State-Dependent Retrieval and Chlorpheniramine

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State-dependent retrieval is demonstrated when material learned under drug is best recalled in that same drug state. To test whether state-dependency can be induced by an antihistamine, we administered chlorpheniramine (AH) in a 'cross-over' design with four experimental conditions based on drug state at encoding and recall. These were AH–AH, AH–Placebo, Placebo–Placebo and Placebo–AH. There were three measures of retrieval: free recall of a list of 20 words, followed by cued recall of the same list of words and free recall of a short passage of information. For all of these measures, state-dependency was demonstrated: subjects performed better in the congruent (AH–AH and Placebo–Placebo) than in the disparate (AH–Placebo and Placebo–AH) conditions. Given that their sedative effects are well known, many students take antihistamines for the management of hay fever only as necessary. However, the clear implication of the present study is that intermittent use of chlorpheniramine may result in retrieval difficulties. © 1998 John Wiley & Sons, Ltd.

KEY WORDS — antihistamine; human memory; retrieval; context; state-dependency

INTRODUCTION

Explanations of human memory have been framed in terms of encoding and/or storing material and the retrieval of memory traces. Storage failure can be defined as the inability to produce a permanent memory trace of a given event. This inability could be because of a failure of transfer from some short term store to a long term store, because the trace was lost before transfer to the long term store, or because of some initial encoding difficulty. Encoding and/or storage failure cannot provide a complete explanation of forgetting because it is possible to later remember something once forgotten. This patchiness in human memory is consistent with explanations of forgetting in terms of retrieval failure (see, for example, Parkin, 1993).

Forgetting because of retrieval failure refers to an inability to locate an existing memory trace after it has been stored. Locating memory traces is likely to depend critically on the degree of overlap between features encoded in the memory trace and features present in the retrieval environment (Tulving and Thomson, 1973). For example, category names (e.g. animal) for word lists (e.g. cow, rat, etc.) provide effective cues to retrieval of

items that would not be retrieved under non-cued recall conditions (Tulving and Pearlstone, 1966). Cues for retrieval can take a multitude of forms and there is an increasing awareness of the importance of context as a determinant of retrieval. In its broadest sense, context can include background environmental stimuli and the stimuli associated with particular psychoactive states such as mood (Bower, 1981; Clark and Teasdale, 1981). In addition, various drug states during learning can provide internal cues that are encoded as memory traces and later matching these cues promotes retrieval of the target memory. The effect of contextual reminders like drug state or mood has been termed state-dependency. Very similar effects are seen when the external environment (e.g. learning and test on land versus underwater) is manipulated as a cue to recall (Godden and Baddeley, 1975).

Early state dependent studies were carried out with animals after Overton (1964) found that sodium pentobarbital produced 'dissociated learning' in rats. Overton found that tasks learned in a particular drug state may not transfer to the non-drugged state, but that learning could be reactivated when the rat was returned to the initial drug state. Investigations of state-dependency in human subjects soon followed. Goodwin *et al.* (1969) conducted one such study with alcohol. Many non-alcoholics have trouble remembering, when sober, events which occurred while they were intoxicated. However, providing the quantity of

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alcohol is not too great, information acquired when the subject was intoxicated is better recalled when intoxicated than when sober (Goodwin *et al.*, 1969). Under these conditions, alcohol affects retrieval rather than encoding or storage *per se* (cf. Goodwin *et al.*, 1970). There were further studies of the state-dependent effects of recreational drugs, of which the best known study used marijuana (Eich *et al.*, 1975). Eich and coworkers showed that whilst there was no state-dependent effect of marijuana when the subjects were provided with explicit cues to recall (in this case category labels), there was a clear state-dependent effect when no (external) cues to recall were available.

Not all psychoactive drugs induce clear state-dependent effects and interest in the phenomenon was reduced because of its apparent lack of robustness. For example, Hurst *et al.* (1969) found no evidence that amphetamine treatment could provide a cue to recall of paired associates. On the other hand, using a free recall task (drawing geometric shapes), Bustamante *et al.* (1970) reported that amphetamine administration did result in state-dependency. Subsequently, Eich (1980) clarified the circumstances under which state-dependent effects are reliably induced: 88% of the studies showing evidence for state-dependent effects measured free recall, whereas 90% of studies that failed to show state dependency used either cued recall (e.g. the paired associates used by Hurst *et al.*, 1969) or recognition tests (that simply require a judgement of familiarity). This suggests that internal state becomes important as a cue in conditions in which testing takes place in the absence of the 'observable' cues typical of cued recall and recognition tasks. Thus when contextual cues are not overshadowed by more explicit reminders, state-dependent effects are consistent and reproducible. Furthermore, since the effectiveness of any such internal cue may depend on its salience relative to other available cues, state-dependency is rarely produced by treatments that do not also result in main effects on learning and/or recall (e.g. Eich *et al.*, 1975; Goodwin *et al.*, 1969; Swanson and Kinsbourne, 1976).

Antihistamine tablets are taken sporadically to relieve the symptoms associated with allergic reactions, e.g. itchy eyes and runny nose, and to treat nettle stings and insect bites. They are also taken over longer periods to manage seasonal rhinitis or hay fever. Hay fever is the commonest of all allergic diseases: up to 20% of the population of Western countries suffer from non-viral rhinitis

and about 50% are allergic in origin (Jackson and Cerio, 1989). In the majority of cases antihistamines will be prescribed for such allergies, and in many cases they may be bought over the counter without visiting a doctor. Most freely available antihistamines are first generation H₁ antagonists, e.g. diphenhydramine and chlorpheniramine. There is some concern over their uncontrolled use because they have been linked to increases in accidents, decreases in well being and poor performance (Berman and Ross, 1996; Rombaut and Hindmarch, 1994). For example, diphenhydramine has been shown to impair performance that requires sustained attention or a skilled visual-motor response and to produce sleepiness (e.g. De Roeck *et al.*, 1990; Schweitzer *et al.*, 1994). Similarly, diphenhydramine significantly altered the ability of (non-allergic) office workers to accomplish tasks requiring clerical, arithmetic, memory and attentional skills (Adelsberg and D'Amico-Beadon, 1990).

However, whilst several studies have examined the effects of antihistamines on performance and memory (see, for example, Rombaut and Hindmarch, 1994) there are none on state-dependent effects. The present study was designed to establish whether the internal state produced by chlorpheniramine maleate provides cues to retrieval that when missing result in retrieval impairment. We selected this treatment first because it is associated with several non-specific effects such as drowsiness and should therefore be salient to our subjects (Harvey *et al.*, 1996). Second, Eich (1980) presents evidence that state-dependent effects are clearest when there is also an effect of the drug on encoding or recall and such main effects seem most likely to be associated with an antihistamine treatment that results in drowsiness.

We used three recall tasks of varying levels of difficulty because (if they do occur) main effects can also hinder interpretation because of ceiling or floor effects. For example, drugs that improve learning might facilitate recall to the extent that memory tests are simply not sensitive to any possible difference due to drug state (see, for example, Hurst *et al.*, 1969). Alternatively, material learned while the subject is drugged may be poorly encoded in the first place (Goodwin *et al.*, 1970). We also used a 24 h interval between learning and recall to allow elimination in the cross-over (AH-Placebo) condition (chlorpheniramine tablets would normally be taken at four hourly intervals). This recall interval also allowed us to control for

The three measures of retrieval were free and cued recall of the same word list and free recall of textual material. Following Eich (1980), we predicted that any state-dependent effects will be manifest in free but not cued recall. In addition to providing a more difficult free recall task, the inclusion of a passage of text was intended to test the generality of any effects to stimulus materials more similar to those encountered in tasks like revising and recalling for examinations. A pilot study confirmed that the passage selected supported consistent recall without ceiling or floor effects.

Subjects

100 undergraduates at the University of Nottingham (Table 1). Respondents were asked to rate their general state of health by marking a point on a scale with extremes of 'very good' and 'very poor'. Subjects were not included if they marked below halfway on the line, nor if they were taking any other medication, nor if they had any previous allergic reaction or unpleasant side effects in response to antihistamines. The questionnaire also allowed exclusion of those with known contraindications for antihistamine use (pregnancy, breast feeding, glaucoma, epilepsy, enlarged prostate, overactive thyroid, very high blood pressure, heart, liver or chest disease).

Of the 76 respondents, 28 met all criteria for inclusion in the study and of these 23 volunteered with a firm commitment to return for the re-test. To make up numbers, one subject was included who had never taken antihistamines before: she was assigned to the Placebo–Placebo condition. All of the 24 volunteers were university undergraduates of average age 19.6 years (range 18–21 years). There were 17 women and seven men reading a range of degree courses, none of whom were aware

Table 1. Questionnaire for selection of subjects

Name _____
Degree Course _____
Age _____

1) Please mark the line below to indicate your general state of health
Very Good _____ Very Poor _____

2) Are you taking any medication (not including anti-histamines) _____ Yes/No

3) Have you ever taken an anti-histamine tablet before _____ Yes/No
if yes;
i) When was the last time you took a anti-histamine tablet _____
ii) Was this taken (please circle appropriate) as a one off _____
over a period of days _____
over a period of weeks _____
over a period of months _____
other (please specify) _____

iii) Did you have an allergic reaction or any unpleasant side effects _____ Yes/No

iv) What brand of anti-histamine was it? _____

4) If you are pregnant or breast feeding or have Glaucoma
Epilepsy
Enlarged Prostate
Overactive thyroid
Very high blood pressure
Heart, liver or chest disease
or are unsure of any of the above, please tick box []

Thank you for your time and cooperation

of the purposes of the study. The subjects were allocated (six each) to the four conditions: encode under AH, recall under AH (AH–AH); encode under placebo and recall under placebo (Placebo–Placebo); encode under AH, recall under placebo (AH–Placebo) and encode under placebo, recall under AH (Placebo–AH).

In the final sample, six of the volunteers had taken antihistamines as a one off, three had taken them over a period of days, six over a period of weeks and eight over a period of months (and one subject in the Placebo–Placebo condition had never taken antihistamines before). On the question of when antihistamines had last been taken, six were uncertain, 13 had taken them over the preceding spring/summer and four had last taken them over 1 year ago. Most of the sample were uncertain as to which brand they had taken. None of the subjects were taking antihistamines at the time of the study. Four willing subjects who were not eligible to participate in the study, as they had not taken antihistamines before, were used to pilot the passage of text for the second free recall task.

Ethics committee

The project was approved by the Ethics Committee, Department of Psychology, University of Nottingham, who agreed that the selection criteria provided protection for the subjects.

Materials

The antihistamines used were *Piriton* allergy tablets containing 4 mg of the antihistamine chlorpheniramine maleate. The placebo used was provided by a *Lloyds Chemist* vitamin C tablet containing 500 mg vitamin C (safe at doses as high as 10,000 mg per day; Bendich and Langseth, 1995). Both the chlorpheniramine and vitamin tablets were bought over the counter. The initial questionnaire was accompanied with a short description of antihistamine usage. Before testing, all subjects received a written instruction sheet that explained the procedure. This also warned against drinking or driving for 4 h after the antihistamines were taken and functioned as the consent form. Water was provided to aid with the ingestion of the tablets.

The same list of words was used to test both free and cued recall (Table 2). The list was comprised of five categories each containing four taxonomically related nouns derived from Battig and Montague's

Table 2. Word list for tests of free and cued recall

Kitchen Utensil

Knife
Spoon
Fork
Pan

Fruit

Apple
Orange
Peach
Pear

Carpenter's Tool

Hammer
Saw
Nails
Chisel

Weather Phenomenon

Hail
Wind
Rain
Snow

Part of Building

Window
Door
Roof
Wall

(1969) taxonomy norms. Two of the categories had an average word length of four and the remaining three categories had an average word length of five. The overall average word length was five letters, no word had more than six letters or less than three. Each category list was compiled using words within the top eight exemplars of that category (Battig and Montague, 1969). Words with a strong association were chosen to avoid floor effects in recall with the 24 h gap between encode and recall. There were 20 words to be remembered (the subjects were not expected to remember the category names). A stopwatch was used to ensure that the reading length of the list of words did not vary. The passage was selected after a pilot study established the appropriate level of difficulty to avoid ceiling or floor effects with the 24 h interval between learning and recall. The final selection was taken from *Human Factors for Pilots* (Green *et al.*, 1991) reproduced in CG Palacio (font size 14 at 1.5 line spacing) to minimise sensory difficulties. The passage was 134 words long, grouped into 18 units of information for the purposes of scoring recall (Table 3).

Table 3. Passage for test of free recall

Loss of cabin pressurisation can occur in flight. The rate of loss may be very slow with the crew recognising the problem and making appropriate height reductions before passengers are aware of anything amiss. Very occasionally there is rapid decompression such as may result from the loss of a window or door or terrorist action (in June 1990 a British Airways BAC 1-11 en route from Birmingham suffered the loss of the captain's windshield and a pilot was almost lost when sucked out of the cockpit). In that event the occupants are very abruptly exposed to the full rigours of high altitude with all the attendant risks of hypoxia, cold and decompression sickness and all on board may need to use emergency oxygen to avoid hypoxia.

Scoring Criteria

- loss of cabin pressurisation can occur
 - rate of loss may be very slow
 - with the crew recognising the problem
 - and making appropriate height reductions
 - before passengers are aware of anything amiss
 - very occasionally there is rapid decompression
 - such as may result from the loss of a window/door/terrorist action
 - June 1990
 - British Airways BAC 1-11
 - en route from Birmingham
 - suffered the loss of the captain's windshield
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 - occupants very abruptly exposed to full rigours of high altitude
 - with attendant risks of hypoxia
 - cold
 - decompression sickness
 - all on board may need to use emergency oxygen
-

A supplement to the questionnaire asked the subjects to indicate any side-effects associated with the antihistamines they had taken and whether they used antihistamines continuously or intermittently over exam periods.

Statistics

A three-way $2 \times 2 \times 3$ mixed (split plot) design analysis of variance (ANOVA) was performed on the percentage correct recall after encoding and recalling under either AH or Placebo, for each of the three recall tests. Post hoc comparisons were performed by simple main effects analysis and F-scheffe tests. All analyses were conducted using *ExperStat* on a Macintosh.

Procedure

With the exception of the subject who had to be in the Placebo–Placebo condition, each subject was pseudo-randomly assigned to one of the four conditions so that within each group there was

variation in the length of time since the subjects had last taken antihistamines. The four conditions needed to demonstrate state-dependency were generated by a 2×2 between subjects design. The independent variables were drug state at encode (Encode) and drug state at retrieval (Retrieval). Each factor had two levels since subjects received either AH or placebo, thus generating four experimental conditions (AH–AH, Placebo–Placebo, AH–Placebo, Placebo–AH). Any state-dependent effect would be indicated by a significant interaction between Encode and Retrieval. Test-type was within-subjects. Subjects in all four conditions were first tested for their free recall of the list of words. This test was followed by the cued recall test in which the category names were provided for the same list of words. Finally the subjects were directed to recall as much of the passage as they could.

There was one experimental condition per test session. The number of subjects tested at any one time ranged from two to four, depending on availability, and the same people were always together in both the encode and recall condition. For each test

session, the test environment was kept constant between encoding and recall: subjects were asked to return to the same place and to sit in the same seat, at the same time the next day to perform the recall test. The subjects were first given the written instructions, which were also read aloud. They were told that the purpose of the study was to investigate how different antihistamines affect memory and that they should take the antihistamine tablet with water 30 min before the test. Subjects were also informed at this point that the test was to memorize a list of 20 words (given in Table 2), grouped in fours with a descriptive heading (that they need not remember) and that they would also be required to memorize a short passage (see Table 3). They were asked to return at the same time the following day and take another antihistamine before the recall test. Each subject was then given either a placebo or chlorpheniramine maleate tablet to be taken immediately with water and released until the start of the session. Then 30 min after the tablet was taken, the list of words was read through once with a total presentation time of 35 s. Second, subjects were given the passage and instructed to read it at their own pace.

Exactly 24 h later the subjects returned for the retest. They were again given either placebo or chlorpheniramine maleate and asked to return to their respective seats in 30 min to perform the recall test. All the recall tests were written. Subjects started with the free recall of the word list on a single sheet of A4 paper with 1–20 printed in the left-hand margin. Subjects were allowed 2 min to write down as many of the words presented in the previous session as possible. The results sheets were collected and score sheets for the cued recall task were then distributed. For the cued recall task, score sheets had the category labels typed out with numbers 1–4 written underneath each one. Again subjects were given 2 min to write down as many words as they could remember. Finally, the subjects were given a blank piece of paper and asked to write down all they could remember from the passage. They were directed to recall as key (bullet) points or in full sentences, as they preferred, at their own pace. All results from the free and cued recall tests were converted to percentages for comparability.

The supplement to the questionnaire was distributed. This qualitative data was not intended for formal analysis and is reported only in terms of percentage responses. Subjects were thanked for their time and debriefed. They were given the

opportunity to ask questions and a means of obtaining the final results.

RESULTS

Figure 1 shows the percentage of correct responses in each of the recall tasks for the four experimental conditions. Despite differences in the general level of performance with the three recall tests, Figure 1 shows that (especially in the free recall words test) performance tended to be better in the drug congruent (Placebo–Placebo and AH–AH) than in the drug incongruent conditions (Placebo–AH and AH–Placebo). Statistically, neither of the main effects, drug state at encode (Encode) or drug state at recall (Recall), was significant. However, state-dependency was demonstrated as a significant interaction between Encode and Recall [$F(1,20) = 14.13$, $p < 0.005$] shown graphically in Figure 2.

There was also a significant main effect of test type (Test) [$F(2,40) = 73.58$, $p < 0.0001$]. Three unplanned F-Scheffe tests were performed to explore this main effect. First, cued recall of the word list was overall better than both free recall of that same list [$F = 46.29$, $p < 0.0001$] and free recall of the passage of test [$F = 146.40$, $p < 0.0001$]. Second, comparing the free recall tasks, retrieval was overall better with words than with text [$F = 28.05$, $p < 0.0001$]. However, there were no significant interactions involving Test [largest $F(2,40) = 2.48$, $0.05 < p < 0.1$]. This means that although the state-dependent effect looks clearest in the cued recall words task, intermediate in the free recall words task and less clear in the free recall text task (Figure 1), statistically there is no difference between the test types with respect to state dependency (see Figure 2).

Simple main effects analyses confirmed that there was a main effect of Encode when *recalling* in the AH state [$F(1,20) = 11.84$, $p < 0.005$]. Subjects remembered significantly more when drug state was congruent (AH–AH) than when it was not (Placebo–AH). There was also a simple main effect of Recall when *encoding* in AH state [$F(1,20) = 11.06$, $p < 0.005$]. Again subjects remembered significantly more when drug state was congruent (AH–AH) than when it was not (AH–Placebo). However, recall in the incongruent AH–Placebo and Placebo–AH conditions was only marginally different from that in the Placebo–Placebo condition [$F(1,20) = 3.52$ and 3.96 , $0.05 < ps < 0.1$].

Figure 1. Percentage of correct responses in each of the recall tasks for the four experimental conditions. Treatments: AH = 4 mg chlorpheniramine; VIT = 500 mg vitamin C

Figure 2. Statistical interaction between Encode and Recall showing how overall percentage correct depends on congruence of treatments: AH = 4 mg chlorpheniramine; VIT = 500 mg vitamin C

Questionnaire data

The initial questionnaire showed that 58% of our student sample had used antihistamines. In our final sample (of 23 antihistamine users), there were two reports (in the supplement) that the chlorpheniramine maleate tablets caused drowsiness (not experienced with previous antihistamine usage) and one subject reported photosensitivity (also experienced with his previous antihistamine usage). Of the 12 subjects who reported taking antihistamines during examination periods (again in the supplement which was only given to the final sample), 50% indicated that they took them intermittently at such times. Six subjects did not complete this section of the questionnaire (presumably they could not remember whether they had taken antihistamines at exam time or not).

DISCUSSION

Despite the two reports that the chlorpheniramine maleate tablets caused drowsiness, in all of our memory tests, performance in the AH–AH was comparable to that in the Placebo–Placebo condition. This shows that chlorpheniramine does not necessarily affect learning or retrieval. However, when drug state changed between learning and retrieval (the incongruent AH–Placebo and Placebo–AH conditions), performance was impaired relative to the congruent conditions (Figures 1 and 2). This means that taking a standard dose of chlorpheniramine can result in state-dependent learning. Statistically, state-dependency was confirmed by the significant interaction between the drug state at encode and the drug state at recall.

Further analysis partially confirmed the hypothesis that there would be a difference between the congruent (Placebo–Placebo, AH–AH) and incongruent (Placebo–AH, AH–Placebo) conditions. There was a significant increase in memory performance when the antihistamine was taken at both encode and recall (AH–AH) compared to the conditions in which the antihistamine was taken only at encode or recall (AH–Placebo or Placebo–AH). However, the effects of state change relative to the Placebo–Placebo condition were not statistically significant. Similarly, in his marijuana study, Eich *et al.* (1975) found significantly higher levels of recall in their congruent Marijuana–Marijuana state compared to the disparate Marijuana–Placebo state, but there was no

significant difference between the disparate Placebo–Marijuana state and the congruent Placebo–Placebo state. However, in our study, repetition of the AH treatment at retrieval improved performance relative to *both* the disparate conditions (AH–Placebo and Placebo–AH).

Since there is no evidence that an acute dose of vitamin C can affect cognitive performance, it is reasonable to attribute the state-dependent effect we observed to the internal cue provided by chlorpheniramine. This improvement in performance in the congruent drug state is consistent with the view that successful retrieval of a memory requires that the conditions are similar to those at encoding. Furthermore, the statistical pattern of effects we observed (performance in the AH–AH, but not the Placebo–Placebo condition was significantly better than that in the incongruent conditions) indicates some positive benefit of chlorpheniramine, as if the internal state generated by this treatment acts as an active ‘reminder’ or cue to recall.

The conditions in which the investigation was carried out were carefully controlled using the same room, at the same time of day, and testing the same cohort of subjects in each encode and recall session. Despite the plausibility of the cover story (that this was an investigation of the effects of different antihistamines on learning and memory), it is possible that the different sizes and/or tastes of the chlorpheniramine and placebo tablets generated different expectations about their efficacy. However, the data do not support this kind of interpretation of our results. If the subjects had identified the placebo tablet and there was an appropriate expectancy effect then performance in the Placebo retrieval conditions should have exceeded that in the AH conditions. Figure 1 shows that this was not the case. Conversely, if subjects made the assumption that the larger tablet was a bigger more effective dose and there was an appropriate expectancy effect then performance in the Placebo conditions should always have been worse than in the AH conditions. Again this was not the case. In fact retrieval in the AH–Placebo condition was closely similar to that in the Placebo–AH condition.

The only other significant effect was the main effect of test type. However, whilst there was significant variation in the overall level of task difficulty (the cued recall test on the word list was easiest and the free recall of the passage of text was hardest, see below) none of the interactions

involving task type were significant. Although we originally predicted that any state-dependent effect would only manifest in free recall conditions, the fact that the three way interaction between drug state at encode, drug state at recall and test type was not significant means that *post hoc* testing for state-dependency by test type would be inappropriate. Our recall tasks clearly did vary in difficulty, but statistically there was no difference between them with respect to state-dependency. Previous studies have used various target items from (CVC) nonsense syllables to lists of words. This investigation demonstrated that state-dependency may also occur in remembering a passage of information. Subjects were susceptible to the state-dependent effects of chlorpheniramine both with simple word list tasks and using the more realistic test of memory provided by the passage.

Improvement in recall through the provision of cues is well-documented (e.g. Tulving and Pearlstone, 1966). For example, category labels may improve performance because subjects use more categories (rather than because they remember more words within each category, e.g. Eich *et al.*, 1975). In the present study, as expected, performance in the cue tasks was overall better than that in the free recall tasks. In our free recall conditions, the passage was harder to remember than the list of words. This difference is probably related to the length of the passage and the difficulty of the material. Whatever its explanation, it suggests that the state-dependent effect is robust across different levels of task difficulty: near a floor in this recall task and near a ceiling in the cued recall task.

The demonstration of state-dependency in our cued recall condition stands in contrast with Eich's (1980) conclusion that the effect is reliable only in tests of free recall. Eich (1980) described the effects of alternative cues to recall in terms of the accessibility of the memory trace. In free recall conditions, the subject is helped when the internal psychoactive state and any external cues provided by the environment match at encode and recall. The greater the compatibility of the psychoactive state, the greater its effectiveness as a cue to retrieval and the higher the probability that this will be successful. In cued recall, the subject does not need to rely on internal cues since there is already some explicit reminder of the items to be remembered.

Why did our subjects show signs of state-dependency even in the cued recall task in which explicit retrieval cues were provided? First, it is possible that these external cues were not strong

enough to over-ride the disruption in retrieval produced by the discrepancy in the subjects' internal state. Second (because of the 24 h gap between learning and the memory test) the list of words we used was short (cf. Eich *et al.*, 1975) so the subjects may have paid relatively little attention to the category names at encoding. There is evidence that the effectiveness of cued over free recall is directly dependent on list length: the longer the list, the more useful the cues (Tulving and Pearlstone, 1966). Thus a task that was nominally one of cued recall might not be treated as such by the subjects. This possibility could be tested by varying list length in this kind of cued recall task to determine the point at which category labels overshadow any state-dependent effects.

The finding that, in the congruent conditions, neither drug state at encode nor drug state at recall made any difference to retrieval contrasts with the many previous studies showing that state-dependency almost always occurs in conjunction with a main effect of the drug on encoding or recall (e.g. Goodwin *et al.*, 1969; Swanson and Kinsbourne, 1976). In fact, Eich (1980) concluded that a significant main effect of drug is a necessary condition for state-dependence. Our results clearly question this assumption. Not only is the change in the psycho-active state in the incongruent (Placebo-AH and AH-Placebo) conditions sufficient to impair retrieval (the state-dependent effect), our results are also consistent with the possibility that being in a discriminable drug state that is the same as that at encoding can be a positive benefit to retrieval.

The absence of main effects of drug may be related to the development of tolerance to the initial detrimental effects of antihistamines. For example, whilst diphenhydramine initially produces sleepiness and impairs performance, these impairments disappear by the third administration (Schweitzer *et al.*, 1994; Manning *et al.*, 1992). All (but one) of our subjects had prior experience of antihistamines and most (just over 70%) had taken them more than once. If there is rapid and prolonged (cross-) tolerance to the central nervous system effects of antihistamines, this could explain the lack of effect of chlorpheniramine on encoding or recall in the AH-AH condition. In a larger sample, it would be possible to investigate whether there are systematic differences in cognitive performance between subjects who take antihistamines regularly and those who have had little if any prior exposure.

Whilst it is well-established that antihistamines impair cognitive processes such as memory (see review by Rombaut and Hindmarch, 1994), there has been little if any work on their state-dependent effects. Follow-up studies with different types of antihistamine will be necessary to determine the generality of the present result. Some of the newer (more selective) H_1 antagonists used as antihistamines, such as cetirizine and loratadine, do not cause drowsiness (Harvey *et al.*, 1996; Schweitzer *et al.*, 1994) and there is evidence that they have relatively little effect on performance (e.g. De Roeck *et al.*, 1990). But again evidence on state-dependent recall is to date lacking.

When antihistamines are taken intermittently, state-dependent effects are a potential concern with each initiation of therapy. Many students take antihistamines as necessary over the summer months to combat the effects of hay fever and other allergic reactions. In the present study, 50% of the subjects who remembered taking antihistamines at exam time (and completed this section of the questionnaire) had taken them intermittently. Our results suggest that when cognitive performance needs to be optimised, it is better to take antihistamine continuously to aid retrieval of information acquired in the same state.

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