DIAZEPAM-INDUCED IMPAIRMENT IN THE ACQUISITION OF VERBAL MATERIAL

by

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ABSTRACT

Research has indicated that the tranquilizer diazepam produces a transitory amnesia by selectively impairing the acquisition phase of new learning while the retrieval of previously-learned information remains intact. This study was conducted to determine the underlying component deficit in memory processing that ultimately leads to impaired acquisition of newly-presented material. Word lists, composed of 16 common nouns each, were presented on a computer at a rate of 2 or 8 seconds per word to 48 healthy subjects during both a training and an experimental session in which either diazepam or placebo was administered in a double blind manner. As predicted, diazepam subjects were impaired relative to placebo subjects on their immediate free recall of the word lists at both presentation rates. Further, the drug group demonstrated improved recall when presentation time was increased, consistent with the impaired acquisition hypothesis. This deficit was attributed in part to a reduction in short-term memory (STM) capacity, as measured by the number of different words rehearsed aloud between successive word presentations. However, two other measures involving an analysis of the recency portion of the serial position curve, which purportedly reflects recall from STM, yielded equal performance for the two groups. Drug subjects were also consistently impaired on a measure of vigilance that was administered throughout the session during each of the 3-minute intervals separating the lists. Thus, lowered attention and arousal could not be ruled out as confounds of the memory deficit, contrary to the prediction that memory and vigilance measures would manifest different patterns of impairment. Other analyses indicated that, although the drug

subjects appeared similar to alcoholic Korsakoff amnesics in many respects, they did not exhibit an excessive build-up of proactive inhibition as Korsakoff patients do. Instead, their similarity to patients and experimental animals with hippocampal damage supported the view that suppression of hippocampal areas, which contain a high density of benzodiazepine receptors, by high-affinity diazepam binding may be the physiological mechanism by which diazepam impairs memory.

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Dedication

This thesis is dedicated to my mentors, the people who have shaped my thinking and inspired me in my career path:

Kerch

Lonnie

Nelson

Greg

Ken

Lorne

and Ro

Introduction

Two seemingly separate fields of scientific interest, namely drugs and memory, have recently been integrated into a single avenue of research focusing on the relationship between the two. The complexities of human memory, on the one hand, have both befuddled and fascinated man from the time of the ancient Greek philosophers to the present day. Drugs, on the other hand, such as tranquilizers and sedatives, have been in common--even popular--usage in North America since the 1960s for the treatment of anxiety and insomnia, respectively. Because psychotherapeutic drugs are so widely administered in the population at large, extensive studies have been undertaken to determine the behavioral sequelae of these agents. Such efforts have implicated a causal relationship between the benzodiazepines, a class of tranquilizers, and decrements in complex cognitive skills.

Memory abilities, in particular, have consistently been shown to be compromised by this type of drug. The question of which specific components of memory processing are detrimentally affected, however, has not been adequately answered, nor has it been systematically explored in the majority of studies. The general aim of the present study, therefore, was to uncover and clarify the nature of benzodiazepine-induced memory impairment by looking at the underlying processes involved in memory from an information-processing and stage-analysis theoretical framework. For this purpose, the effects of diazepam on verbal learning were measured.

Diazepam appears to be an ideal drug for research studies involving young, healthy subjects because it has been extensively used in the general population (Balter, Levine, & Manheimer, 1974; Janowsky, 1976) and has a wide safety margin even when abused (Finkle, McCloskey, & Goodman, 1979;

Greenblatt, Allen, Noel, & Shader, 1977; Greenblatt & Shader, 1978). Diazepam has a fast onset--peak concentrations may be reached within a half hour following single, oral dosages--which is reasonable for a laboratory setting (Gelenberg, 1983; Greenblatt & Shader, 1974; Greenblatt, Shader, Divoll, & Harmatz, 1981). Further, its action is attenuated quickly due to its rapid distribution from blood into fatty tissues, so subjects can be dismissed when appropriate precautions are taken to assure the termination of the drug's CNS-depressant effects (Greenblatt et al., 1981).

The specific predictions tested in this study were derived, in part, from unresolved issues arising from previous reports of the effects of benzodiazepines, and, in part, from the normal human memory and chronic, organic amnesia literature. These predictions will be presented following a review of drug studies and a presentation of the model of memory on which the present study is based.

Literature Reviews

The effect of diazepam on memory. The first observations of the amnestic effect of benzodiazepines came from the field of oral surgery (Clark, Eccersley, Frisby, & Thornton, 1970; Flinn, Wineland, & Peterson, 1975). In the early 1960s, dental patients were frequently administered benzodiazepines intravenously as a pre-surgical medicant. Anecdotal reports indicated that the drug not only reduced the anxiety surrounding the surgical procedure, but left patients unable to recall the period of their surgery as well. This side effect was considered to be a positive supplement to the drug's known anxiolytic effect and was subsequently exploited to a certain extent as it became the "psychosedative agent of choice" (Greenblatt & Shader, 1974, p. 198) by

dentists who sought to relieve their patients of unpleasant, pain-associated memories.

Even a very cursory review of the experimental literature indicates that diazepam administration in normal, young adults leads to impaired memory performance. This amnestic effect is found regardless of the route of administration, whether it be intravenous, intramuscular, or oral. Likewise, the mode of stimulus presentation may be auditory or visual; test items may be pictures or words; subject responses may be oral or written: still, the phenomenon persists.

This robust finding is remarkable in that it appears to be selective for the learning of newly-presented material (i.e., information presented in the drug-induced state), regardless of whether it is tested immediately, after a delay, or even when the drug has completely worn off. Yet, at the same time as subjects reveal a disturbance in learning new material, their recall of previously-learned material appears to be unaffected, and may even be better than that of normals (Hinrichs, Ghoneim, & Mewaldt, 1984). Thus, their deficit has been described as an anterograde amnesia (i.e., a deficit in new learning) by these and other authors.

Several representative studies assessing the effect of diazepam on memory have been listed in Table 1. In most cases, prior to injection or pill administration, word lists were presented and tested for immediate recall. Subsequent analyses indicated that there were no between-group differences in the initial learning of the lists. Following drug or placebo administration, subjects were instructed to recall as much as they could remember of the previously-learned material. Typically, subjects were also given a recognition test in which they had to choose the familiar items from a list containing the old

Table 1

Studies Assessing the Effect of Diazepam on Memory

Authors	Year	Dose & Form of Drug	Subjects
Clarke, Eccersley, Frisby, & Thornton	1970	IV diazepam .24mg/kg vs saline	12 young normal males
Dundee & Pandit	1972	IV diaz 5 & 10 mg vs saline (2 hours pre-op)	160 women scheduled for minor gyn. surgery
Ghoneim & Mewaldt	1975	IM diaz .3mg/kg vs scopolamine & placebo	18 male &18 fem. healthy students
Ghoneim, Mewaldt, & Thatcher	1975	IV diaz 10 or 20mg vs fentanyl & placebo	10 healthy young males
Ghoneim & Mewaldt	1977	IV diaz .3mg/kg (followed by physo-stigmine) vs scopola-mine & placebo	35 male & 35 female university students
Clark, Glanzer, & Turndorf	1979	IV diaz 10mg	3 exper & 9 young & healthy controls
Ghoneim, Mewaldt, Berie, & Hinrichs	1981	chronic (21 days) vs acute oral diaz ≈.2mg/ kg vs placebo	15 male &15 fem. young normals
Brown, Lewis, Brown, Horn, & Bowes	1982	IV diaz 7.5mg vs lorazepam 3 mg or saline	18 male & 9 fem. volunteer medical students
Hinrichs, Ghoneim, & Mewaldt	1984	oral diaz .3mg/kg vs lactose	120 healthy young adults
Loke, Hinrichs, & Ghoneim	1985	0, .15, or .3mg/kg oral diaz separate or combined with caffeine administration	54 male & 54 female healthy, young volunteers

items interspersed among foils. Again, when tested in this way, no group differences were found between drugged subjects and those who received placebo. Yet when new lists were presented and tested, the drugged subjects consistently performed worse than controls. The major conclusion arising from these studies is that diazepam selectively disrupts the acquisition phase of memory while retrieval mechanisms remain intact, as evidenced by drugged subjects' normal recall for material presented prior to their drug inducement.

Further indications of selectively impaired anterograde memory performance can be found when the search is expanded to include other benzodiazepines. Recent studies have increasingly assessed the effect of lorazepam on psychological functions (Mac, Kumar, & Goodwin, 1985; Shader et al., 1986), and it has itself been compared to other benzodiazepines such as alprazolam (Block & Berchou, 1984) and triazolam (Morgan, Adam, & Oswald, 1984). In fact, when compared to diazepam (Brown et al., 1982), lorazepam was found to produce an even more profound and longer-lasting impairment of new memory formation. However, some authors (e.g., Scharf, Khosla, Brocker, & Goff, 1984) have pointed out that it may not be appropriate to generalize the effects of short- and long-acting benzodiazepines on memory due to their differential amnestic properties. Therefore, they will not be further discussed here.

Diazepam administration alone is sufficient to induce a transient anterograde amnesia, as attested to by the studies reviewed above. The question arising from the literature concerns the exact nature of the memory deficit. That is, what specific component of acquisition is it whose impairment leads to the reduction in new learning? At what stage of memory processing does the breakdown occur? The authors of some of the studies listed in Table 1

have merely concluded that the amnesia is due to impaired acquisition (Ghoneim et al., 1981; Hinrichs et al., 1984); others have suggested that the problem lies in either consolidation or storage (Clarke et al., 1970; Ghoneim & Mewaldt, 1975; Clark et al., 1979).

Information processing and stage analysis in verbal learning studies with normals and amnesics. Behind much of the theorizing within the human learning literature is the basic assumption that memory is a complex system. The component processes that make up such a system may interact in some ways and remain independent in others. A standard reference in this literature is a model of memory proposed by Atkinson and Shiffrin (1968, 1971) in which they postulated that information progresses sequentially through a series of memory stores as a function of the work performed on it; the selection of the type and extent of work performed is under the control of the subject.

According to this model, information initially enters a sensory store which is the first stage of the short-term store. This sensory processing occurs automatically as material is seen or heard, and it doesn't require any effortful work from the subject. Once in the short-term store, processes such as rehearsal and encoding, employed at the subject's discretion, transfer information into the long-term store. The short-term store is viewed as temporary; the information contained in it is what is currently in the subject's consciousness. This store is considered to have a limited capacity, as one can only be consciously aware of a finite number of information bits at any given time.

Conversely, the long-term store is viewed as a permanent memory store with a theoretically unlimited capacity. Flow of information is bidirectional between the short-term and long-term stores. That is, information can be

retrieved from the long-term store, at which point it would return to the short-term store (because it is back in consciousness). When one is presented with a problem to solve, for example, the rules or formulas needed for the solution must be retrieved from the long-term store in order to be applied to the information being held in the short-term store so that the derivation of the correct answer can actually take place.

The elegance of this model becomes apparent when it is used to explain discrepant measures of short-term memory (STM) and long-term memory (LTM). Specifically, since a certain amount of processing necessarily has to occur in order for information to be transferred from the short-term to the long-term store, then a breakdown in a component of that processing would explain (and even predict) an observation of intact STM with impaired LTM. Such cases are frequently encountered in the chronic amnesia literature. Indeed, numerous studies of the patient H.M., who underwent bilateral medial temporal lobe resection for the control of severe epileptic seizures, have consistently revealed that he has a profound anterograde amnesia in which he is unable to learn new information. Despite this severe impairment of LTM however, his STM performance is normal (Milner, 1966). Similarly, alcoholic Korsakoff patients, whose amnesia is attributed to long-term, chronic alcoholism coupled with a nutritional deficiency, often perform better on measures of STM than LTM, although their STM is not completely normal either (Butters & Cermak, 1980).

Since the primary processes used to transfer information into LTM--rehearsal and encoding--are under the control of the subject, they can be altered by task instructions to determine their effect on learning. The most commonly-employed paradigm for this type of study is the free recall of word lists. Analyses of serial position curves, which result when the probabilities of correct recall are plotted as a function of each word's position in the list, have

traditionally shown greater learning for the beginning and end of a list, as compared to the middle, when recall is tested immediately following list presentation. These two portions of the resultant curve are referred to as the primacy and recency portions, respectively.

In general, it has been assumed that the primacy effect occurs because words from the beginning of the list receive more processing (e.g., rehearsal or encoding control processes) because they are available for a greater length of time than other words in the list. This view has been supported by studies in which rehearsal has been restricted by task instructions. For example, when subjects are told to rehearse only one item at a time, so that each item receives the same amount of rehearsal, the primacy effect disappears (Atkinson & Shiffrin, 1971). In contrast, the recency effect has been considered to reflect recall from the subject's short-term memory. The last few words presented are presumed to be in conscious awareness when recall begins, so they have a high probability of being recalled. The notion that these items do not get processed into LTM is supported by the fact that when recall is tested following a delay, the recency portion (primary memory) of the curve becomes flat, while the primacy portion (secondary memory) retains its high level of recall (Craik, 1970; Craik & Birtwistle, 1971).

Since rehearsal processes are assumed to play an important role in free recall, Rundus and Atkinson (1970) analyzed their subjects' overt rehearsal protocols. In addition to the expected U-shaped serial position curve, they found that the probability of recall of individual items was correlated with the amount of rehearsal each item received. These results supported the underlying principles of the original Atkinson and Shiffrin model (1968). Subsequent studies from the same laboratory systematically manipulated rehearsal procedures and further documented the close relationship between

amount of rehearsal and probability of recall (Fischler, Rundus, & Atkinson, 1970; Rundus, 1971). Similarly, Astrom and Nilsson (1977) showed that when overt rehearsals were restricted by having the subject just repeat each word once, recall was considerably reduced.

Atkinson and Shiffrin (1971) emphasized encoding in their memory model as another important processing component controlled by the subject. Craik and Lockhart, two prominent verbal learning theorists of the 1970s, supported this view by proposing several levels of processing by which subjects could analyze or encode incoming information (1972). They suggested that processing could range from low-order, superficial, acoustical analyses of incoming information to high-order, elaborate, semantic encoding. In subsequent studies in which the level of analysis was manipulated by task instruction, it was found that the higher the level of processing devoted to incoming information--reflecting the degree to which words are analyzed for meaning--the better the levels of recall.

The knowledge gained from the studies described above involving normals had a great impact on theories of amnesia. Knight and Wooles (1980) reviewed a number of experiments conducted with amnesics, which offered several explanations for their poor learning, including impaired- acquisition and retrieval-deficit hypotheses. Proponents of the former hypothesis argue that amnesics have trouble acquiring new information, but that which they do learn can be retrieved normally. Conversely, the retrieval deficit hypothesis maintains that incoming information is stored properly, but it somehow becomes inaccessible or at least difficult to access.

The associative network model of memory. A memory model that assigns a role to all the component processes outlined above--rehearsal, encoding, and

retrieval--was developed by Raaijmakers and Shiffrin (1980, 1981), based upon the earlier work of Atkinson and Shiffrin (1968, 1971). The overall view of memory is as an associative network of units called images; it is a complex system in which a defect in any one of its numerous component parts will lead to different patterns of impairment. One of the main ideas inherent in the model is that associations are built up as a list of words is presented. For example, although the words may all be familiar, everyday words, they have to be specifically associated with the list being presented in order to be accurately recalled. The list, in turn, occurs in a particular temporal and spatial context (i.e., on a certain day, at a certain time, in a certain room with a certain temperature, etc.). Thus, the stronger the association between the word and the context in which it is presented, the greater likelihood there is of its being recalled. Likewise, interitem associations are built up as well such that words that are contiguous in the list become more closely associated than those that are presented further apart.

The theory maintains that the word-to-context and word-to-word associations are strengthened as a function of rehearsal. This position is consistent with the previously-presented data implicating a close relationship between rehearsal and recall. Further support comes from studies of amnesics which have shown that alcoholic Korsakoff patients, whose recall is lower than normals, rehearse fewer distinct (i.e., different) words during interitem intervals than do controls (Cermak, Naus, & Reale, 1976). Another group of investigators (Brown, Rosenbaum, Lewis, & Rourke, 1980) also studied alcoholic Korsakoff patients. Although they did not find a significant difference between their groups for the number of distinct items rehearsed during interitem intervals, there was a trend in that direction. The authors did, however, report a lower overall rehearsal rate (i.e., total number of words rehearsed) for the Korsakoff

patients as compared with controls. In a later study, Brown & Donenfield (1982), found that alcoholic Korsakoff patients did have a reduced rehearsal capacity, which had its greatest effect on the recency portion of the serial position curve.

Finally, there have been findings of improved performance with amnesics in certain circumstances (see Butters & Cermak, 1980; Knight & Wooles, 1980; and Levin, 1986 for reviews). It should be expected from Atkinson and Shiffrin's, (1971) model that if acquisition is impaired, then increasing the amount of time each word is exposed should lead to better recall. This would be expected because both the strength of association between context and word and the interitem association of words are viewed as a function of rehearsal; therefore, the more time allotted for presentation of individual items, the more rehearsal should occur, thus building up stronger associations. This in turn should result in higher probabilities of accurate recall for the list of words.

Support for this view came from a study by Huppert and Piercy (1978) who gave their Korsakoff patients 4-8 seconds per stimulus presentation (stimuli were 120 slides) as compared to only 1 second for controls. At the end of a 7-day retention interval, the Korsakoff patients performed as well as the controls in recognizing the previously-seen pictures. Initially, brief exposures were associated with impaired acquisition for the Korsakoff patients, which led the authors to infer that Korsakoff patients' memory impairment lay in a defective acquisition that could be compensated for by increasing the presentation time of items. Similarly, Squire (1981) corroborated the earlier study with his findings of preserved picture retention in Korsakoff patients given longer exposure durations during initial presentation.

Attention and arousal: A link between sedation, rehearsal, and subsequent learning. One of the most frequent adverse effects of certain

benzodiazepines is central nervous system (CNS) depression (Greenblatt, Shader, Divoll, & Harmatz, 1984). Naturally, attentional resources are an important component of any memory model. As Atkinson and Shiffrin (1971) have pointed out, a word has to be attended to before any processing can take place. Most likely, if subjects suffer from a generalized lowering of arousal, then their initial sensory perceptions of incoming words would be compromised, less work would be performed on the items, and overall memory would be reduced.

Thus, the investigators of several of the studies reported in Table 1 were concerned with the sedative and psychomotor effects of diazepam. In addressing that issue, Clarke et al. (1970) concluded that seriously-reduced consciousness was not responsible for the impaired memory; likewise, Dundee and Pandit (1972) found no relationship between the incidence of amnesia and the observed degree of drowsiness in their subjects. Further, indirect evidence for the independence of sedation and memory impairment came from a somewhat complex study (Ghoneim & Mewaldt, 1977) involving multiple drug administrations. When physostigmine injection followed diazepam injection by 70 minutes, it was found that the initial physical and mental sedation produced by diazepam increased while subjects' memory performance remained at the same level. Thus, the general finding appears to be that, while diazepam does lower both alertness and memory, the two effects are distinguishable.

However, Tinklenberg and Taylor (1984), who were also concerned with the question of how much a drug's CNS-depressant effect contributes to the observed memory deficit, found that diazepam reduced attention and arousal. This finding led them to suggest that the memory impairment in their subjects was due not to a reduced memory capacity per se, but rather to a reduced attentional capacity, which they assessed by a dual-task methodology in which

subjects were required to perform two tasks simultaneously. This finding would appear to contradict the evidence obtained from the studies listed in Table 1 in which standardized measures of arousal, such as reaction time, digit cancellation tasks, and mood rating scales were used rather than Tinklenberg and Taylor's dual-task methodology which seems like a rather idiosyncratic measure of arousal.

Still, some investigators (Roehrs, et al., 1983; Roth, Hartse, Saab, Piccione, & Kramer, 1980; Roth, Roehrs, Wittig, & Zorick, 1984) maintain that diazepam induces sleep which, in turn, prevents consolidation processing, thus leading to memory impairment. However, because these studies were carried out in sleep laboratories, and the drugs were given at bedtime, there is no proof that the drug actually put the subjects to sleep. Instead, these studies highlight the need to include arousal measures when evaluating the effect of drugs on memory. That is, since sleep can interrupt consolidation, it must be ensured that subjects do not lapse into sleep either during the presentation of information or during the time intervening between presentation and recall. The overt rehearsal procedure described above is ideal in this respect because the accurate reading of incoming items provides evidence that subjects are indeed attending to the information presented. Further, subjects' interitem rehearsals would show that they are working on the information between successive word presentations.

Predictions

The results from the foregoing review of studies led to the fundamental hypothesis of the present study: Diazepam reduces the ability to learn verbal material by selectively impairing the acquisition of new information in a manner that cannot be fully accounted for by deficits in attention and vigilance.

Accordingly, the specific predictions explored here, mainly derived from the associative network model of memory discussed above, were as follows:

1) As with previous studies of the effect of diazepam on memory, diazepam should impair overall recall.

2) Subjects given placebo or diazepam should show improved performance when list presentation times are increased due to strengthened interitem and word-to-context associations. For the placebo group, such a result would replicate findings from studies with other normals, while for the diazepam group, increased levels of performance with increased presentation time would be consistent with an acquisition impairment rather than a retrieval deficit, which would predict that performance be unaffected by changes in presentation time.

3) Based on the suggestion from previous studies of organic amnesics (e.g., Cermak et al., 1976) that impaired acquisition is due to an underlying deficit in STM capacity, it was predicted that diazepam subjects would have a reduced STM capacity relative to those receiving placebo. Because of the controversy over how best to measure STM capacity, this prediction was tested by comparing three different scoring methods: a) analysis of the recency portion of the serial position curve; b) lag scores (Tulving and Colotla, 1970); and c) overt rehearsals. An impairment in the drug group on each of these measures would not only support the notion of reduced STM capacity as the underlying deficit leading to impaired acquisition of new information, but would also provide evidence for the equality of these measures as reflections of STM capacity. This would especially be true if they produced quantitatively similar results.

4) It was predicted that diazepam would slow psychomotor performance, as measured by a digit cancellation task. In fact, if vigilance were not

compromised in subjects receiving diazepam, a CNS depressant, it would be questionable that drug onset had occurred. However, it was further expected that reduced arousal could not sufficiently account for the expected memory impairment. Specifically, vigilance should fluctuate as the drug reaches its peak effect of activation, with a subsequent ebbing in its behavioral effect as the drug wears off, while memory should be depressed throughout the session in a pervasive and consistent manner.

5) It was predicted that diazepam would increase recall errors attributable to proactive interference (i.e., recall of words presented on previous lists) despite the digit cancellation distractor task which was employed, in part, to reduce this effect. This prediction arose from the amnesia literature in which alcoholic Korsakoff patients have consistently been shown to have an excessive build-up of proactive inhibition (Butters & Cermak, 1980). That is, their memory is reduced in part as a function of the amount of material presented on prior lists.

Method

Subjects

Subjects were 48 healthy volunteers. Half were randomly assigned to the placebo group and half to the drug group. Both the subjects and the examiner were blind to the subject's condition. Subjects were between 19 and 35 years old, weighed 88-220 pounds, and all had at least 12 years of education. Since valium crosses the placenta, pregnant or nursing females were excluded. Subjects were screened for drug use or past medical histories which could influence their reaction to valium (see Appendix 1). In addition to the interview, subjects assigned to the drug condition were given a brief physical and blood work-up to rule out other medical conditions for which valium use is contraindicated by the Physicians' Desk Reference (1986).

The majority of participants were medical students and technicians affiliated with Henry Ford Hospital or students from Wayne State University who volunteered in response to an ad describing the experiment as a study of the effect of valium on memory. Informed consent (see Appendix 2) was obtained with the understanding that subjects in the drug condition had to remain under supervision until the drug wore off. Prior to their actual participation in the study, subjects were told all of the known risks and side-effects of acute valium administration.

Subjects were paid for participating; lunch and parking money were also provided.

Materials

Materials included the capsules administered to the subjects as well as the various baseline and experimental tests used throughout the training

and experimental sessions. Each of these will first be described, and then a comment will be added with regard to its role in the study.

Capsules. The capsules* were prepared under the direction of Dr. Anandan (Pharm D.) of the department of drug information services at Henry Ford Hospital. Four bottles were prepared and divided into two pairs: a drug pair and a placebo pair. All four bottles contained identical, off-white, opaque capsules. In the drug pair, one bottle contained capsules filled with crushed tablets of valium 10 mg for subjects weighing less than 60 kg; the other bottle in the pair appeared the same, with 15 mg of crushed valium tablets compacted into each capsule for subjects weighing more than 60 kg. Each bottle in the placebo pair was filled with lactose, a biologically inert substance.

Word lists. A total of 20 lists, each containing 16 mono- or bi-syllabic words selected from a list of 900 nouns (Christian, Bickley, Tarka, & Clayton, 1978) were prepared for use in the training and experimental sessions (see Appendix 3). The lists were equated for difficulty level according to the free recall measures reported in the Christian et al. study. Further, in order to ensure that the words within a given list were unrelated, no homonyms or rhyming words occurred and no more than two words per list had the same initial letter.

Digit Cancellation Task. This task was developed by Lewis and Rennick (1979). It is simply a page filled with numbers aligned in rows and columns. A modification of the standard procedure was used in which subjects were instructed to cross out every '6' and '9' they came to as fast as they could

* A notice of claimed investigational exemption for an investigator-sponsored study involving the unlabeled use of diazepam was sent to the FDA on May 15, 1986. Permission to obtain and use the drug for this study was granted, and the IND #28,408 was assigned.

until told to stop. Their score was the total number of '6's and '9's cancelled during a 90-second interval.

This test served as a distractor activity between list presentations to minimize rehearsal of words from previous lists during both the training and experimental sessions. The intent was to reduce the build-up of proactive interference across the session (Peterson & Peterson, 1959). A secondary role for the task was to provide a trial-by-trial vigilance measure. It was hoped that its sensitivity in detecting arousal changes would document the hypothesized course of psychomotor decline and subsequent return to baseline in the drugged subjects.

Baseline tests. The following tests were administered during the experimental session only, in order to document baseline levels of performance on various behavioral measures (i.e., memory, coordination, reaction time, and subjective arousal). Subjects in the drug condition had to return to baseline on alternate forms of these tests before they were allowed to leave the hospital. The tests used were:

1) The logical paragraphs, visual reproduction, and paired-associate subtests of both Form I and Form II of the Wechsler Memory Scale (WMS; Wechsler & Stone, 1973) to obtain a standardized measure of general memory.

2) Forms A-D of the digit-symbol substitution subtest of the WAIS-R (Wechsler, 1981) to test psychomotor speed.

3) The Grooved Pegboard Test (Reitan & Davison, 1974) to assess speeded hand-eye coordination.

4) A computerized discriminant reaction-time averaging task (DRAT; Berchou & Block, 1983) that purportedly is sensitive to the CNS-depressant effects of diazepam.

5) Self-judgments of arousal states, encompassing the dimensions of ALERT/DROWSY, TENSE/RELAXED, and GIDDY/SOBER, as measured on three 100 mm lines labeled with the moods at each end (as described by Block & Berchou, 1984).

Apparatus

An Apple II Plus interfaced with a Corvus hard disk and a digitry board were used to present the word lists. Digitry (CTS manual, 1983) was used for some of the randomization and timing elements of the list presentations. A keyboard terminal and screen were connected to a second video display screen which subjects viewed. Subjects spoke into a Telex CS.75 microphone with output to a TEAC stereo 8-track reel-to-reel recorder. The experimenter used Sharpe HA-10-A stereo headphones to receive the dual TEAC output of subjects' rehearsals and the computer-generated beeps that demarcated the inter-stimulus intervals as well as the responses made during recall.

The Apple was also used to run the DRAT program.

Procedure

Following initial screening, subjects were randomly assigned to groups. All subjects participated in both the training and experimental sessions which were separated by approximately one week.

Training session. This session was used to familiarize subjects with the digit cancellation (vigilance) and experimental list-learning tasks. Two blocks of four word lists each were used in this session. The 16 words from each list were presented on the video display terminal one at a time. Subjects immediately read each word aloud as it was presented and then filled the inter-word intervals with overt rehearsals (i.e., repetitions of the list words) as modeled in the explicit instructions (see Appendix 4). During the explanation of

the task, it was emphasized that the overall goal was to remember as many words as possible at the end of each trial, not to say as many words as possible in the limited time between successive word presentations.

Both the repetition of the words as they were being presented and the recall of the words following presentation were tape-recorded in accordance with the method used by Rundus and Atkinson (1970). This procedure allowed for subsequent off-line analyses of individual rehearsal protocols.

All subjects were administered one block of lists at a rate of two seconds per word and the other block at a rate of eight seconds per word. Order of the blocks (block 1 or block 2) and presentation time (PT) were counterbalanced across the 48 subjects. The initial list presented within a block was also counterbalanced, while the order of the lists within a block remained constant.

The recall time was unlimited and was determined by the subject for individual lists. However, a three-minute inter-list interval--from the end of recall of one list to the presentation of the first word of the next list--was enforced in order to reduce the build-up of proactive inhibition across the session (Peterson & Gentile, 1965; Loess & Waugh, 1967). During that time, modifications of the subject's rehearsal style were suggested when necessary, as, for example, if a subject merely read each word as it was presented and failed to fill the inter-word intervals with repetitions. The three minutes were also filled in part by administration of the 90-second digit cancellation task.

Proactive interference effects were also minimized by encouraging subjects to forget the words from lists they had already been tested on, as they were informed that they would not be asked to recall words a second time from lists previously presented. This instruction has been termed intentional forgetting (Woodward & Bjork, 1971) or directed forgetting (Epstein & Wilder,

1972) and has been demonstrated to minimize interference effects in verbal learning paradigms similar to the one employed here.

The two blocks of word lists were separated by a 5-minute interval. This period served as a break for the subjects while the computer was set up to run the next block. No tasks were administered during that time.

It took approximately one hour to go over the consent form, explain the list-learning procedure, present the digit cancellation task, and run the two blocks of word lists. Following training, subjects were taken by an associate to have their blood drawn. Those who were assigned to the drug group were also given a brief physical to ensure that they had no obvious signs of liver damage or other conditions for which valium is contraindicated.

Experimental session. The experimental session followed the training session by 2 to 10 days and was scheduled for 8:30 a.m. Subjects were instructed to have only juice prior to their arrival, to eat nothing after 10 pm of the night before, and, in particular, to refrain from drinking coffee and smoking cigarettes on the morning of the session. Further, they were instructed to not use alcohol or recreational drugs the night prior to the session and encouraged to get at least 7 or 8 hours of sleep. Verbal reports indicated that subjects had followed these instructions.

The experimental session for all subjects began with a 30-minute assessment of the baseline measures. The order of test administration was as follows: 1) Form I or II (counterbalanced across subjects) of the Wechsler Memory Scale subtests; 2) the Grooved Pegboard task; 3) the WAIS-R digit-symbol subtest; 4) the digit cancellation task; 5) an alternate form of the digit symbol subtest; 6) a second trial of the digit cancellation task; 7) the subjective rating scales; and 8) three 50-second trials of the DRAT.

Following the baseline testing, subjects were weighed and subsequently given a capsule containing diazepam or lactose. To further preserve the blinding procedure, the experimenter left the room while a co-investigator remained with the subject. Alternate forms of the digit-symbol subtest were given every 15 minutes (up to a maximum of one hour) until the subject showed a decline from his or her baseline performance on this task (drug subjects only). A drop in scaled score of 2 or more served as the critical marker to indicate that the drug had taken effect.

Subjects in the placebo group also completed alternate forms of the digit-symbol task at 15-minute intervals. Rather than by a drop in performance, however, the time elapsing between taking the capsule and starting the list-learning task was based on the distribution of times seen in the drug subjects so that they would be equated on the length of time spent with my colleague.

The amount of time intervening from drug ingestion to the start of the experimental tasks was titrated as a result of observations made during initial runs of the experiment with Dr. Brown and myself. Our self-administrations of 15 mg of diazepam indicated that the drug activation latencies could be quite variable between subjects. Because manipulation of the onset and offset of memory impairment was key to the experimental paradigm, careful monitoring of the precise onset of diazepam's acute behavioral effects was clearly required in order to ensure that the drug subjects would actually be under the influence of the active phase of the drug when they were tested on the word lists. Thus, alternate forms of the digit symbol task provided a convenient, easy-to-administer, repeatable method of measuring the variable drug onset latencies among subjects.

At that point, the subject completed a third practice trial of the digit cancellation task followed by presentation of the first word list. Subjects were seated in front of the video display screen used during the training session and reminded of the instructions that they had previously learned. For this session, two blocks (Block 3 and Block 4) containing 6 lists each were used. Words again varied in presentation time from block to block, with a 2-second rate for one and an 8-second rate for the other. The counterbalancing scheme of initial block, list, and PT involved a permutation of all possible orders, and the combinations of these variables were randomly assigned within each group. For example, if the combination were 3-4-8, the trials would be started with the 4th list of Block 3, presented at a rate of 8 seconds per word. The block would then proceed with lists 5, 6, 1, 2, and 3. Following a 5-minute rest period after the first block, during which time subjects would rate themselves for a second time on the subjective mood rating scale, the session would continue with Block 4, List 4, presented at a rate of 2 seconds per word, followed again by lists 5, 6, 1, 2, and 3.

The word lists were again separated by 3-minute intervals which were filled in part with the digit cancellation task. Typically, it took an hour and a half to complete the two blocks.

At the end of the session, the subject's condition was revealed. All subjects were then provided with lunch and paid for their participation. Those receiving the placebo were free to go once they had been debriefed. Upon confirmation of their condition, subjects in the drug group were tested on alternate forms of the baseline measures following lunch. In order to be discharged from the study, subjects had to return to their baseline level of performance on the WMS subtests, Grooved Pegboard test, digit cancellation

task, and the DRAT, as well as indicate that they felt sober and alert on the subjective rating scales.

A summary of the occurrence of events within the protocol is presented in a timetable format in Appendix 5.

Results

Recall

Training session. There were no pre-existing differences in recall between the groups during the training session; that is, subjects who were randomly assigned to the drug group for the subsequent experimental session did not differ from those assigned to the placebo group, as indicated by a 2X2 mixed-model ANOVA $F(1, 46) = 0.003$, n.s. In fact, mean recall for the eight training lists was identical for the two groups (8.4 words per list). As expected, memory performance was superior at the 8-second presentation time (PT) rate than at the 2-second rate $F(1, 46) = 160.18$, $p<.0005$, and there was no group by PT interaction $F(1, 46) =0.106$, n.s.

Experimental session. The number of words recalled for each of the 12 lists presented in the experimental session was recorded for all subjects and is provided in Appendix 6. Table 2 shows that, as predicted, the drug group recalled fewer words on average than the placebo group at both PTs. A 2X2 mixed-model ANOVA confirmed that the group difference was significant $F(1, 46) = 21.52$, $p<.0005$. A significant PT effect was also found $F(1, 46) = 64.05$, $p<.0005$, as predicted. The prediction that the diazepam group would demonstrate improved performance with increased PT when considered alone was upheld by the fact that there was practically no overlap between the 95% confidence intervals for the two PTs within the group, as shown in Table 2. However, the drug group did not benefit from the longer word exposures as much as the placebo group, as indicated by the means in Table 2 and confirmed by a significant group by PT interaction $F(1, 46) = 5.12$, $p=.028$.

Table 2

Mean Recall by Group at Each Presentation Time

	Mean	(S.D.)	95% Confidence Interval
Placebo Group			
2-sec PT	7.94	(1.09)	7.48 - 8.40
8-sec PT	10.65	(2.08)	9.77 -11.54
Drug Group			
2-sec PT	5.99	(1.86)	5.20 - 6.77
8-sec PT	7.50	(2.98)	6.24 - 8.76

Serial Position

When recall was examined as a function of serial position (for raw data see Appendix 7), the traditional bow-shaped curve appeared for all conditions (see Figure 1), indicating that there was greater recall of words presented at the beginning and at the end of the list than in the middle. This differential effect of position on recall was significant, as shown by a main effect for serial position $F(15, 32) = 65.13$, $p<.0005$ revealed by a 2X2X16 (treatment by PT by serial position) repeated-measures MANOVA (Norusis, 1985). Consistent with the 2X2 analysis of overall recall scores, there was a significant drug effect ($p<.0005$). This global analysis of the entire serial position curve did not reveal an interaction between drug treatment and serial position $F(15, 32) = 1.75$, $p=.09$, nor was there a 3-way interaction between treatment, presentation time, and serial position $F(15, 32) = 0.64$, n.s. However, visual inspection of Figure 2 shows a convergence of the points in the recency portion of the curves, and this was subjected to further analysis below.

STM Analyses

Recency portion of the serial position curve. The first method used to compare STM capacity in the two groups involved a component of the treatment by serial position interaction from the 2X2X16 analysis reported above. Figure 2 portrays the recall scores at each serial position for the two treatment groups. To assess the difference between the two groups at the recency portion of the curve, a 2X4 mixed-model repeated-measures MANOVA (treatment by last four serial positions) was run. No group differences in recall were found $F(3, 44) = 2.19$, $p=.102$. However, it had been predicted that STM, as reflected in the recency portion of the serial position curve, would be impaired in the drug

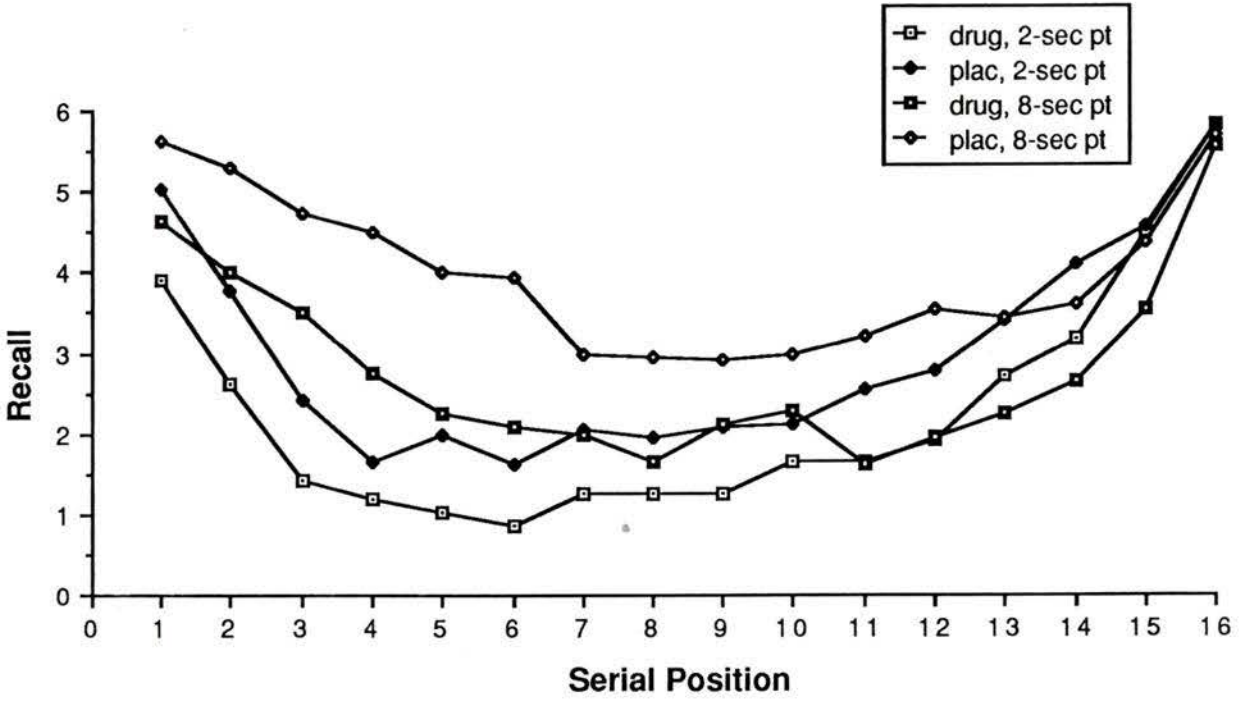

Figure 1. Recall as a Function of Serial Position According to Treatment at Each PT

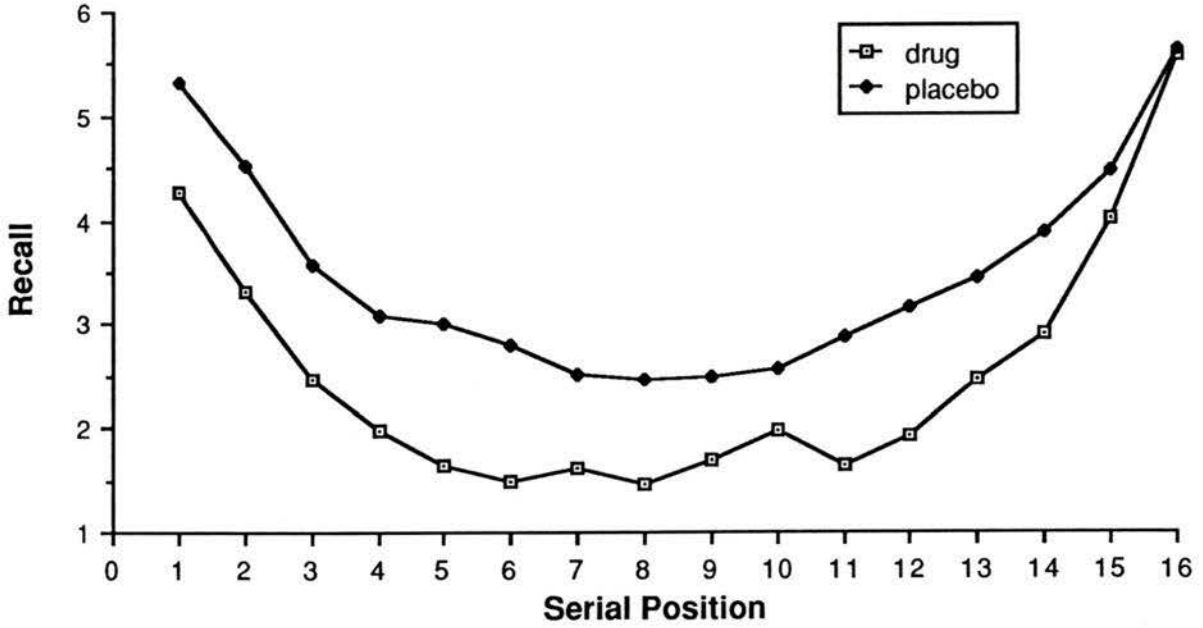

Figure 2. Recall as a Function of Serial Position for Each Treatment Condition

condition; thus, an interaction between treatment and serial position was expected at this portion of the curve. Specifically, if STM capacity were reduced by diazepam administration from its generally accepted level of four words (Raaijmakers & Shiffrin, 1981) to 2 1/2 or 3 words, then an overall group difference wouldn't necessarily be seen over the last four positions. Nevertheless, an interaction should exist, whereby recall at the last 2 or 3 positions should be similar for the two groups, while the 3rd and 4th words back from the end of the list should mark the growing divergence between the two groups (see Fig. 2). This prediction was supported by a univariate (averaged F) test of the treatment by serial position interaction which was indeed significant $F(3, 138) = 3.13$, $p=.028$.

For comparison purposes, a 2X12 repeated measures MANOVA (treatment by serial position) was run on the non-recency portion of the curves (i.e., positions 1-12). In this case, there was no interaction between treatment and serial position $F(11, 36) = 0.56$, $p=.851$, indicating that, as expected, the drug group performed in a consistently depressed manner relative to the placebo group at both the beginning and middle list positions.

Lag scores. The second method used to test the prediction that STM capacity is reduced by diazepam came from work by Tulving and Colotla (1970) in which they calculated lag scores by counting the number of intervening words between a subject's recall of a word and the time it was presented. For example, if words were presented in the order ABCDEF, and the subject responded FCDB during the recall period, the "lags" between presentation and recall would be scored 0, 4, 4, and 7, respectively. Of note in the scoring procedure is that the subject's recall of word C received a lag score of 4. This score included word F twice in its count since both the presentation and recall of

that word intervened between the presentation of word C and its subsequent recall.

The lag scores were then used as a basis for distinguishing between STM and LTM (called primary and secondary memory by Tulving and Colotla). Specifically, in accordance with Miller's (1956) notion that STM holds roughly 7 bits of information, lags of up to 7 words were counted as STM retrievals whereas lags of 8 or more were scored as retrievals from LTM. To test for a reduction in the STM capacity of the diazepam subjects, these measures of STM and LTM were calculated for each recall of each subject (presented in Appendix 8). Contrary to the prediction, a 2X2 repeated measures MANOVA (treatment by PT) revealed that the drug group did not differ from the placebo group on recall from STM $F(1, 46) = 0.418$, n.s. This finding was consistent with the finding that the two groups did not differ in mean recall at the recency portion of the serial position curve.

Interestingly, an extremely significant PT effect was found $F(1, 46) = 17.87$, $p<.0005$, in which the mean number of words recalled from STM at the 2-sec presentation rate (2.83) was superior to mean STM recall at the 8-sec rate (2.33). There was no treatment by PT interaction on this measure of STM recall $F(1, 46) = 0.715$, n.s.

Overt rehearsals. The number of distinct (different) words rehearsed between successive word presentations (i.e., during the interitem intervals) was the third measure of STM capacity. This measure was calculated from subjects' overt rehearsals of the words as they were being presented. These rehearsals were recorded on tape and subsequently transcribed onto a 16X16 matrix scoresheet, as shown in the sample provided in Figure 3. The number in any given square of the matrix represents the number of times a particular word was

rehearsed during a particular interitem interval. Thus, summing the scores across rows down the matrix yielded the total number of rehearsals uttered during each interval in the list; the number of different words rehearsed per interval was obtained by counting the number of squares per row with non-zero entries. Individual scores for each of these measures are provided in Appendix 9.

Since previous studies using distinct rehearsals during interitem intervals as a measure of STM capacity (Brown et al., 1980; Cermak et al., 1976) typically used short presentation time, it was necessary to ensure that this rehearsal measure truly represented STM in the relatively long presentation time (8 seconds) used in the present study. That is, because it was conceivable that subjects might retrieve words from LTM during the rehearsal period and actually rehearse those words along with the new words being presented (which were just entering the STM buffer), a cut-off was introduced to exclude those hypothetical LTM retrievals from the distinct rehearsal score tabulated for each interval. Specifically, if two or more interitem intervals intervened between rehearsals of a particular word, the later rehearsal was assumed to be coming from LTM and was therefore not counted in this STM measure.

Since both total rehearsal and distinct STM rehearsal scores were separate but related dependent variables, each broken down into two scores (corresponding to the two different PTs), a doubly multivariate repeated measures design was performed (SPSSX user's guide, 1986). This conservative test of the two measures and their respective two-level within factors of PT yielded a nearly significant main effect for group $F(2, 45) = 2.92$, $p=.064$. However, since an a priori prediction was made for the direction of the effect (drug < placebo), even the stringent criteria of this test results in a difference at the $p=.032$ level, indicating that the diazepam did indeed lower

	house	bronze	body	lip	dawn	engine	rock	invoice	glacier	chaos	salute	mercy	decree	flower	time	sickness
1	6															
2	4	4														
3	3	3	3													
4	1	3	3	3												
5	2	1	3	3	3											
6	2	2	2	2	2	2										
7	1	1	1	2	0	3	3									
8	0	0	0	0	0	1	3	2								
9	1	1	1	2	0	0	1	1	2							
10	1	1	1	1	0	0	0	0	1	3						
11	0	0	0	1	0	0	0	0	0	2	3					
12	1	1	1	1	0	0	0	0	0	0	1	2				
13	0	0	0	1	0	0	0	0	0	0	0	2	3			
14	0	0	0	0	0	0	0	0	0	0	0	2	2	3		
15	0	0	0	0	0	0	0	0	0	0	0	2	3	3	3	
16	0	0	0	0	0	0	0	0	0	0	0	3	1	0	1	2

Figure 3. Sample Rehearsal Matrix

rehearsal rates, both for the absolute number of rehearsals made and the number of different words rehearsed per interval.

The within-subject effect of PT was naturally highly significant across the two measures (chi^2=19.09, df=2, 45, p<.0005), confirming the intuitive expectation that subjects, regardless of treatment, would rehearse more words--distinct or otherwise--given four times as much time to speak, especially when instructed to spend all their time practicing aloud the words from the list. More importantly, there was no interaction between group and PT F(2, 45) = 0.952, p=.394 which essentially means that the group difference at each PT was constant across the two rehearsal measures.

Because the multivariate test was significant, it was permissible to look at the contribution each rehearsal measure made individually in terms of discriminating between the drug and placebo groups. Thus, a 2 (group) X 2 (PT) repeated-measures analysis was performed on the distinct STM rehearsal scores. This analysis revealed what is perhaps the most important finding of the present experiment: Diazepam reduced the rate of distinct word rehearsals F(1, 46) = 4.04, p=.05, as predicted (means = 3.2 and 2.9 words, respectively). Naturally, significantly more words were rehearsed per 8-second interval (mean=3.9) than per 2-second interval (mean=2.3) F(1, 46) = 273, p<.0005, but there was no treatment by PT interaction F(1, 46) = 1.08, n.s., indicating that the two groups increased their distinct STM rehearsals from the shorter to the longer PT condition in a parallel way.

Likewise, analysis of the total rehearsal scores yielded the same pattern of results, with even more pronounced treatment and PT effects (F=4.83, p=.033 and F=745, p<.0005, respectively). Thus, the diazepam had a general lowering effect on rehearsal rates. Again, there was no differential benefit for either

group from the increase in PT, as evidenced by the nonsignificant interaction (p=.289).

In sum, diazepam significantly reduced the number of distinct rehearsals per interval (a measure of STM capacity), but did not reduce the number of words recalled from STM as assessed both by the recency portion of the serial position curve and by lag scores. The different results obtained with these measures suggest that the discrete rehearsal measure may assess a different memory component than the recency and lag score measures.

In addition to testing the effect of diazepam on memory measures, several tests were run to test the predictions of diazepam's non-specific effects. The results of those analyses will now be presented.

Digit Cancellation (Vigilance) and List Order Effect

Training session. There were no pre-existing differences in vigilance between the groups, as shown by scores on this measure obtained during the training session. The groups performed at the same level of psychomotor speed, as can be seen in Figure 4 which shows the number of 6's and 9's cancelled on each administration of the digit vigilance task. A 2X8 (group by trials) mixed-model repeated-measures MANOVA confirmed this observation $F(1, 46) = 0.34$, n.s. Interestingly, despite the claim by the authors of this test (Lewis and Rennick, 1979) that scores should increase over the first two or three administrations and then level off at a consistently maintained plateau, performance improved continually across the session, as evidenced by a strong trials effect $F(5, 42), = 15.29$, $p<.0005$. The fact that there was no group by trial interaction $F(5, 42) = 1.14$, n.s., coupled with the nonsignificant main effect for

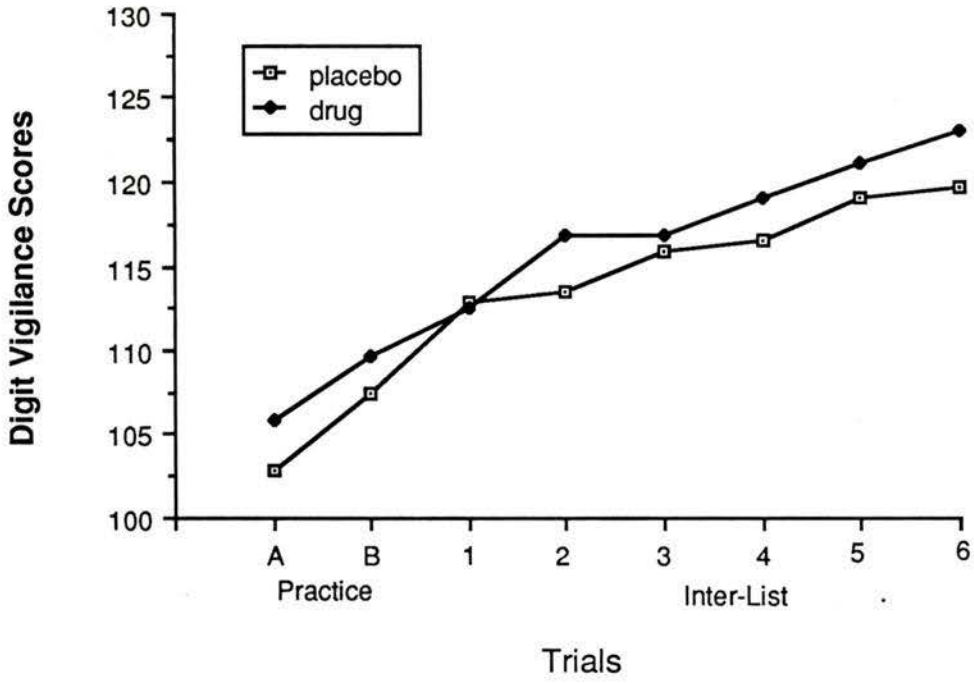

Figure 4. Digit Vigilance Scores as a Function of Time Across Training Session According to Subsequent Group Assignment

treatment, indicates that the groups were the same on this measure at all points tested.

The goals of this session, which were to: 1) familiarize subjects with the task procedure and computer set-up; 2) provide exposure to both types of list presentation (2-sec and 8-sec); and 3) answer any questions so that no learning to learn would have to take place during the experimental session, were achieved successfully, as evidenced by a significant trials effect $F(7, 40) = 3.12$, $p=.01$. Thus, it can be concluded that training actually took place during this session, as subjects steadily improved from a mean recall of 7.94 words for the first list to 9.21 for the last (8th) list (see Figure 5). The slight drop in performance from the 4th to the 5th trial can be attributed to the start of the second block in which the alternate PT was used (counterbalanced across subjects and within group).

As with the vigilance task, the groups did not differ in their memory performance across the training session, once again indicating that the groups were not different prior to treatment. This conclusion was confirmed by a 2X8 (group by trials) repeated-measures MANOVA, which revealed that the groups recalled the same number of words averaged over trials $F(1, 46) = 0.008$, n.s. Naturally, there was no group by trials interaction ($p=.44$).

Experimental session. Twelve trials of the digit vigilance task were administered to each subject during the experimental session, including two practice trials during the baseline testing and one trial each during the five inter-list intervals of the two blocks; individual scores are presented in Appendix 10. As can be seen by the mean scores plotted across trials in Figure 6, diazepam lowered performance throughout the session, with an overall mean difference of 15 cancelled digits between the two groups per trial (mean = 121.4 for placebo subjects vs 106.3 for drug subjects). A 2 (treatment) by 10 (trials) mixed-model

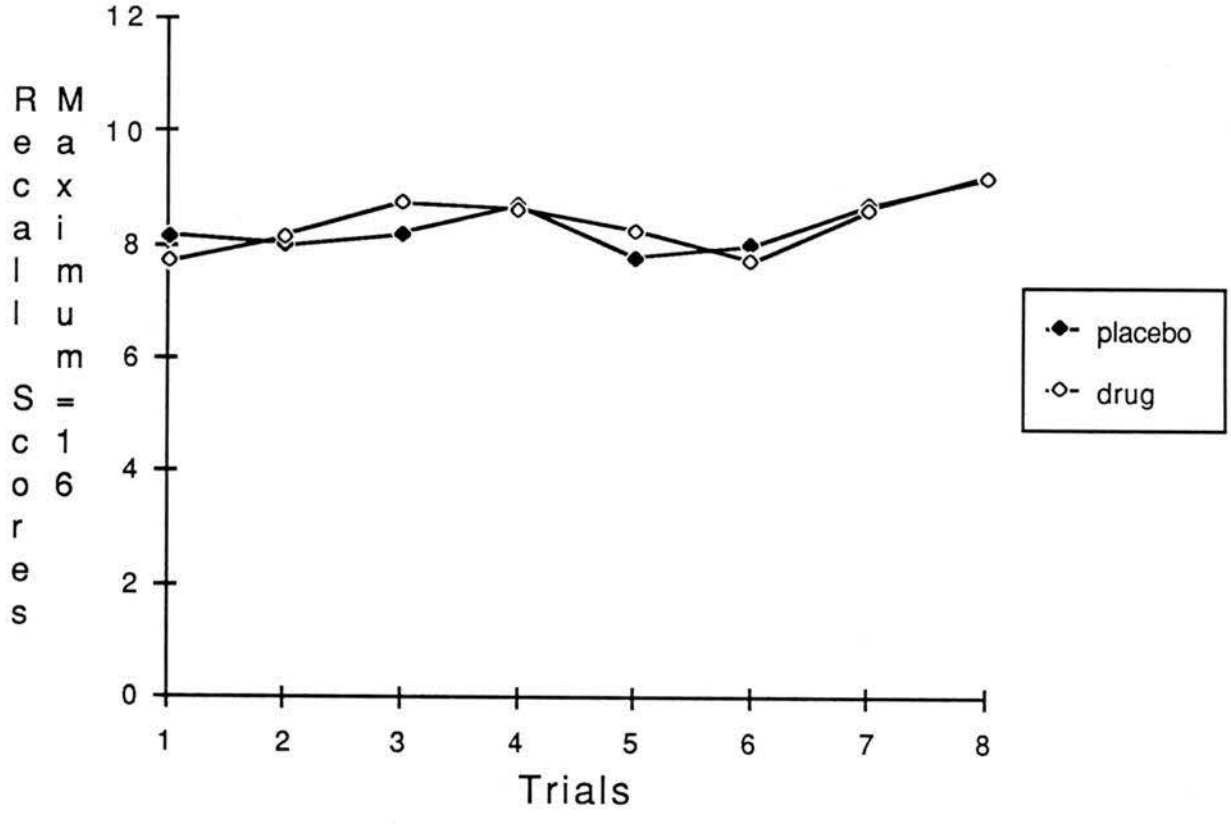

Figure 5. Recall Scores as a Function of Time Across Training Session According to Subsequent Group Assignment

repeated-measures MANOVA performed on these scores revealed the group difference to be significant $F(1, 46) = 10.85$, $p=.002$. Again, in contrast to Lewis and Rennick's (1979) claim that this test would yield a stable score on repeated administrations, performance improved across the session, as evidence by a significant trials effect $F(9, 38) = 4.68$, $p<.0005$.

It was expected that the plot of vigilance scores for the drug group would assume a bow shape, as psychomotor speed fluctuated across the session as a function of the drug's CNS-depressant effect. Indeed, the graph in Figure 6 of the drug subjects' scores does appear somewhat bow-shaped. However, in contrast to the prediction and the appearance of the graph, there was no significant interaction between treatment and trials $F(9, 38) = 0 .96$.

It had been predicted that the drug would depress memory in a consistent manner across the session. That is, it was not expected that there would be an order effect on recall for the various word lists. This expectation appears to have been upheld (see Figure 7). A 2 (treatment) X 12 (trials) mixed-model MANOVA was consistent with the prediction that recall did not vary as a function of time $F(11, 36) = 0.97$, n.s., suggesting that there was no practice effect as there had been in the training session nor was there a fatigue effect in this session. However, contrary to prediction, the groups did not maintain a constant difference across the session, as suggested by a significant treatment by trial interaction $F(11, 36) = 2.37$, $p=.025$. Inspection of Figure 7 suggests that the improvement of placebo subjects during the second half of the first block of lists (trials 4-6) was responsible for the interaction.

Proactive Interference

To test the prediction that diazepam would produce an excessive build-up of proactive interference as is seen in Korsakoff patients, a 2X2 (treatment by

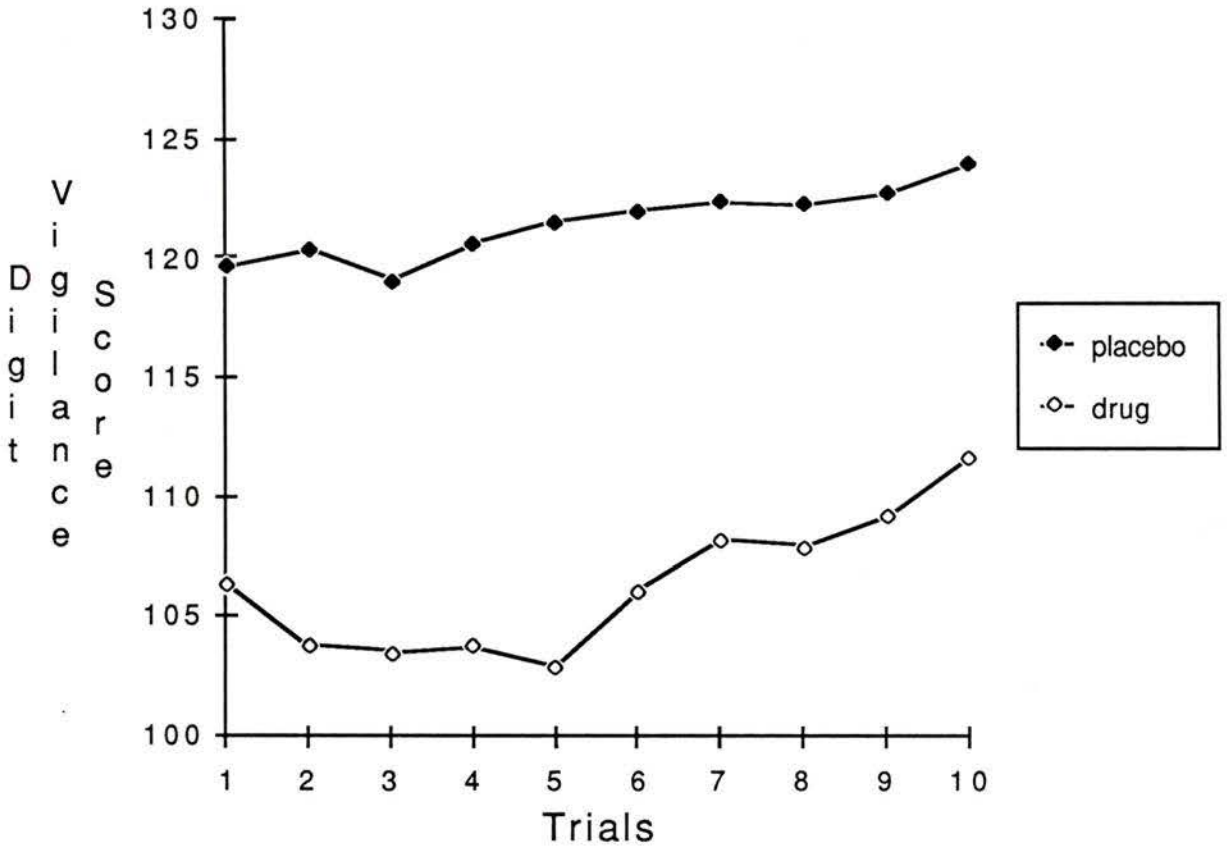

Figure 6. Digit Vigilance Scores as a Function of Time Across Experimental Session According to Group

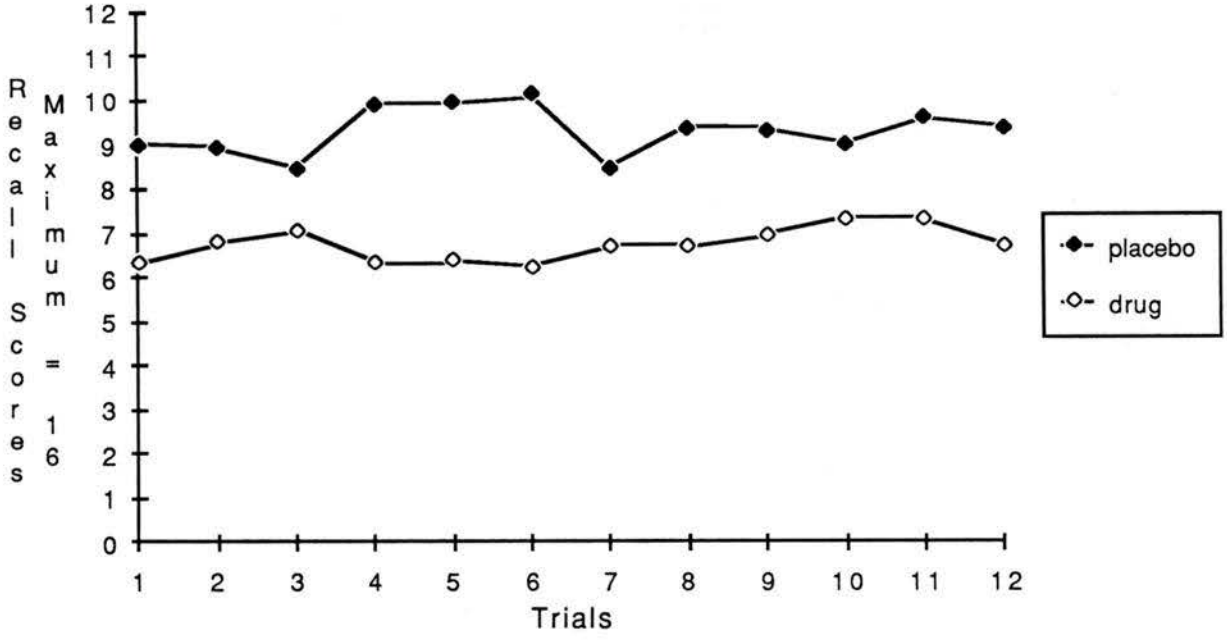

Figure 7. Recall Scores as a Function of Time Across Experimental Session According to Group

PT) mixed-model repeated-measures MANOVA was performed on the number of PI intrusions made per block of 6 lists for each subject. The measure was defined as recall of a word that had been presented prior to the current list. Contrary to prediction, there was no difference between the groups $F(1, 46) = 0.04$, n.s. Overall, very few errors were attributed to proactive interference for either group (less than one word per list, on average). Interestingly, the analysis revealed that more PI intrusions occurred during the recall of lists presented at the 8-sec PT (mean = .771) than for those presented at the 2-sec rate (mean = .437) $F(1, 46) = 4.94$, $p=.031$, which was probably a reflection of the greater number of words recalled overall in the longer PT condition. There was no interaction between treatment and PT $F(1, 46) = 2.78$, n.s.

Discussion

The purpose of this study was to uncover the specific component of memory processing that is impaired as a consequence of diazepam ingestion. The present results showed clearly that diazepam lowers overall memory performance. This finding, which replicated previous research, was essential to provide a basis from which subsequent analyses of the nature of the underlying deficit could be performed.

The results were congruent with the acquisition impairment hypothesis which states that diazepam decreases memory performance by selectively reducing the acquisition of new information. In previous studies, this position has been upheld by findings of impaired performance on tests of newly-presented material with preserved retention of material presented prior to drug administration. In the present study, this hypothesis was addressed by manipulating presentation time. If the memory impairment were due to defective acquisition, then increased presentation time should result in improved performance as a result of the extra processing time for interitem and word-to-context associations to be developed and strengthened (Atkinson & Shiffrin, 1971). If, in contrast, a retrieval deficit were responsible for the poor memory, then performance would not be expected to improve significantly with increased processing time. Presumably, when the difficulty is in retrieving stored information, then it is of no consequence whether words are exposed for a short or a long time because they would be acquired and stored adequately in either case. Thus, the finding here of facilitated performance with increased presentation time supports the view that acquisition, and not retrieval, is impaired by diazepam.

Both the analysis of the recency portion of the serial position curve and the lag scores analysis of STM failed to yield group differences. However, there was a reduction in the number of different words being rehearsed per interval by subjects in the drug group, as predicted. Thus, one can conclude that these three methods are not equivalent. The recency method and the lag score method of analyzing STM are both based on serial position; the former measures the probability of correct recall at each of the last four list positions, while the latter score is derived as a function of a recalled word's original position in the list presented. Conversely, the distinct rehearsal score is a count of the number of different words that a subject practices as words are still being presented; therefore, it reflects the contents of the subject's STM buffer (i.e., the information that is in consciousness).

Thus, while the recency and lag score measures probably reflect recall of material from STM, they do not necessarily measure the maximum capacity of STM. Rather, the distinct rehearsal score, which measures the number of words that can simultaneously be held and worked on in STM, appears to be a much better indicator of STM capacity. It follows that if the distinct rehearsal measure is an index of STM capacity, while the other two measures merely characterize a particular portion of recalled information as coming from STM, then the first measure should be quantitatively larger than the other two (i.e., capacity of STM should be greater than observed recall from STM, a subset of total capacity). This was indeed the case. Although diazepam reduced STM capacity to slightly less than three different words being rehearsed per interval (2.9), mean recall from STM, as measured by the recency and lag score analyses, was even lower, with only about 2¤ words being recalled from STM per list.

Considering that the predicted reduction in the number of different words rehearsed per interval was found among the drugged subjects, it was

concluded that the manner in which diazepam impaired acquisition was by an underlying reduction in STM capacity. This finding is consistent with Cermak et al.'s (1976) work with amnesics, in which Korsakoff patients' impaired recall was attributed to their rehearsing fewer distinct words per interitem interval than normals. This finding is also consistent with the results of Ghoneim et al. (1975) who proposed that diazepam interferes with rehearsal processing and the subsequent transfer of information to a permanent memory store.

Although there was support for the view that diazepam impaired recall by a selective action on underlying memory processes specifically, reduced attention and arousal could not be ruled out as contributors to the recall deficit because digit vigilance was lowered by diazepam throughout the session as well. However, the pattern of impairment was not the same for these two measures (overall recall and digit vigilance). Drugged subjects were able to improve with practice at the same rate as normals on the vigilance measure, as evidenced by their increase in performance across trials on the cancellation task. In contrast, the number of words recalled per list by these same subjects did not increase across the session.

Given that psychomotor slowing and reduced memory performance appeared concurrently, no definitive conclusions can be made as to whether arousal and memory are independently affected by diazepam. It should be noted that a lowered arousal level and reduced attentional capacity do not rule out an acquisition impairment. Naturally, when vigilance is reduced, initial sensory perceptions may be affected, which would result in the storage of degraded engrams and ultimately lead to impaired recall. The fact that the diazepam lowered overall total rehearsal rates provides some support for the view that lowered arousal is an important factor leading to diminished recall. However, a reduction in arousal alone would not be expected to reduce the

capacity of STM; that is, even if diazepam slowed subjects' total rehearsal rate (which it did) because of a generalized CNS depression, it doesn't necessarily follow that the number of different words being worked on in STM would be detrimentally affected as well. One can envision a case in which the underlying impairment lies solely in the level of subjects' arousal. In such a case, subjects would undoubtedly rehearse fewer total words because their overall speech production rate would be slowed by the drug. Nevertheless, the number of different words rehearsed per interval would be expected to remain at full capacity, if, indeed, the effect were only on arousal and not on any components of memory processing. Thus, the finding that the number of different words rehearsed was reduced seems to point toward a specific detriment in capacity rather than arousal alone. Moreover, the drugged subjects in this study were clearly awake and reasonably attentive, as evidenced by their ability to read the incoming words and rehearse them with other words in brief, successive intervals. They were also able to sustain their attention and fulfill the objectives of the longer presentation time condition. Thus, it would appear that something more than reduced arousal led to their memory deficit.

Some deficits produced by the diazepam were qualitatively similar to (although not as quantitatively severe as) the memory deficits observed in alcoholic Korsakoff amnesics. Both diazepam-induced subjects and Korsakoff patients are impaired relative to normals in overall recall, and both improve with increased presentation time, which points to an acquisition impairment. Further, both have a reduced STM capacity as measured by the number of different words rehearsed at a time, despite intact recall of words from the recency portion of the serial position curve. A striking contrast exists between the two groups, however, as evidenced by the failure of diazepam to produce proactive interference errors. Such errors are commonly observed in Korsakoff patients

(Cermak & Butters, 1972; Cermak, Reale, & De Luca, 1977; De Luca, Cermak, & Butters, 1975) and are often used to explain their poor recall in multi-trial experiments such as the present one.

This problem with proactive interference has been linked to damage to the frontal lobes (Moscovitch, 1982). It is therefore not surprising that Korsakoff patients display an excessive sensitivity to proactive interference, considering that their primary damage site, the dorsomedial nucleus of the thalamus (Victor, Adams, & Collins, 1971), is the major source of projections to prefrontal cortex (Carlson, 1981). Because Korsakoff patients and diazepam-induced subjects differ on this basic measure, it can be concluded that Korsakoff amnesia does not represent the clinical analogue of diazepam-induced memory deficits. Rather, there is support for the view that the drug may be executing its memory effects through a generalized suppression of the hippocampal region.

Evidence for this claim comes from the field of psychopharmacology in which is has been shown that a specialized benzodiazepine (BZ) receptor exists in brain tissue (Kuhar, 1980; Mohler & Okada, 1977, 1978; Snyder, 1981). The highest densities of this receptor, identified by high-affinity diazepam binding in homogenized preparations of rat cerebral cortex, have been found in parts of the limbic system and cerebellum. Kuhar (1980) has made several tentative links between anatomical structures rich in BZ receptors and the known clinical effects of diazepam. For example, he has linked the anxiolytic and anti-convulsant properties of diazepam with the suppression of the limbic system. He has further hypothesized associations between diazepam's muscle relaxant, appetite stimulant, and ataxia/incoordination effects with receptors in the reticular formation, lateral hypothalamus, and cerebellum, respectively. Yet, despite these numerous speculations, Kuhar conspicuously failed to mention diazepam's memory-reducing effect.

Clearly, documentation of memory impairment resulting from diazepam intake is abundant in the psychopharmacology literature, as has been discussed and confirmed in this study. Thus, it would seem just as likely as the other associations made above that suppression of structures containing high levels of BZ receptors in the limbic system, such as the amygdaloid complex, hippocampal formation, pyriform cortex, and hypothalamus (Kuhar, 1980), from high affinity diazepam binding would produce memory deficits. This association, within the limitations of interpreting correlational data, is consistent with what is known regarding the anatomy of amnesia.

The case of H.M. (Scoville & Milner, 1957), the epileptic patient described earlier who underwent bilateral medial temporal lobe resection, is the most celebrated case of hippocampal amnesia. H.M.'s surgical ablation, which extended beyond the amygdala and temporal pole area to include the hippocampus, has left him with a severe and permanent anterograde amnestic condition in which he is unable to learn new information despite having relatively preserved retention of information acquired prior to his surgery. Similarly, following a review of amnesic symptoms resulting from various surgical interventions, Brierly (1977) concluded that the inner portions of the temporal lobes and the hippocampal formation are essential for normal memorizing.

In the animal literature too, the hippocampus has been shown to play an important role in the acquisition of new information. In several experiments by David Olton (1983, 1985, 1986) rats were studied on a delayed conditional discrimination task in which they had to remember the stimulus present at the beginning of a trial in order to respond correctly at the end of the trial. Thus, in this task, as in the list-learning task used in the present study, subjects (both the rats and the humans) were required to retain newly-presented information for

the duration of the trial. Olton found that bilateral lesions of one of the major outflow pathways of the hippocampus (the fimbria-fornix) resulted in impaired acquisition of new information on this task. Thus, this structural damage within the limbic system produces a selective impairment for a certain type of memory, as seen in the human amnesic syndromes and diazepam-induced memory impairments. It seems reasonable, therefore, to conclude that the encoding deficit seen in diazepam-induced amnesia may result from the binding of diazepam to receptors in the hippocampal region which interferes with the normal memory encoding functions of this region.

Prior to the start of this study, it was known that diazepam would produce a memory impairment. If the overall behavioral effect is reduced recall, one might argue, what good does it do to pinpoint the underlying mechanisms leading to that impairment? The individuals still have difficulty in remembering information presented to them. Yet the academic study of component memory processes can lead to practical therapeutic applications in clinical settings. For example, if the deficit is known to be in acquisition, it will not be beneficial to work on retrieval access strategies with patients because the information was never stored well in the first place. Instead, attention can be focused on strategies intended to enrich contextual associations or to build up rehearsal levels so that better encoding and consolidation can occur, which, in turn, should lead to improved memory performance.

Further research of the mechanisms involved in both normal memory and experimentally-induced memory deficits is warranted in order to achieve a better understanding of the faulty component processes underlying the various chronic amnesia syndromes. Ultimately, the delineation of deficient memory processing will provide a sound basis for developing successful remediation strategies for memory-impaired patients.

References

Astrom, B., & Nilsson, L-G. (1977). Overt repetition as a means of controlling rehearsal. Scandinavian Journal of Psychology, 18, 53-58.

Atkinson, R. C., & Shiffrin, R. M. (1968). Human memory: A proposed system and its control processes. In K. W. Spence & J. T. Spence (Eds.), The psychology of learning and motivation (Vol. 2, pp. 89-195). New York: Academic Press.

Atkinson, R. C., & Shiffrin, R. M. (1971). The control of short-term memory. Scientific American, 225, 82-90.

Balter, M. B., Levine, J., Manheimer, D. I. (1974). Cross-national study of the extent of anti-anxiety/sedative drug use. New England Journal of Medicine, 290, 769-774.

Berchou, R., & Block, R. I. (1983). Use of computerized psychomotor testing in determining CNS effects of drugs. Perceptual and Motor Skills, 57, 691-700.

Block, R. I., & Berchou, R. (1984). Alprazolam and lorazepam effects on memory acquisition and retrieval processes. Pharmacology, Biochemistry and Behavior, 20, 233-241.

Brierly, J. B. (1977). Neuropathology of amnesic states. In C. W. M. Whitty & O. L. Zangwill (Eds.), Amnesia (2nd ed., pp. 199-223). London: Butterworths.

Brown, G. G., & Donenfield, W. (1982). A mathematical learning theory analysis of Korsakoff rehearsal. In R. N. Malatasha & L. C. Hartlage (Eds.), Neuropsychology and cognition, Vol. 2 (pp. 528-551). The Hague: Martinus Nijhoff Publishers.

Brown, G. G., Rosenbaum, G., Lewis, R., & Rourke, D. (1980). The effects of rehearsal rate on serial recall in Korsakoff amnesia. Neuropsychologia, 18, 185-191.

Brown, J., Lewis, V., Brown, M., Horn, G., & Bowes, J. B. (1982). A comparison between transient amnesias induced by two drugs (diazepam or lorazepam) and amnesia of organic origin. Neuropsychologia, 20, 55-70.

Butters, N., & Cermak, L. S. (1980). Alcoholic Korsakoff's syndrome: An information-processing approach to amnesia. New York: Academic Press.

Carlson, N. R. (1981). Physiology of behavior (2nd ed.). Boston: Allyn and Bacon, Inc.

Cermak, L. S., & Butters, N. (1972). The role of interference and encoding in the short-term memory deficits of Korsakoff patients. Neuropsychologia, 10, 89-95.

Cermak, L. S., Naus, M. J., & Reale, L. (1976). Rehearsal strategies of alcoholic Korsakoff patients. Brain and Language, 3, 375-385.

Cermak, L. S., Reale, L., & De Luca, D. (1977). Korsakoff patients' nonverbal vs verbal memory: Effects of interference and mediation on rate of information loss. Neuropsychologia, 15, 303-310.

Christian, J., Bickley, W., Tarka, M., & Clayton, K. (1978). Measures of free recall of 900 English nouns: Correlations with imagery, concreteness, meaningfulness, and frequency. Memory and Cognition, 6, 379-390.

Clark, E. O., Glanzer, M., & Turndorf, H. (1979). The pattern of memory loss resulting from intravenously administered diazepam. Archives of Neurology, 36, 296-300.

Clarke, P. R. F., Eccersley, P. S., Frisby, J. P., & Thornton, J. A. (1970). The amnesic effect of diazepam (valium). British Journal of Anaesthesia, 42, 690-697.

Craik, F. I. M. (1970). The fate of primary memory items in free recall. Journal of Verbal Learning and Verbal Behavior, 9, 143-148.

Craik, F. I. M., & Birtwistle, J. (1971). Proactive inhibition in free recall. Journal of Experimental Psychology, 91, 120-123.

Craik, F. I. M., & Lockhart, R. S. (1972). Levels of processing: A framework for memory research. Journal of Verbal Learning and Verbal Behavior, 11, 671-684.

CTS Manual. Edgecomb, ME: Digitry Company, Inc.

De Luca, D., Cermak, L. S., & Butters, N. (1975). An analysis of Korsakoff patients' recall following varying types of distractor activity. Neuropsychologia, 13, 271-279.

Dundee, J. W., & Pandit, S. K. (1972). Anterograde amnesic effects of pethidine, hyoscine and diazepam in adults. British Journal of Pharmacology, 44, 140-144.

Epstein, W., & Wilder, L. (1972). Searching for to-be-forgotten material in a directed forgetting task. Journal of Experimental Psychology, 95, 349-357.

Finkle, B. S., McCloskey, K. L., & Goodman, L. S. (1979). Diazepam and drug-associated deaths: A survey in the United States and Canada. JAMA, 242, 429-434.

Fischler, I. Rundus, D., & Atkinson, R. C. (1970). Effects of overt rehearsal procedures on free recall. Psychonomic Science, 19, 249-250.

Flinn, F. J., Wineland, P., & Peterson, L. J. (1975). Duration of amnesia during sedation with diazepam and pentazocine: Preliminary report. Journal of Oral Surgery, 33, 23-26.

Gelenberg, A. J. (1983). Anxiety. In E. L. Bassuk, S. C. Schoonover, & A. J. Gelenberg (Eds.), The practitioner's guide to psychoactive drugs (2nd ed., pp. 167-201). New York: Plenum Publishing Corporation.

Ghoneim, M. M., & Mewaldt, S. P. (1975). Effects of diazepam and scopolamine on storage, retrieval and organizational processes in memory. Psychopharmacologia (Berl.), 44, 257-262.

Ghoneim, M. M., & Mewaldt, S. P. (1977). Studies on human memory: The interactions of diazepam, scopolamine, and physostigmine. Psychopharmacology, 52, 1-6.

Ghoneim, M. M., Mewaldt, S. P., Berie, J. L., & Hinrichs, J. V. (1981). Memory and performance effects of single and 3-week administration of diazepam. Psychopharmacology, 73, 147-151.

Ghoneim, M. M., Mewaldt, S. P., & Thatcher, J. W. (1975). The effect of diazepam and fentanyl on mental, psychomotor and electroencephalographic functions and their rate of recovery. Psychopharmacologia (Berl.), 44, 61-66.

Greenblatt, D. J., Allen, M. D., Noel, B. J., & Shader, R. I. (1977). Acute overdosage with benzodiazepine derivatives. Clinical Pharmacology and Therapeutics, 21, 497-514.

Greenblatt, D. J., & Shader, R. I. (1974). Benzodiazepines in clinical practice. New York: Raven Press.

Greenblatt, D. J., & Shader, R. I. (1978). Dependence, tolerance, and addiction to benzodiazepines: Clinical and pharmacokinetic considerations. Drug Metabolism Reviews, 8, 13-28.

Greenblatt, D. J., Shader, R. I., Divoll, M., & Harmatz, J. S. (1981). Benzodiazepines: A summary of pharmacokinetic properties. British Journal of Clinical Pharmacology, 11, 115-165.

Greenblatt, D. J., Shader, R. I., Divoll, M., & Harmatz, J. S. (1984). Adverse reactions to triazolam, flurazepam, and placebo in controlled clinical trials. Journal of Clinical Psychiatry, 45, 192-195.

Hinrichs, J. V., Ghoneim, M. M., & Mewaldt, S. P. (1984). Diazepam and memory: Retrograde facilitation produced by interference reduction. Psychopharmacology, 84, 158-162.

Huppert, F. A., & Piercy, M. (1978). Dissociation between learning and remembering in organic amnesia. Nature, 275, 317-318.

Janowsky, D. S. (1976). Psychopharmacology. In H. S. Abram (Ed.), Basic psychiatry for the primary care physician (pp. 231-252). Little & Brown.

Knight, R. G., & Wooles, I. M. (1980). Experimental investigation of chronic organic amnesia: A review. Psychological Bulletin, 88, 753-771.

Kuhar, M. J. (1980). The benzodiazepine receptor: Anatomical aspects. In S. I. Szara & J. P. Ludford (Eds.), Benzodiazepines: A review of research results, 1980 (NIDA Research Monograph No. 33, DHHS Publication No. ADM 81-1052, pp. 12-21). Washington DC: U.S. Government Printing Office.

Levin, H. S. (1986). Learning and memory. In H. J. Hannay (Ed.), Experimental techniques in human neuropsychology (pp. 309-362). New York: Oxford University Press.

Lewis, R. F., & Rennick, P. M. (1979). Manual for the repeatable cognitive-perceptual-motor battery. Grosse Pointe Park, MI: Axon Publishing Co.

Loess, H., & Waugh, N. C. (1967). Short-term memory and intertrial interval. Journal of Verbal Learning and Verbal Behavior, 6, 455-460.

Loke, W. H., Hinrichs, J. V., & Ghoneim, M. M. (1985). Caffeine and diazepam: Separate and combined effects on mood, memory, and psychomotor performance. Psychopharmacology, 87, 344-350.

Mac, D. S., Kumar, R., & Goodwin, D. W. (1985). Anterograde amnesia with oral lorazepam. Journal of Clinical Psychiatry, 46, 137-138.

Miller, G. A. (1956). The magical number seven, plus or minus two: Some limits on our capacity for processing information. Psychological Review, 63, 81-97.

Milner, B. (1966). Amnesia following operation on the temporal lobes. In C. W. M. Whitty & O. L. Zangwill (Eds.), Amnesia (pp. 109-133). London: Butterworths.

Mohler, H., & Okada, T. (1977). Benzodiazepine receptor: Demonstration in the central nervous system. Science, 198, 849-851.

Mohler, H., & Okada, T. (1978). The benzodiazepine receptor in normal and pathological human brain. British Journal of Psychiatry, 133, 261-268.

Morgan, K., Adam, K., & Oswald, I. (1984). Effects of lorazepam and of triazolam on psychological functions. Psychopharmacology, 82, 386-388.

Moscovitch, M. (1982). A neuropsychological approach to perception and memory in normal and pathological aging. In F. I. M. Craik & S. Trehub (Eds.), Aging and cognitive processes (pp. 55-78). New York: Plenum Press.

Norusis, M. J. (1985). SPSSX advanced statistics guide. Chicago: McGraw-Hill.

Olton, D. S. (1983). Memory functions and the hippocampus. In W. Seifert (Ed.), Neurobiology of the hippocampus (pp. 335-373). New York: Academic Press.

Olton, D. S. (1985). Strategies for the development of animal models of human memory impairments. In D. S. Olton, E. Gamzu, & S. Corkin (Eds.), Memory dysfunctions: An integration of animal and human research from clinical and preclinical perspectives (pp. 113-121). New York: Academy of Sciences.

Olton, D. S. (1986). Hippocampal function and memory for temporal context. In R. L. Isaacson & K. H. Pribam (Eds.), The hippocampus (Vol. 4, pp. 281-298). New York: Plenum Press.

Peterson, L. R., & Gentile, A. (1965). Proactive interference as a function of time between tests. Journal of Experimental Psychology, 70, 473-478.

Peterson, L. R., & Peterson, M. J. (1959). Short-term retention of individual verbal items. Journal of Experimental Psychology, 58, 193-198.

Physicians' desk reference (40th ed.). (1986). Oradell, NJ: Medical Economics Co., pp. 1518-1520.

Raaijmakers, J. G. W., & Shiffrin, R. M. (1980). SAM: A theory of probabilistic search of associative memory. In G. H. Bower (Ed.), The psychology of learning and motivation: Advances in research and theory (Vol. 14, pp. 207-262). New York: Academic Press.

Raaijmakers, J. G. W., & Shiffrin, R. M. (1981). Search of associative memory. Psychological Review, 88, 93-134.

Reitan, R. M., & Davison, L. A. (Eds.) (1974). Clinical neuropsychology: Current status and applications. Washington, DC: V.H. Winston & Sons.

Roehrs, T., Zorick, F. J., Sicklesteel, J. M., Wittig, R. M., Hartse, K. M., & Roth, T. (1983). Effects of hypnotics on memory. Journal of Clinical Psychopharmacology, 3, 310-313.

Roth, T., Hartse, K. M., Saab, P. G., Piccione, P. M., & Kramer, M. (1980). The effects of flurazepam, lorazepam, and triazolam on sleep and memory. Psychopharmacology, 70, 231-237.

Roth, T. Roehrs, T. Wittig, R., & Zorick, F. (1984). Benzodiazepines and memory. British Journal of Clinical Pharmacology, 18, 455-495.

Rundus, D. (1971). Analysis of rehearsal processes in free recall. Journal of Experimental Psychology, 89, 63-77.

Rundus, D., & Atkinson, R. C. (1970). Rehearsal processes in free recall: A procedure for direct observation. Journal of Verbal Learning and Verbal Behavior, 9, 99-105.

Scharf, M. B., Khosla, N., Brocker, N., & Goff, P. (1984). Differential amnestic properties of short- and long-acting benzodiazepines. Journal of Clinical Psychiatry, 45, 51-53.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. Journal of Neurology, Neurosurgery, and Psychiatry, 20, 11-21.

Shader, R. I., Dreyfuss, D., Gerrein, J. R., Harmatz, J. S., Allison, S. J., & Greenblatt, D. J. (1986). Sedative effects and impaired learning and recall after single oral doses of lorazepam. Clinical Pharmacology & Therapeutics, 39, 526-530.

Snyder, S. H. (1981). Benzodiazepine receptors. Psychiatric Annals, 11(Suppl.), 11-23.

SPSSX user's guide (2nd ed.) (1986). New York: McGraw-Hill Book Co.

Squire, L. R. (1981). Two forms of human amnesia: An analysis of forgetting. Journal of Neuroscience, 1, 635-640.

Tinklenberg, J. R., & Taylor, J. L. (1984). Assessments of drug effects on human memory functions. In L. Squire & N. Butters (Eds.), Neuropsychology of memory (pp. 213-223). New York: The Guilford Press.

Tulving, E., & Colotla, V. A. (1970). Free recall of trilingual lists. Cognitive Psychology, 1, 86-98.

Victor, M., Adams, R. D., & Collins, G. H. (1971). The Wernicke-Korsakoff syndrome. Philadelphia: F. A. Davis.

Wechsler, D. (1981). Wechsler adult intelligence scale - revised (WAIS-R). New York: The Psychological Corporation.

Wechsler, D., & Stone, C. P. (1973). Wechsler memory scale. New York: The Psychological Corporation.

Woodward, A. E., & Bjork, R. A. (1971). Forgetting and remembering in free recall: Intentional and unintentional. Journal of Experimental Psychology, 89, 109-116.

Appendix 1

Telephone Screening Interview

Name_____

Age_____ Sex_____ Weight_____

Phone: Work #_____ Home#_____

Educational level_____ Handedness_____

Medical history:

Have you ever been to a: neurologist_____
psychologist_____
psychiatrist_____

If YES to any of the above, describe history of treatment.

Do you have: blood disease_____
liver disease_____
kidney disease_____
narrow angle glaucoma_____

Have you recently noticed any yellowness of your skin or eyes?_____
Have you had any recent changes in sleep habits and/or energy level?_____
Do you suffer from: memory problems_____
headaches_____
Have you ever been hospitalized for a head injury?_____
If so, when?_____ Describe history and present status.

Have you ever had a loss of consciousness for more than 5 minutes?_____
Describe_____

Do you have epilepsy?_____
Have you ever had a seizure?_____
Are you currently taking an anti-convulsant?_____

Are you pregnant or nursing?_____

Are you currently on any medications?_____

_____

Do you have a history of substance abuse or alcohol abuse?_____

Have you ever been treated for it? (when?)_____

Have you ever taken valium?_____

If so, in what dosage and for how long?_____

Have you ever been prescribed other benzodiazepines or barbiturates (like tranquilizers of sleeping pills)?_____

Do you smoke: cigarettes_____
cigars_____
pipe_____

Do you get drunk or high regularly (more than 3 times a week)_____
(What is you drinking pattern?)

Have you ever developed any of the following in response to a prescription drug:

Nausea_____ Slurred speech_____ Confusion_____ Dizziness___
Urinary retention_____ Blurred vision_____ Double vision_____
Drop in blood pressure_____ Skin rash_____ Hallucinations_____
Tremor_____ Headache_____

Do you have any other major health conditions not described above?_____

_____

Appendix 2

Consent Form

PRHRC APPROVAL DATE: 4 / 15 / 86
Protocol Title: The Validity of a Quantitative Theory of Amnesia

The purpose of this study is to examine the effects of valium on memory for a list of words. Because of the new way in which the results of this study will be analyzed, it has the potential to confirm the usefulness of a new method for understanding memory impairment among patients with brain disease. The study will take much of the morning and perhaps part of the afternoon. During that time I will receive several tests of memory, attention, and coordination. I will receive a meal ticket and $20.00 for my participation and transportation.

I have been made aware of the following:

1. I will receive a pill that will either be valium or a biologically inert substance.

2. The pill might temporarily produce a reduction in memory, attention, or coordination. It might make me sleepy, lightheaded, or dizzy, and might upset my bowel or stomach. Throughout the study I will be supervised by hospital staff and a physician will be available to me if I need one.

3. I understand that the information identifying me is confidential and will not be put in my medical chart. It will be kept separate from patient files. The information that identifies me will not be released from the hospital without my permission, except as required by law.

4. I realize that valium use has been associated with infant abnormalities when used by nursing or pregnant women. I acknowledge that I am not pregnant or nursing.

5. I realize that valium might affect my ability to drive or use other equipment. Provided that I have taken valium, I agree to stay at the hospital until my performance on tests of memory, coordination, and attention are as good as they were before I took valium.

6. I realize that no medical benefit will necessarily come to me from participating in the study.

7. I have discussed this study with _____ and she/he has offered to answer any questions I may have concerning the procedures involved. I am aware that I should contact Gregory G. Brown, Ph.D. at 876-2526 and/or the Research Office at 876-2024 if I have any questions regarding the research, research subjects' rights or my participation in the study and its outcome.

8. In giving my consent, I acknowledge that my participation in this research study is voluntary and that I may withdraw from it at any time without prejudice to me.

9. In the event of a medical emergency involving me, emergency medical treatment will be rendered. The cost for said treatment may be covered by my medical insurance; however, I understand that there is no federal, state or private program established to provide research subjects with compensation and medical treatment cost for injuries resulting from research procedures.

_____ _____

Signature of patient, parent of minor patient, or legal guardian — Date

_____

Print name if other than patient

_____ _____

Witness' Signature — Date

_____ _____

Investigator's Signature — Date

Appendix 3

Word Lists

Block 1

List 1	List 2	List 3	List 4
amount	builder	artist	ankle
breeze	car	blister	banker
cigar	cattle	claw	bullet
code	dweller	daylight	disease
freedom	earth	frog	doll
fun	fork	fur	form
health	hour	geese	gem
lemon	idea	golf	gift
mule	letter	love	leopard
noose	ocean	marriage	madness
picture	pleasure	mischief	pressure
pole	python	odor	soil
ship	skin	plant	stain
tool	string	shock	truck
tower	victim	vision	virtue
woman	wine	whale	warmth

Block 2

List 1	List 2	List 3	List 4
army	cabin	apple	arm
baby	college	boy	boulder
cord	goddess	cottage	buffoon
cotton	hurdle	cradle	corner
fortune	judge	deed	custom
hatred	kindness	devil	flood
lark	lake	gold	green
lime	lecture	heaven	hoof
money	metal	ink	kettle
party	peach	joke	lice
poster	prayer	nymph	market
rod	reptile	oats	owner
saloon	square	pencil	pact
shadow	sugar	plain	sadness
toy	tank	speech	unit
venom	valley	sultan	weapon

Block 3

List 1	List 2	List 3	List 4	List 5	List 6
barrel	author	anger	air	bagpipe	bloom
cell	blossom	brute	blood	bottle	boss
doctor	cellar	child	crime	chin	city
elbow	chair	coin	deceit	ego	costume
forest	demon	diamond	dust	fire	death
hammer	ghost	door	fact	fox	forehead
infant	humor	exhaust	girl	keg	genius
jelly	joy	fabric	leaflet	locker	grass
law	leggings	fowl	mend	mantle	hope
monk	meadow	insect	painter	missile	inn
railroad	mother	lump	prairie	nectar	lobster
sunset	passion	poet	salad	priest	nail
thought	plank	pudding	slipper	river	pupil
trellis	queen	sauce	tweezers	snake	shriek
volume	seat	sky	village	shotgun	stub
window	water	tripod	winter	wigwam	wheat

Block 4

List 1	List 2	List 3	List 4	List 5	List 6
bandit	book	advice	arrow	bar	body
beaver	butter	belief	basement	cand	bronze
coffee	chief	board	cash	doorman	chaos
dollar	corn	clock	church	dream	dawn
foam	flesh	dirt	dress	event	decree
friend	juggler	garden	fate	horse	engine
goblet	king	glutton	hall	life	flower
hotel	limb	harness	hide	mast	glacier
kiss	morgue	iron	lawn	method	house
moral	outcome	justice	monarch	prison	invoice
murder	pepper	meat	oven	skillet	lip
pipe	rubble	nun	sea	stone	mercy
rattle	shore	slave	street	table	rock
science	student	strength	ticket	vigor	salute
swamp	truth	thorn	tomb	welfare	sickness
teacher	vest	world	wife	yacht	time

Appendix 4

Instructions to Subjects

> I will say 'ready' and then three asterisks will appear in the middle of the screen. Then a number of words will be presented, one at a time, also in the middle of the screen. As each word appears, say it aloud and try to remember it. To help you remember the word, practice it by saying it over and over again until another word appears. Then read that word aloud; spend the time you have until the following word appears by repeating aloud some of the words you have already seen.
>
> For example, if the first word is *desk*, you'll read it as soon as you see it--desk--and then repeat 'desk, desk, desk.' If the next word is *tissue,* read it when you see it--tissue--and then repeat 'desk, tissue, desk.' If the third word is *circus,* read it--circus--and then practice by repeating 'circus, desk, tissue, circus, circus, tissue, desk,' or whatever you have time to say until another word appears.

Subjects were further told that the goal was not to say as many words as possible as fast as they could. Instead, they were encouraged to build up to a constant, comfortable level of repetition in which they would repeat approximately the same number of words during each interval that elapsed between words (the inter-stimulus interval). They were told that there would be 16 words in all. Instructions continued as:

> Following the 16th word, the number 1 will appear in the top left-hand corner of the screen. That will be your cue to start recalling as many of the words from the list as you can, in any order. Each word that you recall will appear on the screen as you say it (I'll be typing it in from the terminal).

Don't worry how fast or slow you go. I won't be timing you, so take as long as you want to recall as many words as you can. This stage will continue until you tell me that you can't remember any more words.

Appendix 5

Timetable of Events for the Experimental Session

8:30	Baseline tests
9:00-9:15	Ingest pill
9:15-10:15	Alternate forms of the WAIS-R digit-symbol subtest every 15 minutes
9:30-10:15	Begin trials of experimental word lists
11:00-12:00	End experimental trials
12:00	Lunch
1:00-?	Alternate forms of baseline tests for subjects in the drug group

Appendix 6

Recall Scores per List and
Mean per Block for Each Subject

Drug Subjects

	2-sec Presentation Time							8-sec Presentation Time						
	Trial							Trial						
ID #	1	2	3	4	5	6	Mean	1	2	3	4	5	6	Mean
03	7	7	6	6	5	5	6.0	11	5	9	10	11	9	9.2
05	5	6	7	6	4	4	5.3	3	3	3	7	4	4	4.0
06*	11	16	13	11	10	10	11.8	14	16	16	14	16	12	13.0
12	5	8	9	10	9	10	8.5	15	16	16	15	16	12	15.0
13	7	5	8	9	9	7	7.3	11	9	11	12	15	14	12.0
15	3	4	4	5	4	4	4.0	6	6	6	8	5	8	6.5
16*	8	6	7	9	6	5	7.5	6	3	6	6	5	5	5.2
18*	3	5	4	3	5	3	3.8	5	6	6	4	5	6	5.3
19	9	10	11	9	7	8	9.0	10	11	11	12	11	13	11.3
21*	4	4	6	9	8	4	5.8	5	5	5	5	5	8	5.5
22	2	4	6	5	5	5	4.5	7	3	6	7	3	4	5.0
25	4	5	4	4	5	3	4.2	5	4	5	4	5	4	4.5
29	5	5	3	4	6	6	4.8	6	7	6	7	8	6	6.7
30*	5	4	6	8	7	4	5.7	8	5	6	5	5	7	6.0
32*	5	7	8	7	6	6	6.5	7	7	8	6	6	5	6.5
35*	6	6	8	3	7	6	6.0	5	7	7	10	7	6	7.0
37	4	5	6	5	3	3	4.3	3	3	3	5	5	4	3.8
39	5	6	6	6	5	6	5.7	5	8	7	6	8	8	7.0
40	4	5	5	6	5	7	5.3	9	9	7	7	6	7	7.5
41*	7	6	5	3	3	5	4.8	5	7	9	7	7	5	6.7
44*	5	7	4	5	8	6	5.8	14	13	8	10	8	7	10.0
46*	6	6	6	8	8	9	7.2	8	10	9	9	9	10	9.2
47*	6	5	5	6	6	6	5.7	10	10	9	8	8	7	8.7
48*	4	4	5	4	4	4	4.2	5	4	6	3	5	4	4.5

*The 8-second block preceded the 2-second block for these subjects.

Appendix 6 cont.

Placebo Subjects

	2-sec Presentation Time							8-sec Presentation Time						
	Trial							Trial						
ID #	1	2	3	4	5	6	Mean	1	2	3	4	5	6	Mean
01*	11	10	8	9	11	5	9.0	16	14	13	14	15	15	14.5
02*	8	9	7	6	9	6	7.5	9	10	11	10	10	11	10.2
04*	8	6	8	8	11	8	8.2	12	12	9	15	13	14	12.5
07	6	10	7	8	10	8	8.2	10	11	13	11	13	13	11.8
08	9	8	9	6	8	8	8.0	8	9	9	7	9	12	9.0
09	4	5	3	7	8	8	5.8	7	7	6	4	10	7	6.8
10	7	7	4	8	7	8	6.8	7	7	6	5	3	5	5.5
11	6	6	8	7	7	5	6.5	7	14	12	15	14	15	13.2
14*	8	8	9	9	9	8	8.5	10	7	9	10	11	11	9.7
17*	8	7	6	5	6	8	6.7	9	12	12	11	9	9	10.3
20	6	6	10	7	7	9	7.5	7	9	12	9	14	11	10.3
23*	5	9	5	8	8	6	6.8	11	11	10	11	10	12	10.8
24*	7	9	9	11	9	7	8.7	9	11	10	12	10	10	10.3
26	10	7	8	7	12	12	9.3	10	11	14	14	14	16	13.2
27	9	6	6	9	4	8	7.0	7	10	8	7	9	10	8.5
28	10	9	9	11	11	10	10.0	14	12	12	12	12	9	11.8
31*	9	8	10	8	9	8	8.7	9	11	9	9	13	12	10.5
33*	9	10	10	9	6	11	9.2	7	9	8	15	16	11	11.0
34*	9	11	9	8	9	8	9.0	13	12	11	11	10	13	11.7
36	7	7	7	9	8	7	7.5	11	12	10	11	10	11	10.8
38*	6	7	10	7	7	9	7.7	13	12	9	12	14	12	12.0
42	8	8	9	11	10	10	9.3	12	11	11	16	15	13	13.0
43	8	8	5	9	7	11	8.0	9	11	12	11	8	11	10.3
45*	6	7	8	6	5	8	6.7	8	6	7	9	9	9	8.0

*The 8-second block preceded the 2-second block for these subjects.

Appendix 7

Recall Scores by Serial Position
at Each PT for Each Subject

	2-Second Presentation Time																8-Second Presentation Time															
	Number of Words Recalled at Each Serial Position (out of 6 trials)																Number of Words Recalled at Each Serial Position (out of 6 trials)															
Drug Subjects																																
ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
03	5	3	2	1	0	1	1	3	1	2	2	0	1	4	4	6	5	3	3	3	0	4	1	3	2	3	2	5	5	5	5	6
05	5	3	1	1	1	2	0	0	0	1	3	3	2	1	3	6	1	2	2	1	0	0	1	1	0	0	0	1	1	3	2	5
06	6	6	3	5	6	4	5	5	2	1	4	1	6	5	6	6	4	4	4	3	5	5	5	4	5	5	5	5	6	6	6	6
12	6	5	3	3	2	1	1	2	2	0	3	1	5	5	6	6	6	6	6	6	6	6	6	6	4	5	5	5	6	6	5	6
13	5	5	1	1	2	1	4	1	1	3	1	2	4	4	5	5	6	6	5	5	5	5	5	3	3	4	3	5	3	4	4	6
15	3	1	1	2	1	0	1	0	1	0	3	1	1	1	3	6	6	5	2	2	2	3	2	1	2	3	0	2	1	2	1	5
16	6	3	2	1	0	3	0	2	2	1	2	2	3	4	4	6	6	5	2	0	2	2	2	0	1	1	1	0	0	2	1	6
18	2	0	0	1	0	0	1	0	0	1	3	1	1	3	4	6	5	4	3	3	0	0	2	2	1	1	2	1	0	0	3	6
19	5	5	3	2	2	0	5	2	2	2	1	4	4	5	6	6	6	5	5	6	5	3	4	3	5	3	2	2	3	4	6	6
21	5	3	1	2	3	3	2	1	2	0	0	2	0	1	4	6	6	4	6	1	1	1	1	0	2	4	0	0	3	0	1	3
22	4	1	1	2	0	0	1	1	1	1	1	0	2	2	4	6	5	4	3	0	1	1	0	1	1	1	2	1	2	1	1	6
25	2	1	0	0	0	0	0	0	1	0	4	2	1	3	5	6	5	5	3	4	0	0	1	0	0	0	1	0	0	0	2	6

Appendix 7 cont.

	2-Second Presentation Time																8-Second Presentation Time															
ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
29	2	0	0	1	1	0	1	1	3	2	1	2	2	2	6	5	3	3	3	2	1	1	2	2	2	2	2	1	2	3	5	6
30	5	2	1	0	2	0	1	2	1	1	2	2	0	4	5	6	6	5	5	4	3	1	1	1	2	1	0	1	1	0	3	2
32	3	1	2	1	0	0	0	1	0	3	2	5	4	5	6	6	2	1	0	3	2	0	2	1	3	2	2	1	3	5	6	6
35	4	2	4	2	1	1	0	1	3	2	0	4	3	1	1	6	4	3	4	4	2	4	3	1	1	2	0	1	1	2	5	5
37	0	1	0	0	1	0	0	0	1	1	1	3	2	5	5	6	0	0	0	0	0	1	0	0	1	1	0	0	3	5	6	6
39	5	3	0	0	0	2	0	1	0	1	0	1	6	3	6	6	6	3	4	3	2	1	1	0	1	2	2	2	1	3	5	6
40	3	3	0	1	0	0	2	0	2	5	1	2	0	3	4	6	6	5	5	3	3	3	2	1	3	1	1	3	1	0	2	6
41	1	1	1	0	0	1	0	2	2	0	2	2	2	3	6	6	3	2	2	3	2	1	3	2	3	2	3	2	3	1	2	6
44	6	3	1	1	0	0	0	1	1	0	1	2	5	5	5	4	6	6	3	3	5	1	1	3	2	5	3	3	4	4	5	6
46	5	6	3	2	1	2	2	1	1	1	2	1	3	4	3	6	6	6	6	3	4	3	2	3	2	1	1	4	2	4	2	6
47	4	4	3	0	2	0	2	1	0	0	1	0	5	2	4	6	5	5	6	3	3	3	1	1	2	4	1	2	3	2	5	6
48	2	1	1	0	0	0	1	2	1	0	1	3	3	1	3	6	3	4	2	1	0	1	0	1	3	2	1	0	0	2	2	6
Placebo group																																
01	6	4	1	0	2	3	3	3	2	3	3	3	5	5	6	6	6	6	6	6	5	6	6	6	5	5	5	5	4	5	6	5
02	6	2	2	1	2	2	1	3	2	3	4	3	4	2	3	6	6	6	6	6	4	5	3	2	2	2	3	3	2	2	4	5
04	6	6	2	1	2	1	0	2	2	2	4	4	2	4	5	6	6	6	5	5	4	6	4	4	4	5	5	3	5	3	4	6
07	4	3	2	2	5	3	2	1	2	2	1	4	4	3	5	6	6	6	5	2	4	3	3	5	5	3	5	6	2	4	6	6
08	3	4	1	3	2	2	4	2	1	2	2	3	5	2	6	6	6	5	3	1	3	3	3	2	2	3	4	3	3	2	5	6
09	5	3	3	2	0	0	3	2	1	0	2	0	1	4	3	6	6	5	3	5	2	2	0	1	2	1	2	0	1	3	2	6
10	4	1	2	1	1	1	2	1	1	3	4	3	2	5	4	6	4	4	3	2	2	2	2	1	0	2	0	2	1	1	1	6
11	6	5	3	2	2	0	1	0	4	2	2	1	4	3	2	3	6	6	6	5	5	5	5	6	4	3	4	4	4	3	5	6
14	5	5	3	3	4	1	2	1	2	2	1	4	2	6	5	6	6	5	4	5	5	4	2	3	2	3	5	2	2	3	4	3
17	4	1	1	1	2	2	2	1	2	0	3	2	2	6	6	5	3	4	6	5	3	4	4	4	4	2	2	5	3	4	5	5
20	4	2	0	0	4	3	1	3	2	2	1	5	3	4	5	6	6	6	5	4	3	3	3	1	1	3	5	5	4	2	5	6
23	5	4	5	3	2	1	1	3	1	3	2	3	0	2	1	5	5	6	6	3	4	5	3	3	3	4	5	3	3	3	3	6

Appendix 7 cont.

	2-Second Presentation Time																8-Second Presentation Time															
ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
24	6	5	4	4	4	1	2	5	3	3	0	1	3	2	4	5	6	5	4	5	6	3	1	2	4	5	2	5	3	3	3	5
26	6	5	1	2	1	3	3	2	2	2	2	4	5	6	6	6	6	5	6	6	6	6	5	3	4	3	3	3	6	6	5	6
27	6	5	2	1	1	1	3	2	2	1	0	3	2	4	4	5	6	6	5	5	4	1	1	3	1	1	0	5	2	2	3	6
28	6	3	3	3	2	2	4	3	3	3	3	2	6	5	6	6	6	6	6	6	5	3	2	4	2	5	2	3	5	4	6	6
31	5	4	1	0	0	2	2	1	2	3	4	4	6	6	6	6	6	6	6	5	5	5	3	2	2	3	2	4	2	2	4	6
33	3	3	3	3	2	2	1	1	3	3	4	3	6	6	6	6	5	4	2	4	5	4	3	3	4	4	4	2	6	6	4	6
34	6	5	3	2	1	3	2	2	1	2	5	4	4	5	3	6	6	5	3	5	5	5	5	4	4	2	4	2	4	6	4	6
36	6	4	4	1	2	1	0	1	2	1	2	2	3	6	4	6	5	6	4	6	3	3	2	2	3	3	1	5	6	4	6	6
38	5	5	4	1	2	0	5	4	2	1	2	3	2	1	4	5	6	5	6	6	4	4	5	4	3	2	4	5	3	4	5	6
42	6	4	3	1	1	2	1	1	2	3	5	3	6	6	6	6	5	3	5	6	5	5	3	4	3	4	6	5	6	6	6	6
43	5	4	2	1	1	0	2	2	3	5	2	2	3	4	6	6	6	6	3	3	3	5	3	1	3	3	3	2	4	6	5	6
45	3	4	3	2	3	3	2	1	3	0	3	1	2	2	4	4	6	5	6	2	1	3	1	1	3	1	1	3	2	3	4	6

Appendix 8

Tulving and Colotla STM and LTM Scores for Each List

Drug Subjects

	2-second Presentation Time												8-second Presentation Time											
	STM Recall Trial						LTM Recall Trial						STM Recall Trial						LTM Recall Trial					
ID	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
03	3	3	2	3	1	2	4	4	4	3	4	3	4	3	4	4	4	3	7	2	5	6	7	6
05	2	2	4	2	3	3	3	4	3	4	1	1	2	2	3	3	2	0	1	1	0	4	2	0
06*	3	4	3	4	4	4	8	12	10	7	6	6	4	4	4	4	4	4	10	12	12	0	12	8
12	3	4	4	4	4	3	2	4	5	6	5	8	3	4	4	4	4	4	12	12	12	11	12	8
13	3	5	2	5	4	3	4	0	6	4	5	4	3	3	3	2	3	3	8	6	8	10	12	11
15	2	2	2	3	1	2	1	2	2	2	2	2	1	0	1	2	2	3	5	6	5	6	3	5
16*	3	3	1	3	3	2	5	3	6	6	3	3	2	2	1	1	1	1	4	1	5	5	4	4
18*	3	3	3	2	2	3	0	2	1	1	3	0	1	2	2	1	2	2	4	4	4	3	3	4
19	4	2	3	3	3	4	5	8	8	6	4	4	3	2	3	4	3	2	7	9	8	8	8	11
21*	2	2	2	3	2	2	2	2	4	6	6	2	1	1	1	0	0	1	4	4	4	5	5	7
22	2	1	3	3	2	3	0	3	3	2	3	2	1	1	1	2	1	3	6	2	5	5	2	1
25	3	4	2	2	3	2	1	1	2	2	2	1	1	2	2	1	2	1	4	2	3	3	3	3
29	2	4	1	4	3	2	3	1	2	0	3	4	3	2	3	2	3	3	3	5	3	5	5	3
30*	2	2	2	2	3	3	3	2	4	6	4	1	1	0	1	1	1	1	7	5	5	4	4	6
32*	3	4	4	3	4	4	2	3	4	4	2	2	2	2	4	4	3	3	5	5	4	2	3	2
35*	1	3	2	1	2	3	5	3	6	2	5	3	1	3	1	2	2	1	4	4	6	8	5	5
37	3	4	4	4	3	3	1	1	2	1	0	0	3	3	3	4	4	3	0	0	0	1	1	1
39	3	3	4	4	3	3	2	3	2	2	2	3	3	2	3	2	3	2	2	6	4	4	5	6
40	2	3	2	2	2	2	2	2	3	4	3	5	2	2	1	1	1	1	7	7	6	6	5	6
41*	4	4	3	2	3	3	3	2	2	1	0	2	2	2	2	2	3	1	3	5	7	5	4	4
44*	4	4	3	4	4	3	1	3	1	1	4	3	1	4	3	3	2	3	13	9	5	7	6	4
46*	3	2	1	4	3	3	3	4	5	4	5	6	2	1	1	3	2	1	6	9	8	6	7	9
47*	3	2	4	2	2	2	3	3	1	4	4	4	2	3	2	4	2	3	8	7	7	4	6	4
48*	2	1	2	3	4	3	2	3	3	1	0	1	2	1	1	1	3	1	3	3	5	2	2	3

*The 8-second block preceded the 2-second block for these subjects.

Appendix 8 cont.

Placebo Subjects

	2-second Presentation Time												8-second Presentation Time											
	STM Recall Trial						LTM Recall Trial						STM Recall Trial						LTM Recall Trial					
ID	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6
01*	3	3	4	3	4	3	8	7	4	6	7	2	1	1	0	2	2	3	15	13	13	12	13	12
02*	2	2	3	2	2	3	6	7	4	4	7	3	1	3	2	1	1	2	8	7	9	9	9	9
04*	3	4	2	2	4	4	5	2	6	6	7	4	2	2	1	5	2	4	10	10	8	10	11	10
07	3	2	2	1	4	4	3	8	5	7	6	4	2	2	3	4	2	3	8	9	10	7	11	10
08	3	3	3	3	3	3	6	5	6	3	5	5	2	2	3	2	3	3	6	7	6	5	6	8
09	1	3	2	2	2	3	3	2	1	5	6	5	1	1	2	1	2	1	6	6	4	3	8	6
10	3	4	2	3	3	3	4	3	2	5	4	5	2	2	1	1	2	1	5	5	5	4	1	4
11	3	1	3	1	3	2	3	5	5	6	4	4	1	5	3	6	3	2	6	9	9	9	11	13
14*	4	3	4	3	4	3	4	5	5	6	5	5	2	2	1	1	2	4	8	5	8	9	9	7
17*	3	3	2	4	3	3	5	4	4	1	3	5	2	3	5	4	3	2	7	9	7	7	6	7
20	4	3	3	3	3	4	2	3	7	4	4	5	2	4	3	3	3	4	5	5	9	6	11	7
23*	2	2	1	1	2	1	3	7	4	7	6	5	2	3	3	2	2	2	9	8	7	9	8	10
24*	1	3	3	2	1	2	6	6	6	9	8	5	2	2	3	2	1	3	7	9	7	10	9	7
26	4	3	3	5	4	3	6	4	5	2	8	9	3	4	3	4	2	4	7	7	11	11	0	12 12
27	1	2	2	2	2	3	8	4	4	7	2	5	2	1	1	2	3	1	5	9	7	5	6	9
28	2	3	3	4	4	3	8	6	6	7	7	7	0	3	1	2	0	1	14	9	11	11	0	12 8
31*	4	4	4	4	4	3	5	4	6	4	5	5	1	1	1	1	2	1	8	10	8	8	11	11
33*	3	4	4	3	4	3	6	6	6	6	2	8	3	4	2	4	4	3	4	5	6	11	12	8
34*	2	3	4	2	3	2	7	8	5	6	6	6	3	2	3	0	1	2	10	10	8	11	9	11
36	3	3	4	3	3	3	4	4	3	6	5	4	2	4	4	4	4	3	9	8	6	7	6	8
38*	2	2	2	1	1	3	4	5	8	6	6	6	3	3	1	5	3	3	10	9	8	7	11	9
42	4	4	4	4	4	3	4	4	5	7	6	7	3	4	4	4	4	4	9	7	7	12	11	9
43	4	3	3	2	2	5	4	5	2	7	5	6	3	4	4	3	2	5	6	7	8	8	6	6
45*	2	2	2	2	2	3	4	5	6	4	3	5	2	1	3	2	3	2	6	5	4	7	6	7

*The 8-second block preceded the 2-second block for these subjects.

Appendix 9

Total and Distinct
Rehearsal Scores

Drug Subjects

	2-second Presentation Time		8-second Presentation Time	
ID	Total number of words uttered per inter-item interval	Number of different words rehearsed per interval	Total number of words uttered per inter-item interval	Number of different words rehearsed per interval
03	2.82	2.38	11.69	3.73
05	2.96	2.52	7.69	3.42
06	2.74	1.38	6.82	2.21
12	2.70	2.29	7.19	3.26
13	3.59	2.75	10.84	4.42
15	2.64	2.42	5.84	4.21
16	2.35	1.83	5.75	4.21
18	2.60	1.71	8.29	3.49
19	3.25	2.68	9.30	4.35
21	2.39	1.90	7.08	3.85
22	2.17	1.88	6.34	3.89
25	2.01	1.74	6.39	4.05
29	3.34	2.62	9.08	3.53
30	3.46	2.27	8.47	3.91
32	2.30	2.17	5.86	2.53
35	3.80	2.49	8.77	4.50
37	3.17	2.21	7.84	2.43
39	2.67	2.38	8.26	3.36
40	2.26	2.02	7.19	4.22
41	2.65	2.09	6.58	3.03
44	2.86	2.49	6.79	3.57
46	2.11	2.36	6.55	4.52
47	2.79	2.67	6.94	3.92
48	2.22	1.81	5.54	3.48
Mean:	2.74	2.29	7.55	3.67

Appendix 9 cont.

Placebo Subjects

	2-second Presentation Time		8-second Presentation Time	
ID	Total number of words uttered per inter-item interval	Number of different words rehearsed per interval	Total number of words uttered per inter-item interval	Number of different words rehearsed per interval
01	2.47	1.83	6.78	3.05
02	2.73	1.65	6.86	3.65
04	3.24	2.72	8.24	3.98
07	4.31	2.88	10.95	4.24
08	3.78	1.85	7.20	3.52
09	2.33	2.02	7.72	4.24
10	2.64	2.43	8.45	3.57
11	4.17	3.22	7.82	4.61
14	2.58	2.28	6.12	3.47
17	3.38	2.35	9.79	4.15
20	3.25	2.56	8.96	4.02
23	2.78	2.43	6.97	4.86
24	2.73	1.97	8.92	5.41
26	3.78	2.15	8.38	3.63
27	1.94	1.63	6.44	4.21
28	3.10	2.31	8.28	3.40
31	3.61	3.26	11.30	6.53
33	2.82	2.00	7.88	3.14
34	3.83	2.28	9.42	4.26
36	3.18	2.50	10.01	3.64
38	3.24	2.14	8.78	3.60
42	3.42	3.10	8.67	3.97
43	3.09	2.76	10.27	4.29
45	3.13	2.65	5.98	3.61
Mean:	3.15	2.37	8.34	4.04

Appendix 10

Digit Vigilance Scores, Experimental Session

Number of 6s and 9s cancelled in 90 seconds
during inter-list intervals

Drug Subject

	Baseline		Block 1						Block 2					
ID	1	2	1-1	1-2	1-3	1-4	1-5	Mean	2-1	2-2	2-3	2-4	2-5	Mean
03	125	123	116	117	118	119	112	116.4	121	114	133	126	118	122.4
05	119	123	122	101	91	81	72	93.4	74	62	48	67	90	68.2
06	119	120	101	97	94	94	101	97.4	105	106	102	99	103	103.0
12	121	127	105	102	105	106	112	106.0	116	118	117	111	117	115.8
13	114	133	116	117	117	120	125	119.0	122	131	122	125	120	124.0
15	108	110	62	71	73	73	73	70.4	83	86	87	88	92	87.2
16	119	109	91	80	83	85	69	81.6	89	101	99	106	98	98.6
18	140	140	120	121	130	124	116	122.2	128	134	133	134	135	132.8
19	142	149	155	148	151	150	140	148.8	144	139	144	145	155	145.4
21	133	140	121	119	124	126	124	122.8	124	126	124	129	127	126.0
22	119	122	98	102	108	107	101	103.2	103	100	98	88	93	96.4
25	119	119	78	68	56	56	74	66.4	54	61	71	80	76	68.4
29	122	122	117	119	121	121	120	119.6	120	120	119	116	120	119.0
30	120	126	106	88	68	82	78	84.4	95	86	87	100	91	91.8
32	125	122	115	101	97	112	103	105.6	112	113	119	112	117	114.6
35	116	115	82	95	97	100	99	94.6	103	108	114	107	108	108.0
37	107	115	98	88	83	79	75	84.6	78	74	80	88	91	82.2
39	116	119	108	111	111	116	110	111.2	113	111	119	116	118	115.4
40	119	122	105	109	107	110	113	108.8	114	117	115	112	119	115.4
41	106	112	85	85	80	90	100	88.0	91	96	79	93	89	89.6
44	128	132	120	112	113	101	100	109.2	94	117	117	112	116	111.2
46	114	117	103	102	104	104	101	102.8	109	111	105	107	114	109.2
47	142	145	131	137	148	133	148	139.4	140	148	151	144	152	147.0
48	125	128	98	101	104	100	104	101.4	112	116	105	113	120	113.2
Group mean	122	125	106	104	104	104	103	104.1	106	108	108	109	112	108.5

Appendix 10 cont.

Placebo Subjects

	Baseline		Block 1						Block 2					
ID	1	2	1-1	1-2	1-3	1-4	1-5	Mean	2-1	2-2	2-3	2-4	2-5	Mean
01	123	127	117	119	119	117	116	117.6	118	113	116	116	129	116.6
02	116	119	117	117	121	122	121	119.6	121	122	121	120	121	121.0
04	115	117	119	114	116	111	118	115.6	115	118	119	119	118	117.8
07	139	146	138	146	127	138	144	138.6	129	133	142	129	135	133.6
08	117	131	131	125	130	124	129	127.8	130	133	135	136	137	134.2
09	98	92	102	105	98	108	101	102.8	106	107	91	105	98	101.4
10	115	120	124	121	120	119	126	122.0	125	120	120	119	119	120.6
11	138	146	145	144	142	145	150	145.2	149	154	148	156	150	151.4
14	123	129	126	123	124	128	128	125.8	130	128	131	131	142	132.4
17	116	120	112	115	114	115	108	112.8	109	118	111	115	120	114.6
20	110	117	121	118	121	120	121	120.2	127	125	125	123	127	125.4
23	119	121	112	117	124	117	119	117.8	122	119	120	126	119	121.2
24	126	131	127	132	134	133	130	131.2	137	134	133	130	135	133.8
26	127	128	125	123	122	130	126	125.2	127	126	126	127	133	127.8
27	100	100	106	109	112	113	107	109.4	112	116	113	113	112	113.2
28	116	114	123	121	120	118	120	120.4	120	120	118	121	120	119.8
31	106	108	106	101	101	98	103	101.8	105	100	103	104	100	102.4
33	125	125	123	123	120	123	123	122.4	119	121	122	123	128	122.6
34	120	124	120	133	121	121	123	123.6	122	121	120	123	122	121.6
36	103	94	109	108	103	112	105	107.4	115	111	116	118	117	115.4
38	105	110	112	109	107	115	114	111.4	112	114	116	104	119	113.0
42	117	118	114	117	115	109	120	115.0	114	115	118	119	118	116.8
43	111	122	112	118	116	118	120	116.8	121	130	130	129	119	125.8
45	142	125	130	130	130	139	143	134.4	141	138	139	138	145	140.2
Group mean	118	120	120	120	119	121	122	120.2	122	122	122	123	124	122.6

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Author [redacted]

Jill Bee Rich

January 11, 1988