on the test day. Previous data has suggested that under these conditions peak plasma concentrations of both diazepam and oxprenolol are achieved approximately 1 h after oral dosing (Breimer, 1979; Barnett *et al.*, 1980). For experiment 2 only, in order to assess possible somatic response to oxprenolol, subjects were asked to complete in addition to the A-state form, a 'bodily symptoms' scale (Tyrer, 1976), prior to drug administration, immediately prior to memory testing and finally at the completion of the test. Examples of 'bodily symptoms' included shaking, trembling, palpitations etc., and subjects were instructed to mark along a 10 cm line the extent to which they felt each symptom. Three measures of resting pulse rate were also obtained in experiment 2 at similar time points.

Task

Tests were performed on each subject individually. The running memory task consisted of the recall of the last eight items of an indeterminate length of randomly generated consonants displayed on the Visual Display Unit of a PET microcomputer. An average of thirty items (range 18 to 40) were always presented for each sequence. A total of 40 sequences were presented to each subject; a block of 10 sequences for each of the four experimental conditions

Table 1 Mean anxiety scores and s.e. mean for the four experimental groups in experiments 1 and 2

	Drug treatment	Anxiety level	Number of subjects	Mean anxiety* score
Experiment 1	Diazepam	High	6	43.8 $\pm$ 1.62
		Low	6	29.0 $\pm$ 0.51
	Placebo	High	6	41.8 $\pm$ 1.06
		Low	6	32.2 $\pm$ 1.68
Experiment 2	Oxprenolol	High	5	35.8 $\pm$ 0.80
		Low	5	29.8 $\pm$ 1.12
	Placebo	High	5	41.2 $\pm$ 1.47
		Low	5	26.0 $\pm$ 0.80

* Anxiety score was derived from responses to the Spielberger A-state scale (see text), and the maximum score was 80. Analysis of statistical differences between scores in each group are detailed in the results section.

Table 2 Experimental conditions used during the running memory test*

Experimental conditions		Number of trials
Rate of presentation**	Articulatory suppression†	
slow	+	10
slow	—	10
fast	+	10
fast	—	10

* order of experimental conditions was randomly allocated to each subject

** slow presentation = 2 s between items

fast presentation = 0.5 s between items

† subjects continuously repeated aloud the word 'the' during test sequence

+ = with articulatory suppression

— = without articulatory suppression

(Table 2). An auditory tone indicated both the end of each sequence and also the that subject had 10 s to correctly recall and write down the last eight consonants in their order of presentation. Because each sequence varied in length, subjects were not aware of which eight items they would have to recall until after the tone had been presented. This made the task more difficult and provided additional stress for the subject. Subjects performed the task under four different experimental conditions. These were formed by combination of either slow or fast item presentation with or without articulatory suppression (Table 2). The latter condition required the subject to continuously repeat aloud the word 'the' during the test sequence. All items remained on the screen for 0.5 s and the four test conditions were presented in random order for each subject. Subjects were monitored continuously via an intercom system during the experiment to ensure that test conditions were correctly observed and in particular that articulatory suppression was uniformly and adequately carried out. The number of errors in consonant recall in correct serial order for each category of item presentation, were recorded for all subjects. The results were then analysed by analysis of variance comparing in each experiment drug and placebo groups, high and low anxiety subjects and conditions of item presentation in the digit span test. The level of statistical significance was accepted at $P < 0.05$.

Results

The mean scores for high and low anxiety subjects were significantly different ($P < 0.01$) within each treatment group for both experiments (Table 1). Conversely the mean scores did not differ significantly between placebo and drug groups within each anxiety group except in experiment 2 in the high anxiety group where placebo subjects scored significantly higher ($P < 0.05$) than drug subjects (Table 1).

Experiment 1

Two subjects both in the placebo group spontaneously complained of drowsiness, otherwise there were no side effects. From the analysis of variance, the main effects of rate of item presentation, ($F(1,20) = 5.51$, $P < 0.01$), articulation instructions, ($F(1,20) = 11.88$, $P < 0.001$) and serial position, ($F(7,140) = 313.75$, $P < 0.007$) were significant, performance being worse for earlier serial position items, during articulatory suppression conditions, and at the fast rate of item presentation. The five-way interaction between all factors was also significant, ($F(7,140) = 2.79$, $P < 0.01$). Subsequent four-way analysis of variance between drug treatment, anxiety level, articulation instructions and serial position, produced a significant interaction under the slow rate of item presentation, ($F(7,140) = 2.16$, $P < 0.05$), but not under the fast rate, ($F < 1$). Further investigation indicated that the interactions between drug treatment, anxiety level and serial position were significant under articulatory suppression conditions, ($F(7,140) = 2.26$, $P < 0.05$), but absent when subjects were free to articulate the items ($F = 1.2$).

Overall, in this experiment in the placebo group, high anxiety subjects produced significantly more errors of recall than low anxiety subjects during the slow rate of item presentation under articulatory suppression conditions ($P < 0.05$). This was particularly noticeable for early serial positions (Figures 1a and b). Furthermore, under these test circumstances diazepam significantly improved the performance of the high anxiety group as compared to placebo ($P < 0.05$) and as previously this effect was more noticeable for early serial positions (Figure 1a). Conversely the performance of the low anxiety group deteriorated with the active drug (Figure 1b) although this was not significantly different. The overall effect, however, was seen as a distinct separation of the responses to diazepam of the two anxiety groups under these particular test conditions.

Figure 1 Effect of diazepam (●—●) or placebo (○—○) in high (a) and low (b) anxiety subjects on short term memory test performed under the conditions of slow item presentation and articulatory suppression (see text).

Percentage errors in recall of items presented in the running memory test are plotted according to serial position preceding the auditory tone. '↓' indicates the auditory tone; thus, serial position 8 identifies the item most recently presented.

Experiment 2

Separate analyses were carried out on the scores obtained for the 'bodily symptoms' scale and pulse rate measures. There was no differences between oxprenolol or placebo for the bodily symptoms rating scale. Mean pulse rate for all subjects significantly decreased during the test period from 80.6 ± 2.3 to 70.0 ± 3.3 ($P < 0.01$), but there was no significant difference between treatment groups or high and low anxious individuals. The error data for the digit span test were analysed as for experiment 1. There was a main effect of serial position, ($F(7, 112) = 151.39$, $P < 0.001$), articulation instructions, ($F(1, 16) = 48.16$, $P < 0.001$) and rate of item presentation ($F(1, 16) = 36.38$, $P < 0.001$). Thus, for all subjects, more errors were made for early serial position items and when subjects were instructed to suppress subvocal or overt rehearsal of items at the fast rate of presentation.

In this experiment, however, no significant differences were found in the placebo group for errors produced between high and low anxiety subjects ($F = 1.23$). In addition, no differential main effect of oxprenolol was seen between the groups under any of the test conditions used ($F < 1$). For comparison with diazepam the results for slow item presentation with articulatory suppression after oxprenolol or placebo are depicted in Figure 2a and b.

Discussion

The results of these experiments suggest that under particular test conditions, the short term memory of

highly anxious subjects is improved by a small dose of diazepam, whereas in low anxiety subjects, the drug may have the opposite effect. These findings are in contrast to those of other workers who have reported a generally deleterious effect of diazepam on short term recall in groups of volunteers unstratified for differences in levels of anxiety (Groves-White & Kelman, 1971; Hart *et al.*, 1976; Jones *et al.*, 1978). In the test procedure from at least one of these other studies the task was group administered and the subjects were known to each other (Jones *et al.*, 1978). This may have produced a sample of subjects low in state anxiety, and thus, directly comparable to the low anxiety group of the present work. Oxprenolol was not effective in altering the performance of either high or low anxiety subjects in the same memory task. In addition, there was no effect of the drug on any of the measures of somatic anxiety. Although oxprenolol, in similar doses of those we have used, has been shown to be anxiolytic in previous work, this effect was in situations in which sympathetic (primarily somatic) reactions to anxiety were prominent. For example, 'stage-fright' in musicians (James *et al.*, 1977) or public speaking (Taggart *et al.*, 1973). The apparent lack of effect in this study may be due to the absence of excessive peripheral sympathetic responses to anxiety in the normal individuals we have tested.

Significant differences in short term memory were seen in experiment 1 between high and low anxiety subjects in the placebo group, using slow rate of item presentation with articulatory suppression. This was not reproduced in experiment 2. This discrepancy underlines the difficulty of assessing the effects of

Figure 2 Effect of diazepam (●—●) or placebo (○—○) in high (a) and low (b) anxiety subjects on short term memory test performed under the conditions of slow item presentation and articulatory suppression (see text).

Percentage errors in recall of items presented in the running memory test are plotted according to serial position preceding the auditory tone. '↓' indicates the auditory tone; thus, serial position 8 identifies the item most recently presented.

mood variation in normal individuals and would, perhaps, have been more consistent with a greater difference between the 'state' anxiety groups. However, marked separation in performance of the two anxiety groups was produced with diazepam under specific test conditions and this may provide a useful basis for further investigation of the interrelationships of anxiety and memory. The fact that oxprenolol did not produce this differential effect may be due to its lack of anxiolytic activity in this group of volunteers or to the lower scores of the high anxiety group administered this drug as compared to those who took diazepam.

The differential effects of diazepam in high and low anxiety subjects may be due to functional differences in short term memory performance. The effects of diazepam were apparent when sequences of consonants were presented at a slow rate with articulatory suppression, i.e. in the absence of subvocal or overt rehearsal. Initially, this result seems surprising, as we had expected the detrimental effect of high anxiety to be apparent under the test conditions producing greatest stress, i.e. fast item presentation with articulatory suppression. However, previous work (Quarton & Talland, 1962) has suggested that slow item presentation allows subjects to use more complex memory strategies which might be adversely affected by anxiety (Meller, 1976). Thus, although both high and low anxiety subjects have the same variety of strategies available to them, highly anxious individuals may be less flexible than low anxiety subjects in their choice of strategies. It is possible, therefore, that the drug does not affect the rehearsal mechanism but instead effects higher order 'be-

havioural strategies', such as the ability to code or chunk together items for recall (Atkinson & Shiffrin, 1968). Further supportive evidence for this general concept comes from our study where the effects of anxiety were evident for early serial position items, which can only be maintained in memory with more complex strategies, but not for later serial position items which need only rote rehearsal for their retention. However, it would be reasonable to suppose that the effects of anxiety are not just restricted to one component of short term memory but that other functional mechanisms are being affected (Hitch, 1980).

In summary, 5 mg diazepam was effective in improving the short term memory performance of highly anxious individuals under certain test conditions, but 80 mg oxprenolol had no effect. This is an important finding as previous work has almost always shown an adverse effect of diazepam in similar tasks. Interestingly, a recent study of psychomotor performance in normal individuals has shown a similar facilitatory effect of low dose diazepam in subjects stratified for high anxiety (Nakano *et al.*, 1978). We would, therefore, suggest that when assessing the effects of anxiolytics on memory performance the subjects baseline 'state' anxiety level be taken into account and an appropriate method for individual testing be adopted, so that drug effects may be highlighted. In addition, the differential response made by high and low anxiety subjects to diazepam may be attributed to differences in their choice of strategies for retaining items in short term memory. This hypothesis is being investigated with studies now in progress.

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