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The effects of paroxetine on cognitive function in healthy volunteers and depressed elderly patients

Pasteur, Mary-Anne L.

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The Effects of Paroxetine on Cognitive Function in Healthy Volunteers and Depressed Elderly Patients

Mary-Anne L. Pasteur

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SUMMARY

Evidence from studies exploring the effects of selective serotonergic drugs on cognitive processes in animals, healthy volunteers and clinical patients have suggested that they have cognitive enhancing properties. The primary aim of this thesis was to assess the effect of the selective serotonin reuptake inhibitor, paroxetine, on cognitive performance in young and elderly healthy volunteers and in depressed elderly patients who participated in a clinical trial comparing the effects of paroxetine with the tricyclic antidepressant, lofepramine. As there were no published memory tests with multiple versions available for repeated use in the proposed healthy volunteers studies, four memory tests were devised and assessed for equivalence and the effects of practice.

Paroxetine improved the delayed verbal recall performance of the young healthy volunteers and one elderly subject from a series of three single case studies. Performance on a range of other attention, verbal, visual and spatial memory tests was not impaired or enhanced by paroxetine. No significant differences were found on any of the cognitive measures between the elderly depressed subjects treated with paroxetine and those treated with lofepramine. A dissociation between clinical and cognitive recovery was identified in a group of patients who did not respond to treatment with paroxetine.

A secondary aim of the thesis was to assess the effects of depression on cognitive function in unmedicated elderly depressed patients by comparing baseline data from the clinical trial with data from non-depressed control subjects. Cognitive deficits were identified in the depressed patients on measures that required effort and spontaneous organisation of materials for recall, such as word list recall, and on the Speed of Comprehension test (Baddeley, 1992). The results of this study were compared to previous studies, particularly those involving medicated depressed subjects.

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CHAPTER 1

The Theory of Memory and Attention

Introduction

In order to provide a theoretical framework for the research presented here, the first chapter considers some theoretical memory models and the theoretical components of memory that have been postulated to account for observed memory phenomena. The components of memory that are sensitive to depressive illness and serotonergic drugs will be identified and the corresponding aspects of memory performance that can be measured in clinical and experimental studies will be discussed.

First, a brief overview of the major theoretical approaches to the study of memory will be covered, followed by a consideration of the models of the separate memory sub-systems.

Theoretical Approaches

The first conceptual model of memory was postulated by William James as early as 1890. James viewed memory as comprising two sub-systems, primary memory, which supports consciousness, and secondary memory which is a permanent record of the past. This early model of memory developed into a more complex multistore model in the sixties.

The Multistore Model of Memory

Atkinson and Shiffrin (1968) proposed that memory contains three separate stores through which information flows. New information first enters the sensory store which holds visual, auditory and tactile information very briefly. Information then passes into the second, short-term store (STS), where it is stored or processed by a various 'control processes'. One such control process is rehearsal which determines whether information is passed into the third permanent store, a structure known as the long term store (LTS). Experimental evidence suggests that

the more frequently an item is rehearsed, the more likely it is to be recalled (Rundus, 1971). A second short-term memory control process is encoding, which involves information being stored in memory in the form of a code. A number of studies have demonstrated that information in the STS is encoded phonologically, while long term storage requires semantic encoding (Baddeley, 1966).

Despite the considerable body of evidence supporting the multi-store model of memory it failed to accommodate some of the neuropsychological evidence of memory processes (Shallice and Warrington, 1970) and provides an over-simplistic explanation of how information is processed and encoded. Such problems were not easily overcome within this framework and lead to the evolution of other theoretical frameworks and models of the separate components of memory.

The Levels of Processing Model

Craik and Lockhart (1972) proposed an alternative approach to the study of memory. The 'levels of processing' theory emphasises the mode in which information is processed, rather than the actual memory structures involved. The model is based on the premise that information which is processed at a deep level is more likely to be remembered than information that is only processed at a shallow level. Orthographical encoding is considered to occur at the shallowest level, then phonological encoding, with semantic encoding occuring at the deepest level. There is considerable evidence demonstrating that semantic orienting tasks facilitate retention better than non-semantic orienting tasks. Consequently, the deeper the encoding, the better the subsequent learning (Craik and Tulving, 1975). Objections to this theory have focused on the circularity of the LOP approach which stems from the problem associated with defining and measuring 'depth of processing'. The framework also failed to

account for neuropsychological findings. Furthermore, despite the fact that the original levels of processing concept included a short-term memory system, its primary concern was the role of encoding in long-term memory.

Models of Memory

The Working Memory Model

The lack of a satisfactory conceptualisation of short-term memory lead to the formulation of the working memory model which was designed specifically to account for short-term memory phenomena. The working memory model developed by Baddeley and Hitch (1974) proposed a multi-component system in place of the STS. A dual task paradigm was used to demonstrate that the STS is not a single structure. Subjects were required to simultaneously perform a primary task (e.g. learning a list of visually presented words) and a secondary task (e.g. retaining a sequence of six digits). Subjects' performance on a primary task was only slightly impaired when they were required to do both the tasks, but not to the extent that would be expected if the entire STS capacity was involved in retaining the digits. These results lead Baddeley and Hitch to postulate that the retention of digits involves a speech-based system which they called the 'articulatory loop'.

Evidence for the existence of the articulatory loop came from several experiments. The first illustrated the word length effect by comparing the memory span for words which take longer to say (e.g harpoon), with those with the same number of syllables but a short spoken duration, (e.g. bishop). Subjects demonstrated a shorter memory span for the longer words (Baddeley, Thompson and Buchanan, 1975). In a second experiment subjects were required to remember words of different spoken durations while repeating meaningless spoken sequences (articulatory suppression). Articulatory suppression was found to negate the word-

length effect by dominating the articulatory control process, thus preventing material from being maintained in the phonological store or converted into a phonological code.

The working memory model also incorporates a system responsible for the processing of visual images, known as the visuo-spatial sketch pad, and a controlling attentional system, known as the central executive. The visuo-spatial scratch pad is responsible for setting up and manipulating visual images. The existence of this system was established using dual task studies. In an experiment by Brooks (1968), subjects were required perform a visuo-spatial task while answering questions regarding the task in one of three ways;-vocal, (yes-no), tapping, (one tap for yes and two for no), or by pointing to Y and N symbols. The pointing response produced slower reactions than the other types of response. In a verbal version of the task, in which subjects had to work through a proverb and indicate whether or not each successive word was a noun, no difference between response modes was found. The finding that the pointing task resulted in a significant delay in the visual, but not the verbal condition, indicated that a response requiring additional visuo-spatial resources i.e. pointing, interfered with the retention of a visual image.

The central executive component of working memory is involved in a wide range of conscious mental activities and is consequently highly complex. The theoretical role of the central executive overlaps with the functions attributed to the frontal lobes i.e. planning, decision making and controlling actions. Evidence for this overlap comes from patients with damage to the frontal lobes who demonstrate problems that reflect an impairment in the central exectutive component of memory (Baddeley, 1990). The role of the central executive has also been equated with the supervisory attentional system component of a model of attention proposed by Norman and Shallice (1986). They proposed that most

actions are controlled by schemata which, once initiated, will carry out an action relatively automatically. The second component of their model, the supervisory attentional system (SAS), is likened to the operation of the will, i.e. it is under conscious control. It is therefore called into operation where planning or decision making is required.

The working memory model of memory has successfully accounted for a range of experimental and neuropsychological evidence. It also provides a useful conceptual tool for the study of a spectrum of psychological phenomena, including the effects of depression and drugs on short term memory.

Long Term Memory

As with the early concept of short-term memory, the original fomulation of the long-term store by Atkinson and Shiffrin (1968) was considered to be oversimplified. Further research into the organisation of long-term memory lead to the widely held view that it is made up of a number of separate systems, each with a different function. This view is based on the work of the philosopher, Gilbert Ryle (1949) who proposed that the LTS was made up of two components, one concerned with memories of the 'knowing that' kind and one based on memories of the 'knowing how' kind. Tulving (1972) rejected Ryle's view on the grounds that it does not take into account the distinction between those memories that are linked to personal experience and those that are not. Tulving argued that the LTS is made up of three separate components; episodic, semantic and procedural memory. He described episodic memory as being concerned with 'personal experience and their temporal relations'. Semantic memory was defined as 'a system for receiving, retaining and transmiting information about the meaning of words, concepts and classification of concepts', and procedural memory was described as being similar to Ryle's 'knowing how' memories and includes memory for motor

skills and problem solving. Tulving (1983) further conceptualised these memory systems in terms of the degree of conscious awareness they involved. He defined episodic memory as being autonoetic or 'self-knowing', as it involves an awareness of having experienced an event without specific knowledge of the actual learning incident. Episodic memories can in turn be assimilated into semantic memory, which he described as neotic or 'knowing' as it involves an awareness of the information stored but not its point of origin. At the deepest level of the structure is procedural memory which requires no conscious recollection and is therefore defined as aneotic or 'not knowing'.

Although the three memory systems are considered to be functionally distinct, they are also interactive. The interdependence of semantic and episodic memory systems makes it difficult to demonstrate their separate roles in normal subjects. However, evidence in support of the differentiation of the two systems is provided by amnesic patients who appear to have intact semantic memories, while their episodic memories are highly impaired. This can be inferred when amnesic patients are seen to hold a normal conversation in which they rely on the retrieval of stored information. However, they are unable to learn new information such as names and places and perform very poorly on measures of story recall. This observation has been used to support the claim that episodic and semantic memory are functionally distinct from each other, while being interdependent.

In the next section episodic memory will be considered is some detail as research has indicated that verbal episodic memory is sensitive to the deficits resulting from depression and drug-related memory changes. Episodic memory receives and encodes information for specific, temporally dated episodes and events, and the temporal-spatial relations among them. It therefore stores verbal, visual and spatial information.

Studies exploring each of these different aspects of episodic memory will be reviewed separately.

Verbal Episodic Memory

Verbal episodic memory can be probed experimentally by presenting materials, e.g. word lists, and asking subjects to recall as many items as possible. The word serves as a focus for a specific learning event and is therefore often refered to as a 'word event'. Verbal learning experiments generally involve a recall and recognition condition aimed at tapping both the temporary and permanent memory store. The relationship between recall and recognition is not well understood and it is unclear whether the two processes involve a common or distinct retrieval mechanism. This relationship will be discussed in terms of the different models developed to account for the retrieval of verbal information from episodic memory.

The earliest attempts to explain retrieval are provided by generate-recognise models. One influential example of such a model was developed by Anderson and Bower (1972). They proposed that words are represented in memory as nodes in a semantic network. According to the model, when a word is presented to a subject in a verbal learning experiment, a change occurs at the node so that it is effectively marked or tagged. Recall then involves two processes; firstly all possible candidate words are generated and then, secondly, they are examined for markers which, if detected, will result in recognition of the word. In the recognition condition, access to the relevant node simply requires the detection of a marker.

Generate-recognise (GR) models account for the finding that free recall is more difficult than cued recall, which in turn is harder than recognition, by proposing that recall involves two stages of processing and recognition only involves one. GR models also accommodate the well-

established finding that high-frequency words are easier to recall than low-frequency words, whereas the reverse is true in recognition. High frequency items are easier to recall as they are more likely to be generated as candidates for recognition. However, in the recognition condition of a verbal memory test, high-frequency words are likely to have occured more often and recently outside the experiment, making low-frequency words easier to identify correctly.

GR models nevertheless have their limitations. Tulving and Thomson (1973) critised GR models on the grounds that they failed to account for the finding that words can be correctly recalled, but not recognised. If, as the theory suggests, recall involves a generation and recognition stage of processing this would be impossible. Tulving and his associates demonstrated what is now known as 'recognition failure of recallable words' (or recognition failure) in a four phase experiment involving the presentation of pairs of words. In phase 1 of the experiment, subjects were presented with target words e.g. 'hot' paired with unrelated cue words e.g. 'knife', and asked to attend to them but not remember them. In phase 2, subjects were presented with strong associates of the target words e.g. cold, and asked to generate associated words. Frequently this would lead them to produce the original target words e.g. hot. Subjects were then required to work down the list and tick any items that they thought had been on the previous learning list e.g. hot (phase 3). It was found that although they did generate many of the words on the original list, they were not very good at recognising them as items that had already been presented. In the final stage of the experiment, subjects were presented with the unrelated cue words e.g. knife, and asked to recall the items that had been paired with them in phase1 (i.e. hot). Under these conditions many items that the subject failed to recognise in phase 3 were recalled.

These results lead to the proposal that recognition and recall basically involve the same retrieval processes, but different kinds of retrieval cues. Remembering was thus conceptualised as a process involving the combination of a memory trace or engram in episodic memory with a retrieval cue from semantic memory. Learning involved the formation of the memory engram and remembering involved an interaction between the engram and retrieval cue to produce a recollection of the event. Tulving and Thompson (1973) formulated the encoding specificity principle (ESP) to explain the powerful retrieval cueing effects they found in the experiment described above. They proposed that a cue could only be effective if it is specifically encoded at the time of learning. In the learning phase of the experiment (phase 1) the target word (hot) was encoded with the unrelated cue (knife) in such a way that emphasised the featural overlap of the two words. So in this case an engram may be formed in which hot is encoded within the context of knife, for example washing-up or carving. In phase 3, recognition was poor because the target words were presented for retrieval with different featural overlap to the learning phase so recognition of the word was made difficult. For example the word 'cold' may have been generated in response to the word 'hot' leading to a very different contextual engram being formed to that in the learning phase. Cued recall was easier as the cue words have a high featural overlap with the target words e.g. 'knife' with 'hot'. Tulving and Thompson thus demonstrated that memory can be manipulated so that cued recall performance is better than recognition.

The encoding specificity prinicple also accounts for the phenonmenon that recall is more difficult than cued recall, which in turn is more demanding than recognition by positing that in the recall condition the retrieval environment is impoverished, as there a minimal featural overlap between the memory trace and the retrieval environment.

In a cued recall condition the retrieval environment is less impoverished, while in recognition condition there is an enriched retrieval environment. The ESP also explains why strong word associates are superior to weak word associates as retrieval cues. When encoding, subjects will generally encode the dominant meaning of a stimulus which will not only be strongly associated with the retrieval cue, but also have considerable semantic overlap e.g. hot with cold.

Recognition memory-one process or two?

Evidence from experiments examining recognition memory suggest that it may comprise two components. Mandler (1980) proposed that recognition involves an initial familiarity response followed by the retrieval of the context of an event or item. Recognition can therefore either be context-free, as in the recognition of recently perceived familiar items, or context-dependent, as with weaker, older memories when explicit information of time and place is necessary for recognition to occur. Mandler and Boeck (1974) illustrated the phenomena they described by asking subjects to sort 100 randomly selected words into categories. They found that subjects sorted the words into different numbers of categories and the larger the number of categories the better the recall and recognition performance. A recognition test was given a week later and subjects' word recognition speeds were recorded. It was found that subjects who had sorted the words into fewer categories had longer reaction times, whereas those who had faster responses were not affected by the degree of organisation they had imposed on the words a week earlier. Mandler and Boeck concluded from this that the slower responses were the result of context dependent retrieval which was affected by the organisation of information, whereas the faster responses were the result of familiarity responses and were therefore insensitive to the effects of organisation. Evidence from electro-physiological studies

(Rugg and Doyle, 1992) and from Korsakoff's patients (Huppert and Piercy, 1978) also suggest that recognition may involve separate familiarity and context dependent aspects .

Tulving (1983) extended the concept of recognition memory requiring two processes and suggested that information could be derived either from a representation in episodic memory or from semantic memory. He adopted an experimental approach in which subjects were asked when they recognised a word to classify their response as either a 'remember' response (R) or a 'know' response (K). They made a 'remember' response if recognition was accompanied by conscious recollection, and a 'know' response if recognition was accompanied by feelings of familiarity without conscious recollection. The remembering (R) response was associated with an episodic memory of the word's prior occurence, while the know reponse (K) was associated with semantic retrieval. A review by Gardiner and Java (1993) indicated that a variety of variables cause a dissociation between 'remember' and 'know' responses. These dissociations have been taken to indicate that remembering is influenced by conceptual and attentional factors and knowing is influenced by data-driven or perceptual factors.

Response Bias in Recognition Memory

In order to compare subjects recognition scores in a verbal learning experiment it is necessary to take into account how people make decisions. In a forced choice recognition situation some subjects will be more likely than others to respond 'yes' when they are unsure than 'no'. This is known as response bias and must be taken into account as it may significantly alter test scores. Signal detection theory can be used to determine the degree of response bias that is in operation. The theory, which was developed originally for the study of sensory judgements, produces two

separate measures (McNicol, 1972). The first of these is a measure of discriminability (d'), which in the case of memory is the extent to which the subject is able to discriminate between the target words and the distractors. The second measure, ß reflects the criterion adopted by the subject i.e. the degree of caution involved in making the decision. These measures therefore allow the separate assessment of objective recognition memory sensitivity and subjective bias in responding. This is particularly relevant when considering the effects of depression on recognition memory as prior research has indicated that apparent recognition memory deficits in depressed patients are due to their conservative response bias, rather than a reduction in memory sensitivity (Miller and Lewis, 1977).

In summary, two main theories have been proposed to explain retrieval processes. The generate-recognise model of retrieval proposes a two stage process in which recall requires both the generation and recognition of information, while recognition occurs without the generation process and is consequently easier. The encoding specificity theory posits that recall and recognition involve a common retrieval process, but different retrieval cues. Studies exploring recognition memory indicate that it may involve two separate processes; context retrieval and familiarity. Context-retrieval and familiarity-based recognition are assocaited with different levels of conscious awareness and have been linked to retrieval from semantic and episodic memory.

Episodic Spatial Memory

Memory for spatial location information is used in everyday situations to recall where objects such as keys and glasses have been put down and to also locate familiar buildings and find a way from A to B. A variety of experimental paradigms have been employed to study spatial episodic memory. The most commonly used is the matrix method which involves small everyday objects being placed on a 6 X 6 matrix. Also used

is the 'map' method , whereby the to be remembered items (TBRs) are line drawings of various buildings and landmarks in a map of a city and the 'real-life' method where the TBR items are presented in a mock up of a real life setting e.g. an office.

Some of the spatial information that can be recalled after walking from A to B, for example, is not information that is specifically attended to. This suggests that at least some spatial information is encoded automatically in long term memory. To test the hypothesis that spatial information is encoded automatically, Mandler, Seegmiller and Day (1977) conducted a series of experiments in which subjects were shown a matrix of 36 locations, 16 of which contained TBR items (small toys). There were three testing conditions; one in which subjects were told that memory for both the objects and locations would tested (intentional learning); one in which they were told that recall of the objects, but not locations would be tested (standard incidental condition) and one in which subjects were not given memory instructions, but asked to estimate the cost of all the items (true incidental condition). The results showed there was no difference between recall of objects and locations in the intentional and standard incidental conditions and only a small (18%) reduction in object recall in the true incidental condition. More objects were recalled than object locations, although when a longer study time was allowed this difference disappeared. These findings lead Mandler and his colleagues to conclude that "active processing does not seem to be required for spatial information to be encoded into long term memory".

This result supports Hasher and Zacks theory (1979) that the processing of spatial location information is an automatic process that requires minimal energy from the limited capacity of the mechanisms used in attention. Hasher and Zachs proposed that in order to consider a process as "automatic" it should not be affected by age, intention, and

simultaneous processing demands or by practice and individual differences. Naveh-Benjamin (1988) evaluated the criteria for the automaticity of the encoding of spatial location information proposed by Hasher and Zacks. He used a paradigm similar to Mandler et al. (1977), i.e. a 36-position matrix and 20 drawings of common objects, to investigate the effects of intention, age, competing task loads, practice and individual differences on spatial location recall and recognition. He found that each of the variables he manipulated affected performance on both a spatial information recall and recognition task and concluded that memory for spatial information is not automatically encoded.

The findings of Uttl and Graf (1993) also failed to support the automaticity theory as they discovered significant age-related deficits in episodic spatial memory. They used two real life paradigms to examine the changes in episodic spatial memory in adults aged 15-74 years; a map test involving subjects remembering the location of items at an exhibition they had visited and a relocation test which required subjects to replace TBR items where they appeared in an office. Similar intentional and incidental conditions as Mandler et al. (1977) were employed. They found an age-related decline on both tests and a greater age difference in the incidental condition that the intentional condition, suggesting that older subjects were less able to encode spatial location information automatically. This could be due to a variety of factors and may reflect an age-related change in processing strategies.

Ellis (1990) considered that the tasks used to investigate automaticity in encoding spatial information were generally too complex and involved effortful subtasks as well as the automatic processes under investigation. He therefore devised a task in which effortful processing was minimal. It involved subjects looking through a picture book with four objects, one in each quadrant on the page, and being tested for

location of the pictures. His results supported the automaticity theory as he found no affect of age, intention, practice or concurrent processing demands.

Spatial memory studies which use verbal stimuli instead of pictures or objects have generally failed to support the automatic encoding effect found by Mandler et al. (1977). This has lead experimenters to question what attributes of a TBR item is retained in memory and whether the spatial location of an item is encoded together with its memory representation. Pezdek, Roman and Sobolik (1986) tested the hypothesis that spatial location information is more likely to be encoded with the memory representation of objects than of words. They presented 16 common items on a display matrix either as objects (small toys), or as one word labels for the 16 objects. Subjects were tested for recall of the items and then asked to re-locate them on the matrix. In each of four experiments a different independent variable known to affect item recall was introduced (e.g. age of subjects, presence or absence of visual imagery instructions, immediate versus delayed recall). The results of all four experiments showed memory of the items was affected independently of location memory for the word labels, but not for the objects. In addition, in each of the four experiments objects were relocated more accurately than the words. These results suggest that different processes are involved in the encoding of item and location information for words, but not for objects.

The question of whether or not spatial information is encoded automatically remains unanswered. Some experimenters claim that encoding in spatial memory requires little or no attentional resources and therefore occurs automatically, while others have shown that the criteria for automaticity on spatial location memory tasks are not fulfilled.

Visual Episodic Memory

Visual episodic memory has not been extensively researched as the majority of studies have focused on memory for verbal information. What research that has been carried out indicates that visual information can be stored for long periods of time. Rock and Engelstein (1959) asked subjects to study a single meaningless shape and then tested their memory for it up to a month later. They found that although subjects' ability to reproduce the shape accurately declined rapidly their ability to recognise the shape when it was presented with distractors remained intact for weeks afterwards. Standing, Conezio and Haber (1970) looked at memory for 2,560 colour slides of items by presenting them initially for 10 seconds and then testing performance using a forced-choice procedure (each target slide paired with a distractor). They found that subjects identified 90% of the pictures correctly when tested several days later.

The forced-choice recognition paradigm employed by Standing et al. (1970) simply required subjects to decide between two options (old and new). Thus, it is only necessary for them to store a minimum amount of picture information to make one of the pictures more familiar than the other. Goldstein and Chance (1971) set out to determine the level of subjects performance when the target stimuli were mixed with a large number of distractors. They used three sets of target stimuli, women's faces, magnified snowflakes and ink blots and presented 14 from each set for 3 seconds each. They tested recognition immediately and then after 48 hours by presenting the 14 target stimuli mixed with 70 distractors. They found that there was virtually no difference between the immediate and delayed conditions. Subjects correctly identified 71% of the faces, 48% of ink blots and 33% of the snowflakes. These results are not as high as in the two- choice condition, but still considerably higher than would be expected by chance.

Semantic Memory

Much research has been carried out into different aspects of the representation and organisation of information in semantic memory. Some researchers have concentrated on the possible ways in which the meaning of words might be represented i.e. semantics. Other theories have considered semantic memory in terms of sentences rather than individual words. Models based on computer programmes that comprehend language were developed in the 1960s and 1970s to explain the way information is represented in semantic memory e.g. Quillian's Teachable Language Comprehender (Quillian, 1969). Other theorists have attempted to develop models based on schema or knowledge structures.

To date none of the numerous paradigms that have been developed for the study of semantic memory have proved to be very satisfactory and the experimental study of semantic memory has consequently not progressed greatly over the years. There are several possible reasons for this lack of progress. Firstly it is inherently difficult to attempt to simulate the semantic system as it is so extensive and rich. Secondly, it is difficult to assess and understand precisely what is actually being measured by the tasks used to explore semantic memory when so little is known about the structure of semantic memory. Further problems result from investigators differing interpretations of the concept of semantic memory. In response to these difficulties Baddeley and his associates devised a task designed to measure subjects' semantic information processing capacity using sentences that were obviously true or false statements about the world. They claim that the sentences 'provide a task in which subjects are required to understand the meaning of sentences varying in syntactic form and complexity, and which unequivocally demands that the subject has access to semantic memory in order to respond correctly'.
(Baddeley, Emslie, Nimmo-Smith and Williams, unpublished paper).

Attention and control of memory

Attention is a very broad concept. The simplest definition of attention is that it corresponds to consciousness, although there are attentional processes to which we do not have conscious access. For example, attention is responsible for selection and processing of specific stimulus features. At a higher level, attention is also involved in the co-ordination of multiple simultaneous tasks e.g. talking while driving. Attention has been conceptualised in a wide variety of frameworks, some of which have been discussed earlier e.g. the central executive component of working memory (Baddeley, 1974) and the supervisory attentional system (Norman and Shallice, 1986). Equally a wide range of tasks have been used to investigate the nature of attention e.g. vigilance tasks, perceptual selection tasks and dual tasks. The theory discussed below is that of attentional 'automaticity' as it relates directly to the performance on the Stroop task.

Some theories propose that attention involves two types of cognitive process; controlled processes that are voluntary, relatively slow and require attention, and automatic processes that are fast and do not require attention. Shiffrin and Schneider (1977) used search tasks to show that performance on novel tasks relies initially on controlled processes, but that after much practice performance becomes automatic. In one such task subjects were required to identify consonants from the first half of the alphabet and reject the rest. At the beginning of the experiment performance was worse when there were more targets and distractors being presented. However after 1,500 trials the subjects became very fast and accurate at the task and were no longer affected by the number of targets and distractors. It was concluded that when when controlled voluntary processes were no longer necessary for accurate performance automaticity on the task was acquired.

Posner and Snyder (1975) applied the distinction between controlled and automatic processes to the Stroop task. The Stroop effect (Stroop, 1935) demonstrates that if a colour word and the colour of the ink it is written in are congruent, colour naming will be faster than when the word and ink colour are incongruent e.g. the word green written in red ink. Posner and Snyder (1975) explained the Stroop effect in terms of automatic and controlled processes, word reading being automatic, and colour naming controlled. They proposed that, in the Stroop task, the automaticity of word reading interferes with the controlled process of colour-naming and results in a slowing of performance. These premises explain why word reading is faster than colour naming and ink colour has no affect on word reading. This result was further investigated by MacLeod and Dunbar (1988) who carried out an experiment using arbitrary shapes and colours. The shapes were presented in a neutral colour and assigned a colour word as a name. Once subjects could name the shapes without difficulty, shape naming was tested using shapes presented in a colour which either conflicted with the name assigned or agreed with it. It was found, as with the words that ink colour produced large interference and facilitation effects. However when subjects were required to name the colour that the shapes were presented in they found that congruity of the shape had no effect. They also found that performance in the control conditions for colour naming was faster than in the shape control condition. These results suggested that colour naming was relatively automatic compared to the more controlled shape naming.

The experiments described above suggest that it may not be appropriate to classify processes as either controlled or automatic, as automaticity is not an all-or-nothing phenonemon. Instead it may be desirable to see tasks such as reading, colour naming and shape naming as

continuous, with the speed of processing and interference effects as further continuous variables that depend on the automaticity of the task.

Selective attention

Two mechanisms have been proposed to explain how action can be selectively directed toward single aspects of a complex environment filled with other distracting stimuli. Early models of selective attention proposed that internal representations of the attended object are differentiated from those of a distractor by being perceptually processed at a higher level of activation (Broadbent, 1982; Van der Heijden, 1981). These models assumed that the representations of task-irrelevant information merely decayed passively. More recent theories have suggested that inhibitory mechanisms are involved in distinguishing between target and distractor items. One model of selective attention proposes that internal representations of items do not simply decay passively but they are actively inhibited during selection. Tipper (1985, 1992) proposes that efficient selection procedures rely on the existence of both excitatory mechanisms working on to-be-attended stimuli, and inhibitory mechanisms on to-be-ignored stimuli.

Evidence for these inhibitory processes comes from the "negative priming" paradigm. Tipper (1985) found that subjects showed lengthened response times (RTs) when asked to identify a target stimulus that had been presented immediately previously as a to-be-ignored stimulus. He demonstrated this in an experiment where subjects were required to view a prime display consisting of a red picture superimposed on a green picture. They were asked to name the red picture. In the probe display a red and green picture were again presented and subjects asked to name the red picture. In the control condition neither of the pictures in the prime display were the same as those in the probe. In "ignored repetition" condition the green distractor picture in the prime display became the red

target picture in the probe display. Results showed that there were longer response times in the ignored repetition condition. Negative priming effects have similarly been demonstrated with a wide variety of stimuli and procedures, frequently with Stroop colour words (Neill & Westbury, 1987) and more recently with spatial localisation (Tipper, Brehaut & Driver, 1990), letter identification (Tipper, Mac Queen & Brehaut, 1988), and word naming, (Yee, 1991).

As the theory of inhibitory mechanisms in selective attention has developed, so the negative priming paradigm used to test it has become more complex. In more recent experiments, e.g. Tipper et al. (1994) priming effects have been examined over seven different conditions of a spatial localisation task. The ignored distractor in the prime display can share seven combinations of its three characteristics with the probe target, which are its location, identity and colour (L, I, C, LI, LC, IC, LIC). In condition L, the probe target appears in the same location (L) as the ignored distractor but does not share its identity or colour. In condition C, the probe target is the same colour as the ignored distractor but does not share its identity or location and so on. There is also a control condition in which the probe target shares none of the characteristics of the ignored distractor.

Milliken, Tipper and Weaver (1994) carried out a series of experiments in which the timing of the presentation of the colour cue was varied. They found that the appearance of the colour cue 300 ms before the onset of the probe target and distractor triggered a colour driven retrieval of the same-coloured items from the immediately previous prime display, in an attempt to verify the presence of an object of the same colour as the cue. If only the colour was the same, negative priming occurs because the distractor's colour representation was inhibited. If both the colour and location were the same negative priming was caused by the

inhibition of the distractor (colour and location) but this is over-ridden by the facilitation caused by the repetition of a nearly identical stimulus. Performance in LC and LIC conditions were consequently found to be facilitated, while performance in C and IC conditions were slowed. It has been suggested that these priming effects are due to a retrieval process driven by the probe colour cue in combination with inhibitory mechanisms of selection.

When the probe cue was presented simultaneously with the probe, thereby disabling any colour driven review process, negative priming was observed in conditions LC and LIC. This would suggest that when the probe is precued the effects of the inhibition of the distractor are masked by a colour-driven retrieval process involving review (Milliken et al., 1994).

The experiments described above indicate that negative priming occurs as a result of the combined effects of inhibitory and perceptual review processes. The pattern of negative priming effects is also critically determined by the behavioural goal of the task i.e. location effects are important in a spatial localisation task.

The effects of ageing on cognitive function

There is a wealth of evidence suggesting that ageing is accompanied by changes in some aspects of cognitive function. As two of the experiments in this thesis involve assessing the effects of serontonergic drugs in elderly subjects, it is necessary to briefly consider the effects of ageing on cognition and the theories proposed to explain them.

Episodic memory

Research into the effects of ageing on episodic memory have shown that despite a marked decline in free recall ability, recognition memory remains relatively unchanged (Schonfield and Robinson, 1966). Micco and

Masson (1992) investigated the recall ability of older subjects by looking at the kinds of cues they use to recall target words and compared their performance to younger subjects. They presented young and old subjects (senders) with a target word and a context cue word that was either a strong or a weak associate (e.g. 'crowd'-'people', 'crowd'-'riot') and asked them to produce a set of one word clues that would help another person produce the target. Another group of young and old subjects (receivers) were then given the clues in the presence of either the strong or weak associate and required to recall generate the target. They found that the clues provided by the elderly subjects were less effective in producing target words especially in the presence of a weak associate. Older 'receiver' subjects also found it harder to identify the target words, especially in the presence of weak rather than a strong associate context word. Their data suggests that older people find it more difficult to encode and retrieve context specific information particularly when it is information not typically associated with the stimulus. This may be because they are less efficient at using cues to specify potential targets.

The fact that the elderly do not show a decline in recognition memory could be explained by the fact that recognising information is an easier, less effortful task than recalling it. Craik and McDowd (1987) carried out an experiment to test this hypothesis by devising a recognition test that was more difficult than a recall test. They found that the elderly subjects still performed as well as, if not better than the young subjects on the recognition test but considerably worse than their younger counterparts on recall.

Earlier in the chapter the evidence that recognition involves two components (a 'familiarity' component and a contextual information processing component) was discussed (Mandler, 1980). Experiments into the recognition processes of older people suggest that the difference

between young and old subjects are not related to the 'familiarity' component, but rather to the contextual component. This explains why older subjects perform as well as young subjects on standard yes-no recognition tasks which maximise the possibility of familiarity-based responding, while on tasks where both the targets and distractors have been pre-exposed older subjects perform less well that younger subjects. One such task is the multiple-item recognition memory (MIRM), devised by Kausler and Kliem (1978). In this task subjects are presented with a list of item words, one of which is indicated to be the target (by underlining) that they should remember while the others are irrelevant distractors. (e.g.. parrot, fern, pliers, tissue). In the test phase the items are presented again without the target indicator in an array with either one or three irrelevant items. It was found that the older subjects made far more recognition errors than the young subjects. The older subjects were also influenced by the number of items in the array, making substantially more errors when there were four items in the array than when there were two. This suggests that they find it more difficult to ignore irrelevant stimuli than younger adults and by processing them rather than ignoring them, they reduce the amount of processing capacity available for relevant stimuli.

Spatial Memory

There is considerable evidence that memory for spatial information declines with age. The most commonly used paradigm is one in which subjects are shown verbal material, pictures or objects on a grid and then required to replace them in their original positions. Substantial age-related differences in both recall and recognition of spatial information have been found using this methodology (e.g. Naveh-Benjamin, 1988). A progressive decline in spatial ability as measured by the ability to recall

the locations of a series of wooden shapes was found in a study of individuals aged 19-76 years (Moore, Richards and Hood, 1984).

Semantic Memory

Experiments into ageing and semantic memory have found that there is no significant decline in ability. Anderson (1983) found no differences between old and young subjects in their ability to use generic knowledge to generate scripts relating to everyday activities, although the young subjects were significantly better at the recall and recognition of such scripts. Evidence from the effects of age on bidding strategy in bridge suggest that the speed at which old people access their semantic knowledge may slow down (Charness, 1983).

Short-term memory

Small, but reliable age-related deficits have been found in a number of short-term memory studies. Parkinson (1982) found the mean digit span for young subjects was 6.4 in one study and 6.8 in another, while the mean span for older subjects was 5.8 in both studies. Johansson and Berg (1989) carried out a longitudinal study of 70-79 year olds and found a small decrement in digit span over the time course of the study.

Attention.

There is considerable evidence that attentional processes are affected by ageing. Young adults perform better than the elderly on a wide variety of tasks e.g. semantic priming, visual search tasks, dichotic listening and dual-task. Stroop task effects have been found to be greater in older people. A number of studies have shown that as people get older their reaction times on the interference tasks increase more rapidly than on the control tasks (Cohn, Dustman and Bradford, 1984; Panek, Rush and Slade, 1984; Comalli, Wapner and Werner, 1962).

Psychological theories of cognitive deficits in ageing

Age-related slowing

Perhaps the best documented and least contested theory of ageing and cognition is that proposed by Salthouse (1985), which suggests that cognitive declines are the result of a reduction of the speed at which information is processed in the cognitive system. Supporting evidence for this theory comes from a number of meta-analyses (e.g. Salthouse, 1985) that have regressed the response times of the old against those of the young on a wide variety of tasks of varying complexity. They found that the more processing a task requires, the larger the difference in response time between young and old subjects. Overall old subjects take approximately 1.5 times longer than the young to complete tasks. Age difference in task speed have been found to remain even if training and practice on tasks is given (Salthouse and Somberg, 1982).

Limited processing resources.

The limited processing resource hypothesis posits that older people do less well on cognitive tasks as they have a processing capacity deficit which makes it more difficult for them to carry out effortful cognitive processes (Craik and Byrd, 1982). Support for this hypothesis comes from the fact that older people perform as well as young on less cognitively demanding tasks, such as word recognition, while on tests of free recall or cued recall young subjects greatly out-perform older subjects (Craik and McDowd1987).

Failure to Inhibit

Hasher and Zacks (1988) proposed that older adults have faulty inhibitory mechanisms in working memory. They consequently attend to irrelevant contextual detail and have difficulty interpreting text. Evidence for this view is demonstrated by an increase in Stroop interference effect with age (Cohn, et al., 1984). This theory is also supported by the findings

of Kausler and Kliem (1978) in the experiment described above in which they found that older adults are more distracted by irrelevant information than young ones.

CHAPTER 2

Neurotransmitters and Memory

A complete understanding of how the different neurotransmitter systems interact and of how pharmacological agents cause changes in learning and memory performance has not yet been achieved. Extensive studies investigating the effects of drugs on learning and memory have been carried out on various animal and human populations, including healthy volunteers, elderly persons and people with cognitive disorders such as Alzheimer's Disease and Korsakoff's Psychosis. The aim of these pharmacopsychological studies has been to determine the relationship between neurotransmitter function and cognitive processes. Some of these studies have investigated the actions of the neurotransmitters themselves using biochemical techniques. The majority of the studies reported here involve the use pharmacological compounds as tools to investigate the actions and interactions of the different neurotransmitter systems.

The aim of this thesis is to assess the effects of a drug that acts on the 5HT neurotransmitter system. As interactions between different neurotransmitter systems in relation to cognitive function remain undefined, it is undesirable to consider the 5HT system in isolation. There is evidence that 5HT may have a mediating role in the release of ACh. It has been demonstrated in rats that inhibition of 5HT synthesis stimulates an increase in release of ACh (Barnes Costall, Coughlan, Domeney, Gerrard, Kelly, Naylor, Onaivi, Tomkins, and Tyers, 1990). By looking at the role of ACh in memory function and considering the memory deficits produced when ACh is blocked, important information may be acquired as to the kinds of deficits likely to be found when manipulating the 5HT system and the measures that should be used to detect them.

The role of acetylcholine in cognitive function.

Acetylcholine (ACh) was the first identified neurotransmitter substance and there is considerable evidence that it is involved in memory function. ACh is synthesised in cholinergic nerve terminals by the enzyme choline acetyltransferase (CAT) and is released from vesicles in the synapse in response to depolarization of the nerve terminals. Two main types of cholinergic receptor in the CNS are now recognised; muscarinic receptors and nicotinic receptors. Drugs which block muscarinic receptors, e.g. scopolamine, impair acquisition and post acquisition performance in animals and humans, while muscarinic cholinergic agonists, e.g. arecholine, enhance learning (McCarley, Nelson and Hobson, 1978).

Administration of the cholinergic blocker scopolamine to healthy young subjects has been found to induce deficits on measures of episodic verbal memory similar to those found naturally in aged subjects. Drachman and Leavitt (1974) gave the same battery of tests to groups of young and elderly subjects treated with scopolamine and found deficits in both groups on measures of free recall of words and supraspan digits. No deficits were evident in short term memory as measured by the digit span test.

Broks, Preston, Traub, Poppleton,Ward and Stahl (1988) gave low oral doses of scopolamine to healthy volunteers and tested them on a battery which included measures of verbal memory, spatial memory (short and long term) and attention. Verbal memory was impaired at the highest dose (1.2mg), while some measures of attention (sustained attention and visual contrast sensitivity) showed linear dose-dependent effects. Performance on a measure of simple reaction time and both measures of spatial memory were found to be resistant to cholinergic blockade. Preston, Brazell, Ward, Broks, Traub and Stahl (1988) also

found treatment with scopolamine lead to reliable verbal memory deficits, but contrary to Broks et al (1988), they found visuo-spatial recall was also impaired. These effects were reversed by treatment with the anticholinesterase agent, physostigmine.

The nature of the verbal memory deficit induced by scopolamine was further investigated by Rusted and Warburton (1989) who examined the relationship between encoding and retrieval factors on a verbal memory task. Healthy young subjects were given a dose of 0.6 mg scopolamine or placebo and required to learn lists of ten words over eight acquisition trials pre-drug (T0), 1hr (T1) and 2h 20 mins (T2) after drug. Delayed free recall and recognition of the lists presented pre-drug and at the previous post drug test phase was also measured. Subjects given placebo reached criterion for list learning after 4 trials, while the scopolamine treated subjects failed to reach criterion at all. Delayed free recall (at T2) of words presented for learning at T1 was also found to be impaired. However delayed recall of information learned pre-drug and delayed recognition of both pre- and post-drug words was unaffected by scopolamine. This indicates that the words were being successfully encoded in long term memory. The experimenters suggest that the poor performance of the scopolamine-treated subjects on immediate free recall and delayed recall may be due to the drug a disrupting the organization of information at storage, thus making the words inaccessible for retrieval at recall. This raises the question of what specific aspects of memory are being affected which is addressed by further studies by Rusted and Warburton (1988).

Rusted and Warburton (1988) attempted to pinpoint the action of scopolamine to specific sub-components of the the working memory model postulated by Baddeley and Hitch (1974). In a healthy volunteer study, Rusted (1988) measured digit span, mental rotation (both found in

previous studies to be unaffected by scopolamine) and free recall of supraspan word lists (previously found to be affected by scopolamine) before and after doses of scopolamine (1.2 mg) and placebo. The aim of the study was to demonstrate the selective disruption of scopolamine on verbal recall performance. The digit span and mental rotation tasks were unaffected by scopolamine when completed alone or with secondary tasks that were unrelated to the primary task. However both tasks were selectively sensitive to interference by task specific interference (concurrent articulation in the case of digit span and concurrent spatial tapping in the case of the mental rotation task). Immediate free recall was impaired by scopolamine and the effects of the concurrent secondary task were non-specific i.e. spatial tapping and articulatory supression impaired performance equally. The experimenters concluded that scopolamine selectively impairs the central executive component of working memory while leaving the two "slave" systems intact. As other theories of short-term memory equate the central executive system with selective attention (e.g. Norman and Shallice, 1986) it would be desirable to examine the effects of 5HT drugs on measures of attention and compare them with the results described above.

The experimental work described above suggests that the ACh neurotransmitter system is involved in specific memory processes e.g. storage and retrieval of verbal information and the control of the central executive component of working memory.

The cognitive deficits produced by scopolamine have been compared to those resulting from Alzheimer's disease and normal aging. These comparisons have lead to the formulation of a separate cholinergic hypotheses for Alzheimer's disease and aging. Bartus, Dean, Beer and Lippa (1982) reviewed much of the biochemical, electrophysiological and pharmacological evidence that supports the cholinergic hypothesis of

memory dysfunction in demented and non-demented elderly subjects and found many inconsistencies in the results. Studies focusing on choline acetyltransferase (CAT) activity failed to demonstrate any reliable age related changes. Other studies (cited by Bartus et al., 1982) attempted to establish an association between age-related cognitive decline (normal and diseased) and deficient cholinergic neurotransmission by assessing decreases in muscarinic receptor density, choline uptake, ACh synthesis and ACh sensitivity. However no clear characterisation of the nature of these changes has been established and the many efforts to formulate a cholinergic hypothesis for dementia have been unsuccessful. Fibiger (1991) points out that research in the area has as yet failed to characterise the function of the central cholinergic systems because it is so extensive and agents such as scopolamine affect a wide variety of targets in the CNS. Attempts to explain the effects of ACh on unitary psychological mechanisms are questionable and will remain so until a more selective toxin for cholinergic neurones is discovered.

The role of the catecholamines in cognitive function

As reviewed above, much of the early research into the involvement of neurotransmitter systems in cognitive function has centred on the ACh system and was motivated by attempts to identify a specific, treatable cholinergic deficit in patients with Alzheimer's Disease. The conclusion that multiple neurochemical deficits are involved in Alzheimer's Disease, and the possibility that the systems interact lead to additional interest in neurochemical systems, in particular the catecholamines. The catecholamines (noradrenaline, adrenaline and dopamine) are a group of neurotransmitters considered to play a role in learning and memory. Neurones containing catecholamines are relatively few in number but have cell bodies that project extensively throughout the CNS.

Mc Entee and Crook (1990) reviewed the existing research carried out on the role of the catecholamines in memory and found an association between diminished catecholamine function and a clinical state defining the loss of memory function in otherwise healthy people over 50 years old, known as "Age-associated memory impairment", or AAMI. Other biochemical studies showed that concentrations of noradrenaline and dopamine or their metabolites were reduced in the brains of aged rodents, monkeys and humans. The performance of Korsakoff's patients improved on measures of the logical memory component of the Wechsler Memory Scale, visual reproduction and a consonant trigram test after administration of the alpha-2 noradrenergic agonist, clonidine (Mair and Mc Entee, 1986). Studies assessing the possibility that adrenergic drugs would enhance memory in Alzheimer's patients and people with AAMI have not proved to be successful. The lack of clear evidence as to the involvement of catecholamines in cognitive processing suggest that cognitive deficits in Alzheimer's Disease and the aged result from multiple neurochemical deficits rather deficits specific to a particular neurotransmitter system.

The effects of tricyclic antidepressants on memory

The effects of psychoactive drugs on cognition have been assessed in 'pure research' studies involving healthy volunteers and in applied studies which assess their effects in psychiatric patients. The tricyclic antidepressants, e.g. amitryptiline and imipramine, exert their therapeutic influence by enhancing the actions of several of the neurotransmitters including 5HT, noradrenaline and histamine and by blocking acetylcholine. They are characterised by their three linked ring structure to which a side-chain is attached. The antidepressant properties of the tricyclics depend on the central ring structure, while their potency and

sedative properties depend on variations in the side-chain. A compound with a fourth ring added is known as a tetra-cyclic. It is for this reason that, despite being very effective therapeutically, they are associated with a variety of adverse side effects. Tricyclic side-effects are largely attributable to their anticholinergic action which causes sedation, blurred vision, dry mouth, tachycardia and disturbed gastrointestinal and urinary tract function. Tricyclic antidepressants have also been found to cause confusion, impaired memory and cognition, most particularly in the over 50 age group.

Some of the tricyclics have been modified in order to decrease their side-effect profile. For example, lofepramine (the reference drug in the clinical trial-see Chapter 7) is relatively free of anticholinergic side-effects due to the absence of a free NH_2 in the side chain.

Over the past 30 years a number of studies have evaluated the effects of tricyclic antidepressants on cognitive function. Imipramine has been the subject of much of this research due to its long history of use and wide range of application. Many of the studies have been carried out on groups of depressed subjects but as the results of these studies are confounded by both the psychiatric disorder and clinical recovery, other studies have used healthy volunteers. The evidence of the effects of tricyclics on cognitive processes present a confusing picture with some studies finding subjects impaired on specific tasks, others finding drug related improvements, and others no drug related changes in cognitive performance. Thompson (1991) reviewed the studies that had been carried out on groups of depressed patients and found that two of them reported beneficial effects, two detrimental effects, one no side-effects, and one both enhancing and impairing effects depending on the measure used. Performance of healthy volunteers follows a similarly inconsistent pattern

with four studies finding improved performance four studies impaired performance and 1 study no change.

The effects of the tricyclic, amitriptyline have also been widely studied in depressed subjects and healthy volunteers. Sternberg and Jarvik (1976) found amitriptyline had the same improving effect as imipramine on short term memory performance in depressed patients. However other studies provide evidence that amitriptyline impairs memory performance. For example, Lamping, Spring and Gelenberg (1984) compared the effect of amitriptyline and clovoxamine (a non-selective 5HT and NE reuptake inhibitor) on the memory of depressed outpatients aged 18-70 years. Cognitive performance was assessed using a test of verbal memory (recall and recognition), the Benton visual retention test and the logical memory test (short story recall). The experimenters employed signal detection analyses on the recognition memory scores in order to establish whether changes in memory performance were due to changes in memory sensitivity or motivational factors influencing the subjects' responses. Memory and depression were assessed during a pre-treatment baseline period and then on days 4, 7 and 28. Although both drugs lead to clinical improvement in depression, they affected memory performance differently. Signal detection measures of the recognition memory scores showed amitriptyline treated patients were impaired on measures of sensitivity as they failied to recognise previously presented words, while subjects on clovoxamine improved over time and their errors tended to involve mistaking new words for old ones. Neither drug caused changes in response bias. No differential drug effect was found on performance on the Benton VRT which suggests that visual and verbal memory are affected differently by treatment with amitriptyline.

A healthy volunteer study by Curran, Saklulsriprong and Lader (1988), compared the cognitive performance profile of amitriptyline,

which is highly sedating and has strong anti-cholinergic effects, with three other drugs with different sedative and anticholinergic properties; trazadone (an SSRI with sedating but low anti-cholinergic effects), protriptyline (non-sedating, but high anti-cholinergic effects) and viloxazine (non-sedating and low anti-cholinergic effects). Ninety young healthy volunteers were divided into 9 treatment groups (two for each drug to allow for dose manipulation, and a placebo group) and tested on measures of free-recall, delayed recall, semantic retrieval, digit span and critical flicker fusion threshold. The less sedating antidepressants (protriptyline and viloxazine) did not impair performance on the memory or component tasks. Trazodone and amitriptyline were found to produce global impairments on all the tasks except for semantic retrieval and amitriptyline produced a greater impairment than trazodone on the verbal episodic memory task. This difference can be explained by the difference in pharmacology of the two drugs, amitriptyline having greater sedative and anti-cholinergic properties than trazadone.

Branconnier, DeVitt, Cole and Spera (1982) attempted to pinpoint the memory processes affected by amitriptyline by administering an acute dose of 50 mg of the drug to healthy elderly volunteers and testing them on a computerised battery of tests. A double-blind placebo controlled design was used. Amitriptyline was found to impair recall on the Buschke Selective Reminding Test, but not recognition. No impairments were found on measures of visual or verbal short-term memory. This selective impairment of verbal episodic memory is similar to that reported in subjects treated with the antimuscarinic, scopolamine. It therefore seems likely that impairing the effect of amitriptyline is associated with its anti-cholinergic effect.

As elderly people experience memory deficits independent of those caused by depression, it is particularly important that they are prescribed

anti-depressants that do not further exacerbate already existing memory deficits. As many elderly people take antidepressants, a body of research has focused specifically on the effects of antidepressant on cognition in elderly depressed patients. Nortriptyline is used extensively in the treatment of elderly depressives as it is known to have fewer anticholinergic properties and is therefore more likely to be tolerated in the elderly. However evidence from a study by Hoff, Shukla, Helms, Aronson, Logue, Ollo and Cook (1990) suggests that treatment with nortriptyline is associated with poor verbal memory recall. Young, Mattis, Alexopoulos, Meyers, Shindledecker and Dhar (1991) found that nortriptyline impaired free recall performance in elderly depressed patients but had no effect on recognition or digit span measures.

The results of the studies reviewed above suggest acetylcholine depletions and tricyclic anti-depressants selectively impair verbal recall performance. Curran et al. (1988) found that treatment with amitriptyline also lead to impairments on measures of digit span and critical flicker fusion in healthy volunteers. The available evidence indicates that the cognitive effects of treatment with anti-cholinergic compounds such as amiytriptyline are similar to those that result from treatment with scopolamine. No studies to date have assessed to cogntive effects of the tricyclic, lofepramine, the reference drug in the drug trial. However, it is known that lofepramine has weak anti-cholinergic effects and is therefore less likely to impair cognitive processes than other tricyclics.

The role of 5HT in cognitive function

The serotonergic (5-HT) system is implicated in cognitive functioning. The 5HT system is made up of relatively few cell bodies situated in the brain stem with processes that extend throughout the CNS.

Serotonin is also involved in a variety of functions such as sleep, mood, sexual behaviour, pain regulation and feeding behaviour.

As with the research into the other neurotransmitter systems, experimenters have attempted to document serotonin related biochemical changes in brain function in the normal and diseased aged subjects. A review of the work in the area by McEntee and Crook (1991) shows the results of studies of 5HT changes in normal aging to be inconclusive. Most studies fail to show an expected change or decrease with age in the concentrations of 5-HT or its primary metabolite 5-HIAA, or a decline in numbers of presynaptic nerve terminals. However there is consistent evidence to show that the density of radio-ligand binding sites for 5-HT receptors decreases with age in humans and rats. Studies of patients with Alzheimer's Disease have shown that they have decreased levels of 5HT and its primary metabolite, reduced numbers of receptor binding sites, decreased 5HT reuptake and release from presynaptic sites in biopsy specimens. Patients with Korsakoff's psychosis also have been found to have decreased levels of 5HT though there is no direct evidence showing that this loss is a consistent feature of the disease.

The role of 5-HT in learning and memory has also been investigated in pharmacological studies in which the 5-HT system is manipulated using agonists, antagonists and 5HT reuptake inhibitors. In their review, McEntee and Crook cite evidence that 5HT agonists (which stimulate 5HT activity) impair memory in rats, Alzheimer's Disease patients and the elderly. Treatment with antagonists (which would be expected to impede 5HT activity) was found to improve memory in rats and mice. These drug actions suggest that 5-HT exerts an inhibitory influence on learning and memory. Drugs which prevent the re-uptake of 5-HT into the pre-synaptic nerve terminals would therefore be expected to raise synaptic concentrations of 5-HT and to impair memory. However this does not

appear to be the case as the studies reviewed below show that 5-HT reuptake inhibitors (also known as selective serotonin reuptake inhibitors or SSRIs) enhance verbal memory test performance in humans and animals (e.g. Weingartner, Rodorfer, Buchsbaum and Linnoila, 1983; Martin Adinoff, Eckardt, Stapleton, Bone, Rubinow, Lane and Linnoila, 1989). This has lead to the speculation that the SSRIs may indirectly interfere with, rather than increase, 5HT transmission.

Neither the paradoxical relationship between the actions of the 5-HT antagonists and the SSRIs, nor the pharmacologic actions by which the 5HT reuptake inhibitors improve memory are understood. One of the aims of the present research is to further define the effects of the SSRIs on the cognitive function of humans. However, it is first necessary to review the the evidence of cognitive effects of 5HT in animals.

Evidence from animal studies of the role of 5HT in learning and memory .

Altman and Normile (1986, 1987) carried out a series of animal experiments with the aim of characterising the role of the serotonergic system in learning and memory. These experiments focused on the effects of a range of 5-HT antagonists and SSRI's on a variety of learning and memory tasks. They also explored the effect of the time that agents were administered with respect to training as inconsistencies in the results of early studies reviewed by Altman and Normile (1988) pointed to the possibility that the action of 5HT antagonists may be dependent on the time they are administered. This hypothesis was tested by comparing the effect of pre-train, post-train and pre-test administration of a variety of serotonergic antagonists (kitanserin, pirenperone, and mianserin) on a lick supression task in young thirsty mice. The results showed that administration of drug 30 minutes prior to training produced a dose-dependent impairment in retention, whereas administration either immediately after training, or 30 min before the retention test, produced a

dose dependent improvement. These results support the hypothesis that the timing of the drug administration influences its effect and raises the possibility that 5-HT may have a differential role in learning and memory.

It is established that rodents, like humans, exhibit age-related impairments in performance and the initial study was expanded to explore the effects of post-train administration of ketanserin and mianserin on a one trial passive avoidance task in middle-aged and aged rats (Normile and Altman, 1988). The results of both this study and the one described above suggest that administration of serotonergic antagonists improve retention of previously learned aversive habits in young, middle-aged and aged rats. However, interpretation of these results is complicated by the fact that the drugs used in the experiment are non-selective in their action and may therefore also be acting on non-serotonergic systems. Research into the pharmacology of 5-HT is still expanding with the discovery of new receptor binding sites and drugs that bind specifically to them.

Altman and Normile (1988) further explored the role of 5-HT in memory and learning by lowering the levels of 5-HT in the brain using a method of peripheral administration of the neurotoxin, p-chloroamphetamine (PCA). They found that the PCA-lesioned rats performed better on the spatial discrimination maze learning task than controls. Pre-treatment of PCA-injected rats with a selective 5-HT reuptake inhibitor, norzimeladine was found to inhibit the decrease in 5HT produced by PCA. Altman and Normile also present evidence for the potential differential effects of 5-HT depletion on tasks requiring different memory processes. They found that PCA-induced depletion led to improved performance on a task primarily involving reference memory, whereas no improvement was found on a task requiring working memory. These differential effects of 5-HT depletion in animals have

important implications for research into the cognitive effects of 5-HT in humans.

Altman, Nordy and Ogren (1984) showed memory enhancing effects of the selective 5-HT reuptake inhibitors zimeldine and alaproclate on a shock avoidance learning task in mice. This effect was found to be completely blocked by pretreatment with the 5-HT agonist quipazine, but potentiated by pre-treatment by the 5-HT antagonist, cyproheptadine.

The animal experiments conducted by Altman and Normile demonstrated that a reduction in 5HT as a result of neurotoxin treatment or administration of an SSRI improves the performance of young and old mice on a shock avoidance learning tasks and a spatial discrimination learning task. These result show that although SSRIs should theoretically enhance 5HT activity by increasing synaptic 5HT, they may in fact be interfering with 5-HT transmission and by doing so increase ACh activity. By varying the time they administered the SSRI they were able to establish that treatment impairs acquisition but improves retention.

Further evidence for the memory enhancing effects of the SSRIs comes form a series of experiments in which the 5-HT reuptake inhibitor, fluoxetine was administered to young adult mice (Flood and Cherkin, 1987). Fluoxetine was found to enhance retrieval and memory consolidation but not acquisition. This enhancement was found after one week whether fluoxetine was injected pre- or post-training. Fluoxetine, injected post-training was also found to block the amnesia induced by scopolamine and a protein synthesis inhibitor, anisomycin. Strek, Spenser and DeNoble (1989) found that post-training treatment of rats with fluoxetine prevented the performance deficit in passive avoidance behaviour produced by hypoxia.

Neurochemical interactions of 5HT

An extensive body of animal research suggests that the serotonergic and cholinergic neurotransmitter systems are functionally interactive in memory retrieval. Altman, Stone and Ogren (1987) examined the effects of combined serotonergic and cholinergic manipulation on the retrieval of a previously learned aversive response in mice. They increased synaptic levels of acetylcholine and serotonin by administering the 5HT reuptake inhibitor, alaproclate and the muscarinic agonist, oxotremorine, alone and in combination prior to a retention test. It was found in all cases that there was an dose-dependent enhancement in performance and the two drugs combined were found to facilitate retrieval at much lower dose levels than each of the drugs on their own. When quipazine, a 5-HT agonist, was administered to the different treatment groups it completely blocked the facilitation induced by the alaproclate, but not the combined effects of alaproclate and oxotremorine. This raises the possibility that the individual effects of the alaproclate and its effect in combination with oxotremorine may be mediated by different, but not necessarily unlinked mechanisms. Scopolamine, on the other hand, blocked the effects of oxotremorine alone, the two drugs combined, but not alaproclate. If the enhancement caused by the two drugs alone and together is additive it would be expected that the blockade of either one of them would inhibit the action of the two drugs in combination. However only scopolamine, and not quipazine, blocked the two drugs in combination. This result has lead the experimenters to suggest either that the serontonergic system may function at a later processing stage in the retrieval of memory than the cholinergic system, or that the serotonergic system is assuming a neuromodulatory in the memory retrieval process.

Nilsson, Strecker, Daszuta and Bjorklund (1988) explored the interaction between the serotonergic and cholinergic systems using

lesioning techniques. They found that a serotonergic lesion, induced by 5,7-DHT treatment had very little effect on the spatial learning and memory in the Morris water maze task in rats with an intact cholinergic system. However, rats given an additional lesion in the septohippocampal cholinergic pathway were found to have severe learning and memory deficits. The effects of the lesioning seemed to be long lasting as the rats showed no sign of recovery over a period of at least six months after the operation. This result supports the view that cholinergic and serotonergic systems have interactive effects on memory. The fact that the serotonergic lesion alone had little effect on the rats' maze learning and memory lends further support to the possibility raised by Altman et al. (see above) that the serotonergic system assumes a modulatory role in memory processing and may act by simply enhancing cholinergic responses rather than working independently.

Barnes et al. (1989, 1990) carried out some elegant studies in order to establish the nature of this neurochemical interaction. Firstly they experimented on rats' cortex in order to find out which subtype of receptor is involved in the interaction and found that the highly selective 5-HT3 receptor antagonists are the most effective in the facilitation of ACh release. In a subsequent study, they used the selective 5-HT3 antagonist, ondansetron, on mice, rats and marmosets to assess its effects on three cognitive tasks; a habituation task (mice), a T-maze reinforced alternation task (rats) and an object discrimination and reversal learning task (marmosets). The 5-HT3 antagonist ondansetron, improved performance from baseline on these tests of learning and memory in all the animals groups. The effects were more marked in aged mice as compared with young adult mice. Ondansetron was also found to prevent impairment on the habituation task in mice caused by pre-treatment with scopolamine or lesioning in the cholinergic system. This was inferred to be because the 5-

HT3 antagonist prevents the inhibitory effect of 5-HT on acetylcholine. Treatment with the ACh agonist arecoline was found to inhibit the effects of scopolamine and the nucleus basalis lesions, but not as effectively and directly as ondansetron. This may reflect the experimental difficulties involved in administering arecholine, though it is possible that ondansetron may be more effective at stimulating the cholinergic system than cholinergic agonists.

Results of the studies exploring the effects of SSRIs on animal cognition indicate that they have potential as cognitive enhancers. There is strong evidence that treatment with SSRIs and 5HT3 receptor blockers has an activating effect on the cholinergic system. Lesioning the serotonergic system while leaving the cholinergic system intact had little effect on maze learning and memory in rats, which suggests that the serotonergic system does not enhance memory independently but rather modulates the memory enhancement by the cholinergic system. However the exact nature of the relationship between the serontergic and cholinergic systems remains unclear.

The effects of 5-HT reuptake inhibitors on cognitive and psychomotor processes in humans.

The SSRIs are highly selective inhibitors of the reuptake of serotonin which are thought to exert their therapeutic effect by enhancing serotonergic transmission and down-regulating adrenergic receptors (Feighner and Boyer, 1990). At therapeutic doses they have negligible direct effects on other neurotransmitters systems. They therefore lack the adverse noradrenergic and anticholinergic effects typical of the older anti-depressants as well as being relatively safe in overdose. The most common side-effects resulting from the SSRI's are nausea, vomiting and diarrhoea. Research into the effects of the SSRIs on cognitive and psychomotor

performance suggest that they have no detrimental effects and they may in fact improve cognitive performance. Included in this group are zimeldine (now withdrawn due to toxic side effects), fluoxetine, fluvoxamine, citalopram, sertraline and paroxetine. Studies have been carried out to assess the effects of these drugs on cognitive and psychomotor processes and to compare these effects with those resulting from treatment with the older, less selective anti-depressants or ethanol which provides an initial deficit, which the drug may either potentiate or remediate. Many of these studies have been carried out on normal, healthy volunteers so that the results are not confounded by changes in depressive state or already existing memory deficits resulting from old age.

The effects of the SSRIs, fluvoxamine and fluoxetine have been explored in a number of studies. Healthy subjects' performance on measures of memory and learning while taking repeated doses of the 5-HT reuptake inhibitor, fluvoxamine have been compared to that of subjects taking the 5-HT_2 antagonist, mianserin (Curran, Shine and Lader 1986). Objective measures of memory and psychomotor skills were assessed as well as subjective ratings of mood and sedation using visual analogue scales. Testing was carried out on days 1, 4 and 8 of each treatment week and involved administration of a pre-drug test battery, followed by a post-drug test battery and tests of delayed recall from the previous testing session. Fluvoxamine had no effect on memory performance, while mianserin was found to impair recall and learning on test day 1, although there were no treatment group differences in recall levels pre-drug or on day eight of the trial. The effects of mianserin on memory could be due to the sedative effects of the drug which were evident from the results of the physiological tests and subjective ratings of alertness.

Eckardt, Stapleton, Rio, George, Rawlings, Weingartner, and Linnoila, (1986) examined the interactions of an acute dose of 50 mg or 100

mg of fluvoxamine and ethanol on memory and psycho-motor performance in healthy volunteers. The test battery comprised a verbal memory test, body sway, tracking ability, CPT, and spatial and verbal information processing tasks. Fluvoxamine had no detectable effects on any of the tasks and caused no potentiation of the effects of alcohol. The results of these two studies suggest that the SSRI, fluvoxamine has a neutral effect on cognitve function in healthy volunteers.

Evidence from animal studies suggest that the SSRI, fluoxetine enhances retrieval and memory consolidation in mice (Flood and Cherkin, 1987). The memory enhancing properties of the drug have also been assessed in healthy volunteers. Moskowitz and Burns (1988) compared the effects of acute doses of fluoxetine and amitriptyline alone and in combination with diazepam on a range of cognitive and psychomotor tasks (a critical tracking task, a divided attention task, a vigilance task and a verbal memory test) in 90 healthy men. Fluoxetine alone did not impair performance, though when combined with diazepam performance on a divided attention and vigilance task was adversely affected. Subjects given amitriptyline alone, and in combination with diazepam, were impaired on measures of tracking skills, response times, response accuracy, attention processes and cognitive skills. Diazepam alone was also found to impair performance.

Shaw, Sullivan, Kadlec, Kaplan, Naranjo and Sellers (1989) looked at the interactions of fluoxetine with alcohol using amitriptyline as a reference drug. Memory, manual tracking, body sway, intoxication and sedation measures were taken in sixteen healthy male subjects. Subjects were tested with placebo and ethanol, and placebo and juice before and after taking either a clinical dose of fluoxetine or a low dose amitriptyline for 14 days. Neither drug was found to modify the detrimental effects of ethanol and the experimenters concluded from this that chronically

administered, low doses of these drugs do not have important interactions with ethanol.

The effect of fluoxetine on cognitive function has also been assessed in a group of depressed outpatients (Fudge, Perry, Garvey, and Kelly, 1990). After a week on placebo depressed subjects received either fluoxetine or trazadone for six weeks. No difference in the effect of these two drugs was found on measures of paired associate learning and recall or digit span. The results of these studies indicates that fluoxetine does not impair or improve performance of healthy volunteers or depressed subjects on cognitive tasks.

Two studies have reported a positive effect of an SSRI on volunteer memory. In one zimeldine reversed a dose-dependent ethanol induced impairment of free recall of verbal material (Weingartner, et al., 1983). Zimeldine (200 mg) was administered daily and on days eight, nine and ten subjects received a placebo drink or low or high doses of alcohol two hours after taking either a placebo pill or zimeldine. Subjects were tested 2 hours post-drink. Treatment with alcohol was found to impair recall of material that was presented once but not material that was presented twice. Zimeldine reversed the deficit found on recall of poorly learned material. This reversal appears to be specifically cognitive as zimeldine did not attenuate the alcohol effects on other deficits, such as impaired body balance and visual-motor tracking. Linnoila, Johnson, Dubyoski, Ross, Buchsbaum, Potter and Weingartner (1983) also investigated the effects of zimeldine and two tricyclic antidepressants, desipramine and amitriptyline alone and with ethanol on a continuous performance task and verbal memory task (recall and recognition). Zimeldine was found to antagonize the effects of alcohol on both tasks.

Further evidence of the potential cognitive enhancing properties of the SSRIs comes from studies assessing their effect on episodic memory

performance in patients with alcoholic organic brain syndrome. (Martin et al. (1989) administered fluovoxamine to ten patients with severe memory deficits resulting from various alcoholic organic brain disorders (Korsakoff's Psychosis, dementia associated with alcoholism, and compensated alcoholic liver disease). Treatment was for four weeks in a double-blind placebo controlled cross-over study. Memory was assessed at baseline and at the end of the four weeks on drug and placebo using the Wechsler Memory Scale and a test of verbal episodic memory. Fluvoxamine improved the memory recall (but not recognition) performance of the patients with Korsakoff's Psychosis but not the other patients. A similar study by Stapleton Eckhardt, Martin, Adinoff, Roehrich, Bone, Rubinow, and Linnoila (1989) also found that fluvoxamine produced small improvements in performance on the same battery of tests.

The results of the studies reviewed here suggest that, although SSRIs enhance already existing memory impairments caused by alcoholic organic brain syndrome or treatment with ethanol, they have a neutral effect on memory performance in healthy volunteers. However experimenters examining changes in lower level measures of cognitive performance indicate that 5HT drugs have a central activating effect. Saletu, Grunberger, Rajna and Karobath (1980) found that an acute dose of fluvoxamine produced a significant increase in CFFT, an improvement in finger tapping and an increase in slow and fast EEG activity with a decrease in alpha activity. Performance on letter cancellation (psychomotor test), a reaction time test, an Archimedean-spiral after-effect task, time estimation and nonsense syllable learning were unaffected. Netter (1986) reported that an acute dose of fluvoxamine (75 mg) raised CFFT while a chronic dose (one week) of fluvoxamine (2x50 mg a day) had no effect on CFFT and slowed down subjects' performance of a crossing-

out task on days 4 and 8 (but not day 1). Netter (1986) also reported that 60 mg of fluoxetine raised CFFT levels and all doses of fluoxetine were found to have a slowing effect on subjects performance on a cancellation test.

Hindmarch and Bhatti (1988) explored the effects of varying acute doses of the 5-HT reuptake inhibitor, sertraline, on CFFT and choice reaction time in 10 healthy female volunteers. A double-blind cross-over design was used with a seven day wash-out period between each drug. All doses of sertraline were found to produce significantly higher CFFTs compared to placebo.

The effects of paroxetine on cognitive function

No studies to date have explored the effects of the SSRI, paroxetine on memory performance. To date studies assessing the effects of paroxetine have focaused on psychomotor skills and measures of attention. In a comparative review of the healthy volunteer studies of SSRI effects, Kerr, Sherwood and Hindmarch (1991) found that a raised CFFT was produced by acute doses of zimeldine, sertraline and paroxetine. Sertraline also produced an improvement on a choice reaction time task (CRT). The effects of fluoxetine, fluvoxamine and JO 1017 were indistinguishable from placebo on the CFFT and CRT measures. Dual-task (tracking and peripheral RT) and subjective mood measures were not significantly affected by any of the SSRIs relative to placebo.

Deijen, Loriaux, Orlebeke, and De Vries (1989) found healthy subjects treated with paroxetine for a week were not impaired on measures of mood, perceptual motor skills and eye movements, while subchronic treatment with maprotiline (a new tricylic) resulted in impaired performance on the cognitrone task which suggests that the drug may affect cognitive function. Cooper, Jackson, Loudon, McClelland and Raptopoulos (1989) further explored the effects of an acute dose of paroxetine on psychomotor ability, alone and in combination with

haloperidol (neuroleptic), amylobarbitone (barbiturate), oxazepam (benzodiazepine) and alcohol. The test battery consisted of 16 visual analogue scales to measure subjective feelings, estimation of one minute of elapsed time, a manipulative motor task, two choice reaction time, tapping rate, a rapid information processing task, CFFT and digit span test. The testing was carried out prior to dosing and then 2, 4, 6, 8, and 24 hours later. Each group received four treatments in random order, at least seven days apart (ie. paroxetine alone, haloperidol alone, the two together, placebo). The results indicated that all the drugs except paroxetine, when taken alone produced significant impairment on objective measures of psychomotor performance. There was no potentiation by paroxetine of the sedative effects or impairment of psychomotor performance produced by the other four drugs.

The existing studies assessing the effects of paroxetine on measures of CFFT and other attentional measures present contradictory evidence. The aim of this thesis is to clarify the effects of paroxetine on attentional processes and explore its effects on a variety of memory measures.

The cognitive effects of the 5HT3 antagonist, ondansetron.

The 5HT3 antagonist, ondansetron has been reported to improve episodic memory performance in elderly volunteers who met the diagnostic criteria for age associated memory impairment (or AAMI) (McEntee and Crook, 1990). AAMI is defined as memory loss relative to the individual's previous ability in non-demented and otherwise healthy individuals over the age of 50. The episodic memory test involved the acquisition and delayed recall of name-face associates and face recognition. As evidence from animals studies suggest that the SSRIs have enhancing properties similar to the 5HT3 antagonists (McEntee and Crook, 1991), it is reasonable to assume that despite their theoretically opposing

pharmacological actions, the two groups of drug will have similar enhancing properties in humans.

The cognitve effects of the 5HT agonists, buspirone.

In their review McEntee and Crook (1991) reported all the studies designed to stimulate 5HT activity had resulted in impaired performance, whilst those that were designed to impede 5HT activity had resulted in improvements. It would be predicted from this that 5HT agonists would impair cognitive performance as they exert an opposing action to 5HT antagonists. Indeed, some studies have shown this to be the case in rats and patients with Alzheimer's disease and the elderly (see McEntee and Crook review, 1991). There is also evidence to suggest that the $5HT_{1a}$ agonist, buspirone does not cause significant psychomotor or cognitive impairments in the elderly (Hart, Colenda and Hamer, 1991) and a 5mg dose produced a trend toward cognitive enhancement in young healthy volunteers (Barbee, Black, Kehoe and Todorov, 1991).

Rationale for the exploring the effects of paroxetine on cognitive function.

The results of the studies reviewed above suggest that the effects of SSRIs on normal memory are either neutral or inconclusive. The verbal memory effects of fluvoxamine and fluoxetine were examined in four different studies, but there was no evidence of either impairment or improvement. Consistent with this, in a review of the effects of antidepressants, Thompson (1991) indicated that all reported studies of 5HT reuptake inhibitors show no other effects on memory in healthy volunteers. The only human memory enhancement observed with SSRIs are the improvements seen in volunteers pre-treated with alcohol (Weingartner et al., 1983) and in patients with alcoholic organic brain syndrome (Martin, et al., 1989; Stapleton, et al., 1989)

Other positive volunteer results obtained with SSRIs involve lower level measures. The results of these studies suggest that SSRIs have a

central activating effect, but that baseline verbal memory scores, whilst not impaired, do not improve in parallel with the increased activation. The aim of the first healthy volunteer study in this thesis will be to further establish the cortical activating properties of paroxetine and assses their effect on measures of selective attention and verbal memory. It is reasonable to expect an improvement in some aspect of cognitive processing to accompany SSRI-induced increases in cortical activation. There are several reasons for making this prediction.

Firstly, there is animal evidence of cognitive enhancement with SSRIs that is similar to the animal learning enhancement produced by 5HT3 antagonists (McEntee and Crook, 1991). As the 5HT3 antagonist, ondansetron was also found to enhance memory in healthy elderly volunteers it is predicted that paroxetine will produce improvements in the memory performance of depressed and non-depressed elderly volunteers. Second, as most of the volunteers taking part in the SSRI studies were young rather than elderly, the measures used to assess the cognitive effects of SSRIs in healthy volunteers may not have been the most suitable or the most sensitive to improvement effects. The apparently neutral influence of SSRIs in younger healthy subjects may merely reflect a ceiling on test performance in these groups. Improvements might be demonstrated on tests that are more sensitive to enhancement in subjects whose baseline performance is optimal or near optimal for their age.

The early SSRI volunteer studies were based on the assumption that drugs of this type (i.e. neurotransmitter reuptake inhibitors, in general) would cause sedation and/or give rise to cognitive impairments. In later studies, the aim of the research may have been to test the hypothesis that, whilst other drugs caused unwanted sedation and detrimental cognitive side-effects, the SSRIs did not. In either case, the studies were designed to detect of impairments, and so appropriate tests for the assessment of the

predicted deficits were administered. The use of such tests would have reduced the probability of detecting improvements in memory. With this in mind, it was ensured that the battery of tests designed for use with young and elderly healthy volunteers and depressed patients were of sufficent difficulty to be able to detect both impairments and improvements in performance..

The aim of the present research is to extend the work carried out on the cognitive effects of the SSRIs by exploring the effects of paroxetine on the cognitive processes in a number of different subject groups. By assessing the effects of paroxetine in a variety of different subject groups on a wide range of attentional and memory tasks, it is hoped to establish which populations improvements are most likely to be found in, and the specific nature of the any drug-related cognitive improvements.

CHAPTER 3

Experiment 1(a); Nine parallel versions of four memory tests: An assessment of form equivalence and the effects of practice on performance.

Introduction

In Experiments Two and Three, which are reported in later chapters, the effects of the paroxetine on healthy volunteers will be determined by comparing performance in baseline, active treatment and placebo conditions in a crossover design. This design, which measures change in cognitive performance requires multiple, equivalent test forms that have been assessed for normative performance levels and the effects of practice. Most published memory tests comprise only a single version or form. The aim of the present study was therefore to evaluate four memory tests and determine a learning curve for young healthy adults who completed the nine parallel forms of each test on nine successive occasions. The equivalence of the nine parallel forms will also be assessed.

For the type of design described, it is also important that the tests are sensitive to both improvements and impairments in performance as both directions of effect can be expected in the healthy volunteer studies proposed. Most previous SSRI studies were designed to detect cognitive impairments and the tests may not have been appropriate for the detection of potential improvements the drugs may cause. An attempt was made to develop relatively "difficult" tests i.e. those that would yield mid-range scores with healthy young adults, but would not be too difficult for use with healthy elderly volunteers. Attempts were also made to ensure that the test battery did not cause (and therefore measure) boredom and fatigue and that the tests were appropriate for the subjects being assessed. The four different tests were designed to measure a number of theoretically distinct memory functions.

Crook, Youngjohn and Larabee, (1992) attempted to overcome the problem of measuring drug-related memory change over time by developing eight parallel versions of six automated memory tests. These eight forms of the test were satisfactorily assessed for equivalence when administered on a single occasion to eight subject groups. However, as they did not administer different forms to the same subjects on successive occasions, practice effects were not established. The effects of practice on the tasks could not therefore be controlled for in repeated measures studies. Crook et al. suggested that the use of their battery would reduce the problem of performance over-estimation that occurs when a test with a single form is administered repeatedly, but they did not consider the significant practice and learning effects that may also result from the repeated administration of different parallel forms. There is already some evidence that normal memory performance will improve over repeated exposure to a memory test composed of different forms. In their assessment of the equivalence of four forms of the Selective Reminding Test, Hannay and Levin (1985) reported an improvement in the performance of students who each completed the four test forms on successive occasions. The memory performance of a placebo control group with age-associated memory impairment studied by Crook and Lakin (1991) also showed some improvement over the 12 week study period.

Assuming that repeated assessments are associated with progressive improvements in performance, one possible method of controlling for the effects of repeated testing in a within-subject psychopharmacological study would be to conduct sufficient practice trials to achieve asymptote before a treatment condition begins. Pre-baseline practice is particularly relevant when the experimental manipulation is expected to improve rather than impair performance, as improvements must be distinguished

from the predicted learning effects. The ability to assess the extent to which improvement through practice might counteract drug-related memory impairment is also important. The data from this study should provide information about the type of performance patterns expected under control conditions and the number of practice sessions that are required before performance stabilises. The nine parallel forms examined here are assumed to be sufficient to allow for pre-baseline practice in treatment studies.

The tests were designed to measure verbal recall and recognition, face-name-occupation associate learning (involving cued verbal recall), memory for visual designs and memory for spatial locations. The design of the battery reflects the assumption, based on experimental and neuropsychological evidence, that memory for different types of recently presented information is supported by dissociable verbal, visual and spatial memory systems (e.g. Mayes, 1988; McCarthy and Warrington, 1990).

The verbal memory test described here was based on the Verbal Memory test designed for use in the clinical trial (see Chapter 7). It was intended to have a high performance ceiling; for this reason the target list contains twenty unrelated words that are presented without an orienting task. The test allows immediate verbal free recall to be compared with delayed recall, which, in turn, can be compared with delayed recognition. Three separate tasks are used as they may reflect different underlying processes and so be differentially sensitive to the effects of paroxetine. For example, whilst working memory processes will contribute to immediate recall performance, delayed recall performance will predominantly reflect retrieval from a more permanent store.

A yes-no recognition task was incorporated into the test because the processes underlying recognition and recall may be distinct (see Tulving

and Flexser, 1992) and be differentially affected by drug treatments (Martin et al., 1989). Yes-no recognition memory performance is also susceptible to response bias i.e the tendency of a subject to respond either positively or negatively, especially when guessing, which can significantly alter test scores. Signal detection analysis can determine the degree of response bias, which may reflect motivational factors and therefore partly account for poor overall memory performance, particularly in clinical studies.

The Name-face-occupation associate learning task was intended to provide an ecologically valid verbal memory task that was particularly relevant to predictions concerning drug-related cognitive improvement. Crook and Lakin (1991) report that the 5HT3 antagonist, ondansetron, improved the immediate and delayed recall of face-name associates in individuals with age-associated memory impairment. The task used by Crook and Lakin (which was also examined by Crook et al., 1992) involves the video presentation of individuals introducing themselves by their first names. The individuals appear again, in a different order, and announce the name of the city that they live in. This provides a cue for the recall of the individual's first name. The task designed for the present experiment is based on the same face-cued name-recall principle except that it involves head and shoulder photographs, and the face alone is used as a cue for name and occupation recall.

The cognitive processes underlying word list recall and recognition are considered to be distinct from those underlying memory for nonverbal, visual information such as abstract designs. Evidence from neuropsychology and experimental psychology (e.g. Baddeley, 1986) supports this assumption, which dictates that a memory test battery should examine both verbal and nonverbal aspects. The extended visual retention test described here assesses visual reproduction ability. It is based upon and includes, the three original forms of the Benton Visual

Retention Test (Benton, 1974) plus a further six parallel versions. Each form contains ten geometric designs of increasing complexity, which are viewed and then drawn by the subject.

Benton (1974) describes two procedures for the test: reproduction of each design after a 10 second viewing period, and reproduction after an additional unfilled delay of 15 seconds. The delayed reproduction is reported to be the more difficult (Benton, 1974). A further study suggests that delayed reproduction provides a better measure of visual memory than immediate reproduction, which is more closely associated with perceptual motor abilities (Larrabee, Schunck, Kane and Francis, 1985).

A test of memory for spatial location was included in the test battery as there is increasing evidence for the separate processing of identity and spatial location in perception and imagery as well as memory. Evidence concerning spatial memory comes from psychopharmacology where differential drug effects on verbal and spatial memory tasks have been reported (Preston, et al., 1988; Broks, et al., 1988).

The present task is loosely based on the misplaced objects test, also included in the Crook et al. (1992) study, in which a cross-section picture of a twelve-roomed house is presented on a touch-sensitive screen. The subject distributes pictures of 20 common objects amongst the rooms (with no more than two objects in each room), and recalls the location of each object after a 40 minute delay (Crook, Youngjohn and Larrabee, 1990). The task used in the present study involves a 5 second presentation of six object pictures positioned across a 5 x 5 grid. Immediately after presentation, the subject attempts to recall each object's position on the grid and to relocate it to that position.

Method and Materials

Subjects

27 undergraduate psychology students (22 females and 5 males, aged between 18 and 40 years) at the University College of North Wales participated as subjects and received a course credit for their participation. All subjects had normal (or corrected-to-normal) vision and hearing and were volunteer members of a student subject panel.

Each subject was assessed on the nine versions of each test in a repeated measures design. The nine parallel forms of the four tests were randomly assigned an alphabetic label (A to I) and test administration order followed the alphabetic sequence. Subjects began their assessment at different points in the sequence, according to a latin square. For example, subjects 1,10 and 19 completed form A on test day 1 followed by B, C, D, E, F, G, H and I on subsequent days. Subjects 2, 11 and 20 completed form B on test day 1 followed by C, D, E, F, G, H, I and A, and so on. Thus, the results obtained on each test day had an equal number of data points from each of the parallel forms, and the results obtained with each test form were composed of an equal number of data points from each of the nine test days. This allowed form equivalence and practice effects to be assessed independently.

Subjects were tested individually for 30 minutes on nine successive week days. Testing took place in a small quiet room. In order to control for time-of-day effects on performance, each subject always attended at a specific time of day (although different subjects attended at different times of the day). Individuals were assessed by the same experimenter on each occasion and the tests were administered in the same order, as follows.

The 20 Word Memory test.

Each form of the test comprised twenty target words and an additional twenty distractor words used in the forced-choice recognition

task (see Appendix A). The words were printed on separate cards and bound in booklets in a fixed random order. The words were selected according to syllabic length and word frequency (Kucera and Francis, 1967) criteria. Word length and frequency values were balanced across each target and distractor set, and across the nine forms of the test. Obvious semantic and phonetic associations were removed.

The twenty target words were presented, one at a time, for three seconds each. The experimenter read the word aloud to the subject as it was presented. The subject recalled as many words as possible immediately after presentation and was informed that they would be asked to recall the words again at the end of the test session.

Following the administration of the remaining tests, the subject made a second attempt to recall the word list. Finally, the forced-choice recognition word booklet was presented and the subject made a yes/no response to each word, according to whether or not they recognised it as a previously presented memory test word. One point was scored for each correctly recalled or recognised word.

The Extended visual retention test.

Each form consisted of a series of ten geometric shapes arranged in order of increasing complexity. The nine forms of the test include the three original forms of the Benton Visual Retention Test (1974) as well as six new parallel versions (see Appendix A). The drawings in the additional forms were matched with the originals on numbers of lines and figures.

The test procedure followed the instructions for Administration D of the Visual Retention Test (Benton, 1974). Each design was presented for ten seconds. Presentation was followed by an unfilled delay of fifteen seconds after which the subject attempted to reproduce the design using paper and pencil. Each correctly reproduced design scored one point.

The Name-face-occupation associate learning task.

Each form of the test consisted of four portrait photographs (two men and two women) with a first name, a surname and an occupation printed below each photograph (see Appendix A). Name frequency, syllabic length and occupational status were balanced across the nine forms. Photographs of the appropriate gender were randomly assigned to the sets of verbal materials.

The photographs, with names and occupations printed below, were presented one at a time for three seconds each. The experimenter also read the names and occupation aloud. The presentation order was fixed. Recall of the names, surnames and occupations was then cued by presenting the photographs (without the name and occupation being visible to the subject) in a different random order. The entire trial was repeated until the subject was able to recall the twelve associate words in response to the correct photograph, or until three trials were completed. Subjects scored 4 points for an item (a name or the occupation) recalled appropriately on the first trial, 3 points for an item recalled on the second trial, 2 for recall on the third trial, and 1 if they failed to recall the information within three trials.

The Spatial location memory test.

The subject's task in the spatial location memory test was to recall the positions of six object pictures that had been briefly presented on a 5x5 grid (see Appendix A). Spatial memory was assessed in terms of the number of items whose position was correctly recalled. The procedure was controlled by a Hypercard program run on an Apple Macintosh computer. This was the only test in the study that did not have nine different forms. The single version of the program presented the same set of 36 pictures (as six fixed subsets of six pictures, occurring in the same order) on every testing session in the study. On each trial, however, the

programme generated a random set of to-be-recalled grid positions. Thus, six object pictures were presented on each of six trials and the program randomly generated a set of six picture locations for each trial at the time of testing.

A 5x5 square grid occupied the larger part of the display screen. At the beginning of each trial, the object pictures were displayed to the right of the grid until the subject initiated the trial with a key press. The six pictures were then presented simultaneously in randomly selected grid positions for 5 seconds. The pictures returned to their positions to the right of the grid. The subject's task was to relocate each picture (using the computer mouse to move the icon) to its presentation position on the grid. The subject terminated the trial when she or he was satisfied with the recalled positions. Performance feedback was provided at the end of each trial. Subjects scored a point for each correctly positioned picture giving a maximum possible total score for each test session of thirty six .

Results

Practice effects and form equivalence were assessed in single factor repeated measures analyses of variance. Data organised by test day reflected practice effects whilst data organised by test form reflected form differences. Where an ANOVA revealed a significant day or form effect, Tukey Honestly Significant Difference (HSD) comparisons were performed to determine where the significant differences occurred. The mean scores for all measures in the study over the nine test days (Table 3.1) and the mean score obtained for each test form used in the study (Table 3.2) are presented in Appendix B. A summary table of the ANOVAs is also in Appendix B (Tables 3.3 and 3.4)

The 20 Word Memory test

Analyses were performed on immediate recall scores, delayed recall, correct positive recognition responses and correct negative recognition responses. Scores represented the number of correctly recalled or recognised target words, out of a possible twenty.

Immediate recall

Figure 3.1. presents the mean (and standard error) values obtained for immediate verbal recall on each of the nine test days. Overall mean immediate recall was 9.8 words (out of twenty targets). The graph indicates a considerable decline in mean recall performance on day 2 compared with day 1. However, performance steadily improved over the subsequent four days of the study. There was no improvement over the final five days of the study; the asymptote was slightly higher than the recall performance recorded on day 1. The analysis of variance revealed a significant test day effect ($F = 3.92$, $df = 8,208$, $p<0.001$) and Tukey HSD comparisons indicated that day 2 differed significantly from all of days 5, 6, 7, 8 and 9.

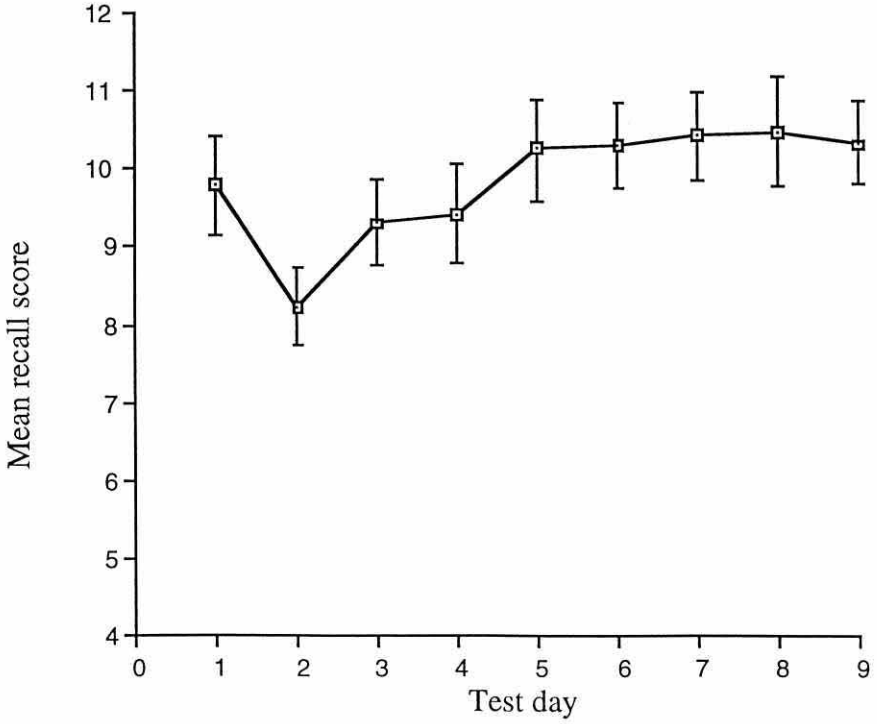

Figure 3.1. Mean immediate recall scores over nine test days

Delayed recall

Figure 3.2. presents the mean (and standard error) values obtained for delayed verbal recall on each of the nine test days. Figure 3.2. presents a similar pattern to Figure 3.1. On average, the subjects recalled three items less on the delayed recall task than on immediate recall (mean = 6.4 words), and this discrepancy was fairly consistent over the study period. The mean delayed recall scores were also more variable in the second half of the study than the immediate recall scores were. ANOVA revealed a smaller, although significant test day effect on delayed recall ($F = 1.99$, $df = 8,208$, $p < .05$). Tukey HSD comparisons indicated that there was a significant difference between scores obtained on days 2 and 8.

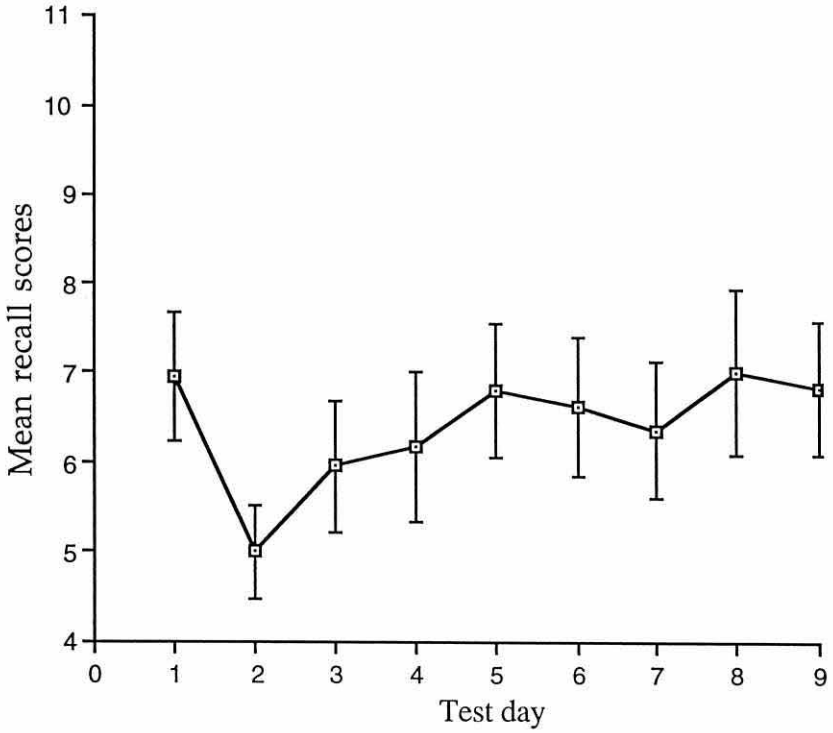

Figure 3.2. Mean delayed recall scores over the nine test days.

Recognition memory

Analysis of the correct positive recognition memory scores indicated no significant differences between test days. The overall mean correct recognition score was between 14 and 15 items, confirming that the recognition performance was considerably better than recall performance. There were, however, significant test day differences in the correct negative response data ($F = 2.61$, $df = 8,208$, $p < 0.01$). The pattern of mean (and standard error) values shown in Figure 3.3. is similar to the profile obtained for the immediate and delayed free recall scores. Tukey HSD comparisons indicated that there were significant differences between scores obtained on day 2 compared with days 7 and 8.

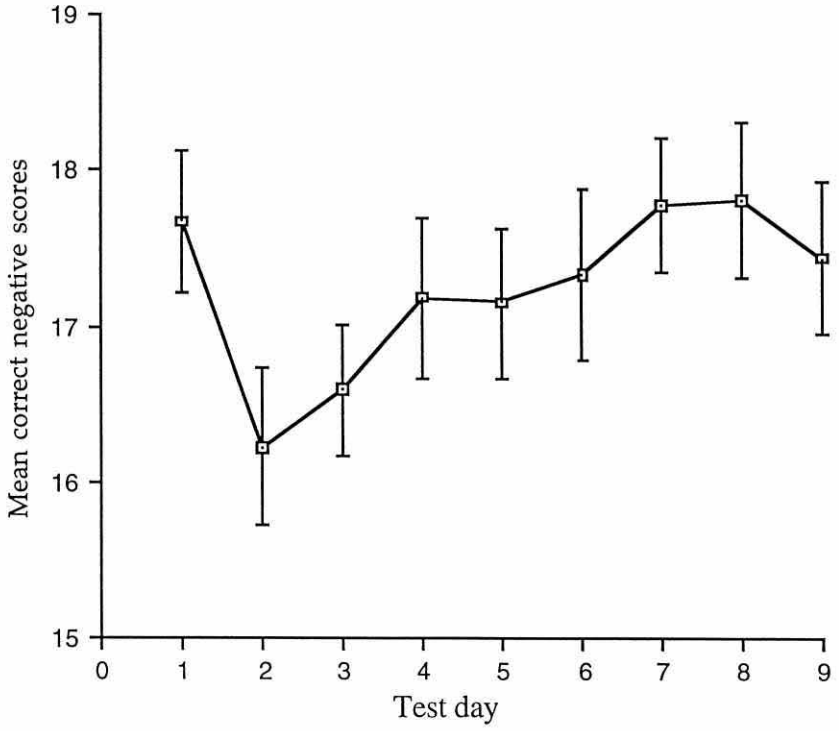

Figure 3.3. Mean correct negative responses over nine test days.

Test form equivalence

ANOVA revealed a significant test form effect on the immediate recall measure ($F = 2.12$, $df = 8, 208$, $p < .05$). There were significant differences between the immediate recall scores obtained with form A and

form D. The ANOVA performed with either form A or form D removed from the data was nonsignificant (with form A removed: F = 1.55, df = 7,182, p = 0.15; with form D removed: F = 1.46, df = 7,182, p =0.18). There were no test form effects on the delayed recall measure or on either of the recognition memory measures.

The Extended Visual Retention Test

Figure 3.4. presents the mean number of designs correctly reproduced out of a possible ten over the nine test days. The bars represent standard errors. The overall mean correct score was 8.35. There was a clear improvement in mean performance over the test days. ANOVA revealed significant test day differences (F = 4.65, df = 8,208, p = .0001), and Tukey HSD comparisons revealed significant differences between day 1 and days 2, 4, 5, 6, 7, 8 and 9 ($p<0.05$). There were no significant form differences in the visual retention test scores.

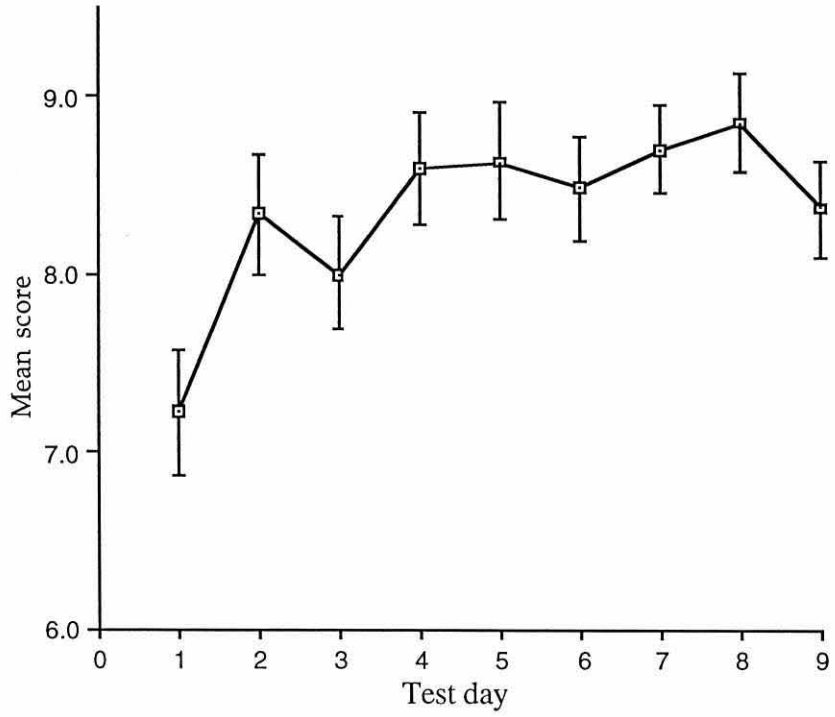

Figure 3.4. Mean visual retention scores over the nine test days

The Name-face-occupation associate learning test

Figure 3.5. presents the mean (and standard error) values obtained with the name-face-occupation associate learning test over the nine test days. The overall mean score was 41.8; possible scores ranged from 12 to 48. There was a decline in performance over the first three test days, followed by a steady improvement and then a plateau. However, the highest scores attained overall were produced on test day 1. Analysis of variance indicated a significant test day effect ($F = 2.28$, $df = 8,208$, $p < .05$), and Tukey HSD comparisons revealed significant differences between the test days 1 and 3.

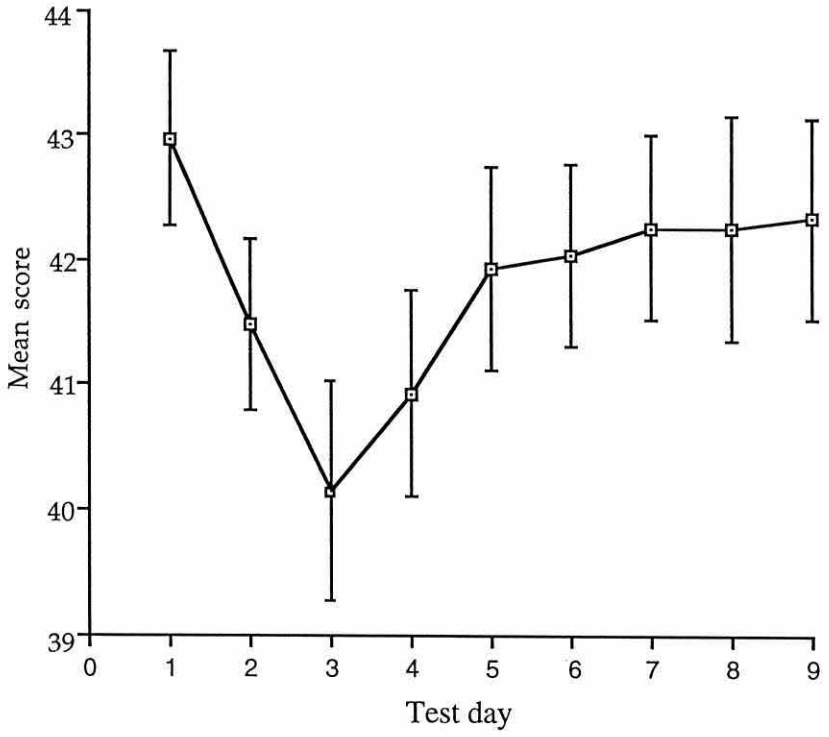

Figure 3.5. Mean name-face-occupation associate memory scores over the nine test days.

There were significant form effects on the name-face-occupation test scores ($F=3.74$, $df = 8,208$, $p < .001$). Scores obtained with Form D were significantly different from those obtained with Form G and with Form F; Form G scores were also significantly different from Form A scores. Table

3.2 (in Appendix B) indicates that Form D was associated with the lowest mean score of the sample, whilst Form G was associated with the highest mean scores. Consistent with this, it was only after data from both Form D and Form G were excluded from the sample that the test form effect became nonsignificant (F = 1.89, df = 6,156, p = .09). Thus, scores from the remaining test forms did not differ significantly from each other.

The Spatial location memory test

The overall mean spatial location memory score was 22.8; possible scores ranged from zero to 36. Figure 3.6. presents the mean (and standard error) scores obtained with the spatial location memory test over the nine test days and indicates an initial steady improvement in performance, followed by a further more dramatic improvement on test days 8 and 9. Analysis of variance indicated that significant differences existed between test days (F = 9.96, df = 8,208,p = .0001). Tukey HSD comparisons revealed significant differences between the test day 1 and days 3, 4, 5, 6, 7, 8, and 9; between test day 2 and days 8 and 9; and between days 3 and

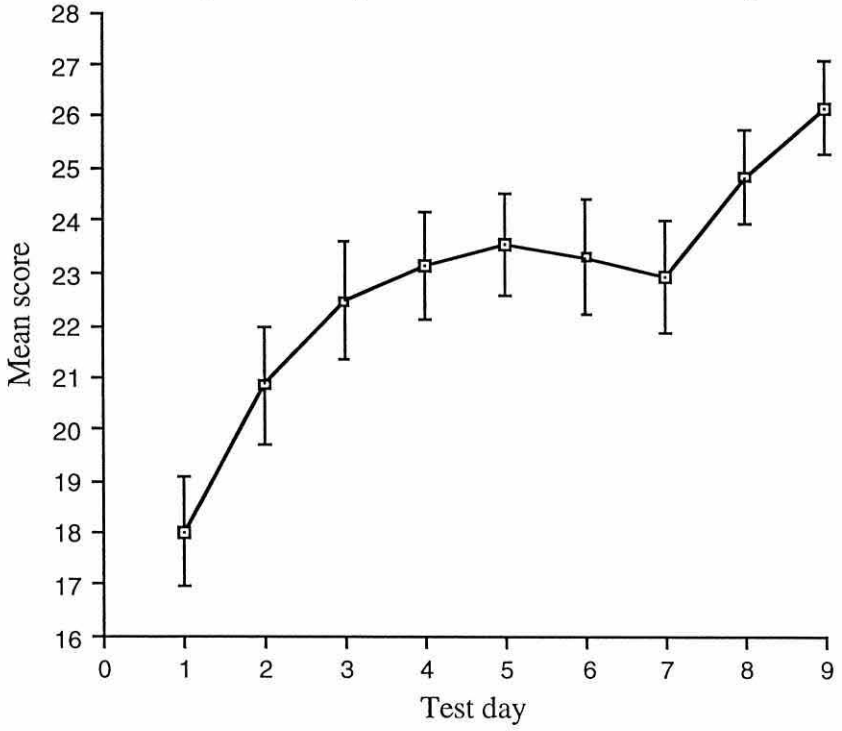

Figure 3.6. Mean spatial location memory scores over nine test days.

Scores from the spatial location memory test could not be examined for form differences as the location stimuli were randomly generated by the computer at the time of testing. Thus, the data were collected using 243 (9 test days x 27 subjects) different versions of the test. Although some stimulus sets would clearly be easier to recall than others, it was assumed that the range of difficulty would be equally distributed over the nine test days. This assumption was tested by taking the 243 versions of the spatial location data and randomly dividing them into nine groupings within the constraint that each grouping consisted of an equal number of data points from each test day and from each subject. A one-way ANOVA was then carried out. This indicated that with test day effects and subject variability controlled for, there were no significant differences between the groups of spatial memory scores ($F = 0.47$, $df = 8,234$, $p = 0.88$). Thus, task difficulty was assumed to be evenly distributed across the sample.

Discussion

Test Form Equivalence

The significant test form effect on immediate recall was caused by the additive influence of two outlying test forms. Form A of the test produced the highest scores whilst Form D produced the lowest. This pattern also occurred in the delayed recall mean scores although these differences were not significant. When data associated with either of these forms was removed from the sample, the size of the test form differences was reduced to a less than significant level. Thus, if the remaining eight verbal memory test forms (either A or D excluded) produced significantly different scores in future experimental studies, the effect could be assumed not to reflect differences in test form difficulty.

There were no significant form differences in the visual retention test data, suggesting that controlling for the number of lines and figures in each design is sufficient to produce materials of equivalent difficulty.

There was a large effect on test form on the name-face-occupation task which could only be reduced to a nonsignificant level by the exclusion of scores associated with both Forms D and G from the dataset. Thus, equivalence can be assumed only for the remaining seven forms. This result suggests that the control of item memorability using frequency and syllabic length variables was more effective for the verbal memory test than it was for the name recall task. This may reflect variation in face attributes and in the name-face-occupation relationships that were not accounted for here.

Practice effects

In contrast to the assumption that memory test scores would progressively improve from the the beginning of the study, three of the 20-word verbal memory measures showed a level of performance on day 1 that was equal to, or only slightly lower than the level attained by the end of the study. This was because the improvement that occurred over the study period began only after the scores had declined dramatically on day 2. Immediate recall, delayed recall and the correct negative recognition measures all showed a large decline in performance between day 1 and day 2, followed by a steady improvement, with an asymptote achieved between day 5 and day 7. This pattern was seen most clearly in the immediate recall measure (Figure 3.1.), where practice with encoding strategies such as semantic clustering and imagery is likely to have improved performance. The decline in performance on day 2 may reflect proactive interference from the previous day's list and the subsequent improvement may have resulted from practice and improved mnemonic strategies counteracting the interference effects. Relatively high

motivation is unlikely to explain the superior day 1 scores as other tests did not show the same pattern.

In contrast to the pattern shown by the recall and correct negative recognition measures, correct positive recognition scores were unaffected by practice and showed, if anything, a modest decline over the test sessions. This may be partly explained by a progressive reduction in the number of positive (correct and incorrect) recognition responses made on each study day; fewer positive responses would be likely to produce fewer correct positive responses. The observed tendency to make fewer positive responses over time may be explained in terms of an accumulation of interference from an increasingly large pool of previously presented targets. Subjects might have recognised a word as an item that had been presented within the study context, but have failed to identify it as a target from the current test session. The ability to positively identify distractors may have improved with practice because this task did not become inherently more difficult over time. When shown a distractor, the subject only had to decide whether or not she or he had seen the word in the context of the study before.

The name-face-occupation associate learning test, which is also a verbal memory task, showed a similar sharp initial decline in performance that extended to day 3. Again, proactive interference is the most likely explanation of this trend. Following a recovery from the initial decline in performance, the mean face-name-occupation scores remained stable over the final five test sessions. However, the final performance level was still lower than the mean score achieved on day 1. Interference may have been more powerful here than in the 20-word test, or at least less vulnerable to the positive effects of practice, possibly because mnemonic strategies could be less easily employed to remember people's names.

Data from the Extended Visual Retention Test showed a clear practice effect, with performance improving significantly over the first four days and reaching asymptote on day 4. Performance on the visual memory test was therefore not vulnerable to proactive interference as the verbal recall appeared to be. These visual retention data most closely approximated the expected learning curve pattern, and inspection of the raw data suggests that although the performance levels achieved by young adults were high, 40% of the scores attained were below 9 (out of ten) and were therefore not at ceiling.

The sharp improvement in spatial location memory performance that followed a gradual seven day learning period may be explained by an increasing familiarity with the sets of pictured objects that were presented on every testing occasion. Many subjects reported the development of strategies that involved giving a short verbal label to each of the thirty-six pictures and associating the verbal label with a location identity (either a grid number or an image of the grid). The capacity to use such a strategy for six pictures within a five second exposure would depend critically on being able to automatically apply a label to each object, which would require familiarity with the stimuli and practice. Thus, there may have been a second learning phase, in which increased stimulus familiarity and labelling speed allowed such mnemonic strategies to improve performance.

Given the brief presentation period involved in this task, it is assumed that the information required by the subject to successfully indicate the target positions was held in one or both storage components of working memory i.e. the articulatory loop and the visuo-spatial sketchpad (Baddeley, 1986). Performance on the spatial location task was therefore unlikely to be affected by interference from spatial locations previously associated with the object. The late improvement in performance obtained

here may present a problem if this task is to be used in further repeated measures studies, as scores cannot be assumed to have stabilised after a number of test sessions. One possible solution would be to limit the number of measurements taken to a maximum of seven and to prevent the late improvement occurring at all.

The patterns of change varied across the four tests in the study. There was a particularly striking difference between performance on verbal and non-verbal tests. The verbal tests were associated with an initial decline in performance, which was attributed to proactive interference. Scores on the non-verbal tests improved progressively over the study period, although the spatial location memory task showed a further large improvement over the last three days. These differences indicate that specific assumptions concerning the size and direction of practice effects for other tests would not be justified without some investigation. Repeated memory test assessment gives rise to unpredictable performance changes that must be accounted for in the interpretation of drug related effects.

In summary, these results demonstrate that repeated cognitive measurement significantly alters episodic memory performance; performance can therefore be assumed to improve independent of a drug intervention. Baseline practice sessions would overcome this problem to some degree but as the point at which asymptote is reached on the tests is unpredictable, additional measures would be required to distinguish between drug effects and practice-related changes on these tests.

Attempts were made to overcome these methodological problems when designing Experiments Two and Three. In Experiment Two subjects spent the first week of the study on placebo treatment to provide practice on the tests before the drug intervention. Their performance was also compared with a group of age and sex matched subjects receiving a

placebo pill over the two weeks. The data presented here indicating the average direction and magnitude of memory performance change over nine test sessions in healthy, young adults will also provide a useful comparison.

Experiment One(b): Nine parallel versions of five memory tests; a study to investigate the effects of practice on performance in the elderly.

Introduction

As the test battery described and evaluated described above was designed for use with both young and elderly healthy volunteers, a smaller scale study was carried out to assess the effects of practice on the tasks in healthy elderly subjects. It was predicted that elderly subjects would not perform as well as the young subjects as they would have age-related cognitive deficits. A secondary aim was to ensure that the elderly subjects were not performing at floor level on any of the tasks. Two additional measures were evaluated for practice effects in the elderly subjects: the digit span test (Wechsler, 1981) and Speed of Comprehension test (Baddeley, 1992). As the test battery was intended for repeated use in a single case design drug study with elderly subjects, the extended visual retention task was removed from the test battery due to the length of time it takes to administer (approximately 10 minutes). It was hoped that a battery of short varied tasks taking 30 minutes to complete would minimise the effects of fatigue and boredom.

Method

Subjects

Four subjects, three female and one male aged between 55 and 75 years were tested. All subjects had normal or corrected-to-normal vision and hearing and were volunteers.

Study Design

A repeated measures design was used with each subject being assessed on all nine versions of the tests. The nine parallel versions of the five tests were randomly assigned an alphabetic label (A-I) and test

administration followed the alphabetic sequence. Subjects began their assessment at different points in the sequence in order to control for order effects. For example subject 1 started on A, subject 2 on B, subject 3 on C and subject 4 on D.

Test materials and Procedure

Subjects were seen individually at home in a quiet room at the same time each day (in order to control for effects of time of day), on nine successive weekdays. The procedure for each test session was as the same as for Experiment One (a), except that instead of the extended visual retention test subjects completed the digit span test and the Speed of Comprehension test. The 20 Word Verbal Memory Test, the Name-face-occupation associate learning task and the spatial location memory test are described above.

The Digit-span test

This task was based on the WAIS (Welschler Adult Intelligence Score-Revised, Wechsler, 1981) procedure and is described in detail in Chapter 7.

Speed of Comprehension Test

This pen and pencil task, based on a task devised by Baddeley (1992) is described in detail in Chapter 7. The original task is made up of four versions ot the test each made up of 100 sentences. As multiple versions of the task were required for use in drug studies, the original versions were divided up to form nine tests of 25 sentences. In the original version of the test subjects are required to process as many sentences as possible in two minutes. In this study the measure taken was the time taken to process 25 sentences.

Results and Discussion

The effects of practice were assessed by presenting individual data and mean group data on simple line graphs. Statistical analyses were not performed as the sample size was so small.

The 20 word memory test

Figures 3.7. and 3.8. show that the mean number of items recalled in the immediate recall and delayed recall conditions of the 20 word memory test initially followed a similar pattern to that of the young healthy volunteers. After a decline in performance on day 2 there was a gradual improvement over the subsequent four or five days. The 'dip' in performance on day 2 is likely to be due to proactive interference reducing the beneficial effects of practice. After a peak on day 4 immediate recall performance declined only to reach an even higher level on day 8. This second increase in scores could be the result of a secondary learning phase. Delayed recall scores on the other hand peaked on day 4 and then declined to a lower level on day 9 than on day 1. Any early effects of practice on the task may not have been sustained.

The mean number of items recalled ranged from 5-8 in the immediate recall condition, 1-3 in the delayed recall condition and 14-18 in the recognition condition. These scores were considerably lower than those obtained by the students in immediate recall (8-10) and delayed recall (5-7) with recognition being much the same as the students' mean scores. The scores in the delayed recall condition were close to floor level which suggests that the task may be too difficult for elderly subjects.

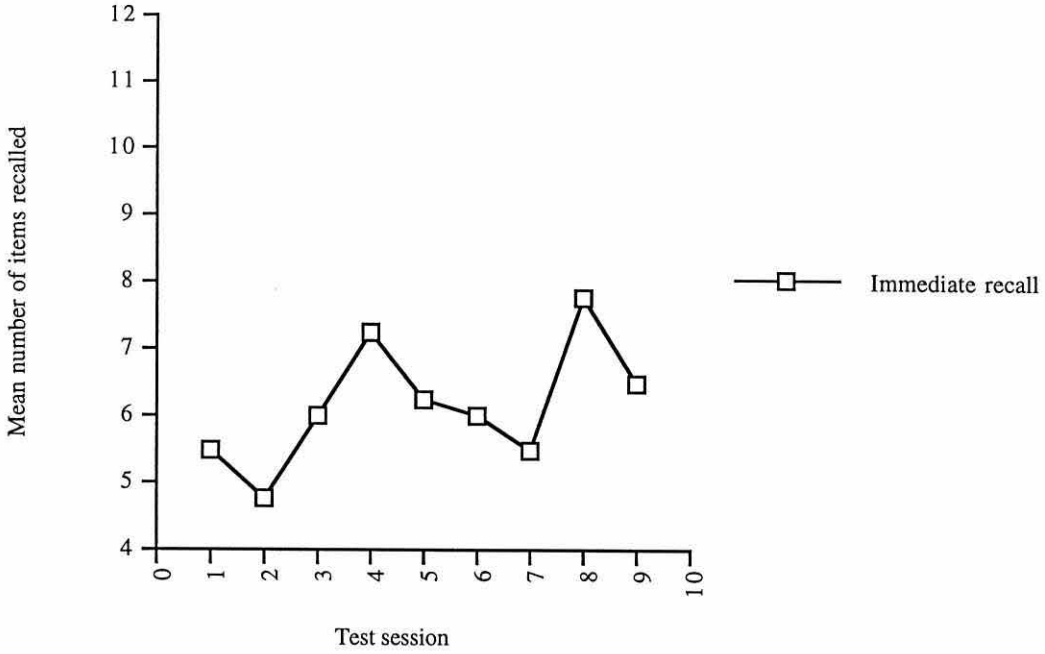

Figure 3.7. Mean immediate recall scores of elderly subjects over nine test days

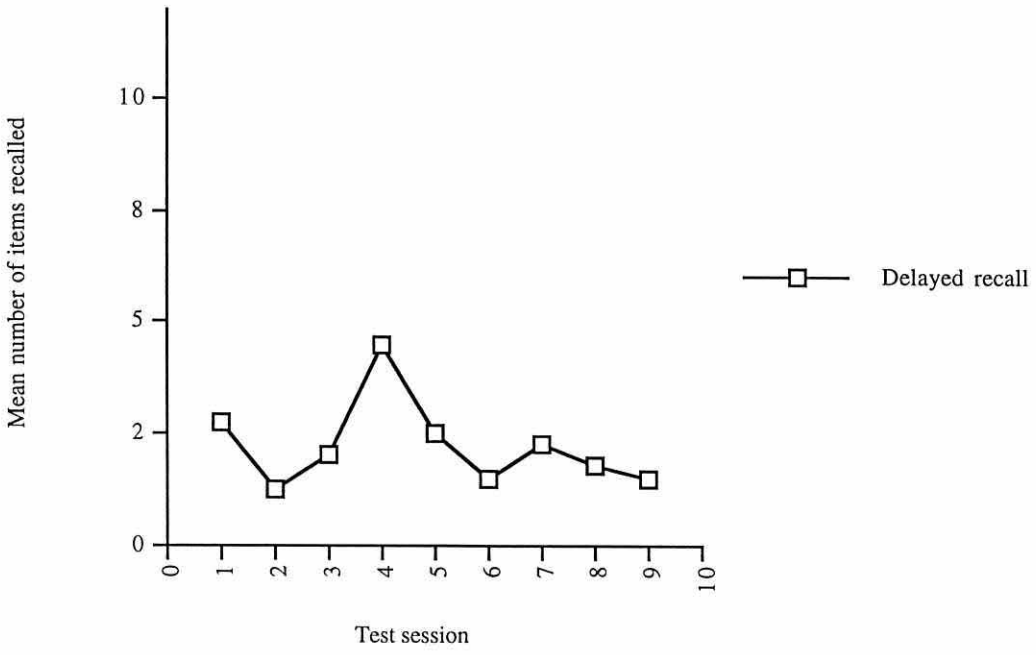

Figure 3.8. Mean delayed recall scores of elderly subjects over nine test days

Correct negatives scores showed a gradual improvement over the first five days which was maintained until day nine when there was a sharp decline in performance. The individual scores show this was mainly the result of subject three's performance which seems to be particularly poor on the last test day. Both the number of correct positive recognition scores and the number of 'yes' responses declined over the nine days which suggests that they were unaffected by practice.

Table 3.1. Mean correct positive and correct negative recognition scores

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Correc + ives	13.3	14.3	13.5	12.8	12.0	13.5	12.0	14.3	12.3
Correc - ives	14.5	15.8	15.8	17.0	18.0	17.0	16.3	17.5	15.3

The Name-face-occupation associate learning test.

The mean scores of the name-face-occupation associate learning task showed an improvement on day 2 compared to day 1 (37 items correct compared with 33 on day one) followed by a gradual decline in performance which picked up on day eight and nine. Initial familiarisation with the task may have improved performance on day 2, but no subsequent learning occured. The individual data indicated no clearly defined effects of practice and though performance was generally better on the first four days, there was no evidence of practice effects over the next five study days. This contrasts with the student data where an initial 'dip' in performance was followed by stable scores over the next five sessions. As with the 20 Word Memory test, the range of Name-face-occupation scores scores was much lower than the students'; 31-37 compared with 40 -43 in the students.

Table 3.2. Mean scores on the Name-face-occupation assocaite learning test

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Mean	32.8	36.8	35.0	34.8	33.3	32.3	31.3	32.5	36.3

The Spatial location memory test.

Data from the spatial location memory test indicated clear practice effects after a decline in performance on day 2. Performance peaked on day 4 and then plateaued from day 5 onwards. Thus, the pattern of performance in the elderly differed considerably from the young subjects. The performance of the students improved gradually up to day 7 and then rose sharply on day 8 (the final test day) indicating the possibility of a second learning phase resulting from familiarity with the pictures and the development of complex mnemonic strategies. There was no evidence of this in the elderly subjects and none of them reported using any particular strategy on the task. As with the other tasks their range of scores was much lower than the students';-8-18 compared with 18-26 in the students.

Table 3.3. Mean scores on the spatial location memory test.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Mean	10	8	12	17	12.5	14.3	14.8	15.0

The Digit span test

Performance on the forward digit span task improved from day 1 to day 2 but there was no evidence of further practice-related improvements. Backward digit span appears to have been more susceptible to the effects of practice as the mean scores showed a sharp improvement on day 2, followed by a more gradual increase in scores up to day 5. However the individual data indicate that only the performance of subject 4 improved, while the other 3 subjects' scores fluctuated between 6 and 8, with two of them ending on day 9 with lower scores than on day 1.

Table 3.4. Mean forward and backward digit span scores

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Digit span-F	6.3	7.8	7.5	7.0	7.3	6.8	6.8	7.3	6.5
Digits span-B	5.8	6.5	6.0	6.3	6.8	6.8	7.0	7.0	6.3

Speed of Comprehension test

The mean scores of the Speed of Comprehension test produced a classic learning curve. An asymptote was reached around day 4. However, the individual scores illustrated that in two of the subjects the improvement between day 1 and 4 was quite dramatic while in the other two subjects it was barely evident.

Table 3.5. Mean scores on the Speed of Comprehension test.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Mean	62	48.5	45.0	43.3	43.5	40.3	39.5	41.0	41.0

Summary and Conclusions

Although data from such a small number of subjects is clearly less reliable than a larger group, the results of this study indicate that elderly subjects' performance improved with practice over the nine testing sessions. As with the students, there were considerable improvements on the majority of the tasks between day two and day five. In the case of the Spatial location memory test and the Speed of Comprehension test asymptote appears to be reached around this point. However, on the immediate recall condition of the 20 Word Memory test initial learning effects did not appear to stabilise after day 4, and considerable fluctuations were evident over subsequent test days. The digit span and the Name-face-occupation associate learning tasks were unaffected by practice after day 2. The scores of the elderly subjects were not as high as the young subjects, although there was no evidence of them performing at floor level on any of the tasks.

In conclusion, the effects of practice on the tests in the test battery were not as pronounced in elderly subjects as with younger subjects. However they were still very much in evidence and must be taken into

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account when designing drug studies and deciding how many pre-drug practice sessions are necessary.

CHAPTER 4

Experiment Two; The effects of the SSRI, paroxetine, on selective attention, memory, vigilance and arousal in young healthy volunteers.

Introduction

Research into the psychopharmacological effects of the SSRIs in young healthy volunteers has shown that they have a general alerting effect as measured by the critical flicker fusion threshold (CFFT) (Kerr et al., 1991). The primary aim of the present experiment was to explore the effects of SSRI-induced cognitive arousal on selective attention processes. More specifically, subjects' ability to inhibit the representations of previously ignored stimuli will be explored. A secondary aim was to examine the effects of paroxetine on various measures of memory, mood and attention in young healthy adults.

As reviewed in Chapter 2, there is evidence that the SSRIs have a cortical arousing effect that leads to improved performance on some measures of attention and arousal. For example Kerr et al., (1991) reported raised CFFTs in response to acute doses of paroxetine, sertraline and zimeldine. An acute dose of zimeldine slightly improved performance on a continuous performance task involving digit identification and weakly antagonised the effects of alcohol (Linnoila et al., 1983). In another study, an acute dose of SSRI, fluvoxamine produced a significant increase in CFFT, and improvements on a variety of cognitive and psychomotor tasks (Saletu et al., 1980). Furthermore, Netter (1986) reported that an acute dose of fluvoxamine and fluoxetine raised CFFT while a chronic dose (one week) of fluvoxamine had no effect on CFFT.

It can be predicted from the evidence described above that paroxetine will increase cortical arousal in healthy volunteers, and by so doing may enhance performance on other cognitive measures. To test this

prediction, a battery of tests was compiled which included a variety of attentional tasks that may be sensitive to the activating effects of paroxetine e.g. the Stroop task and the Continuous Attention Task. However, one healthy volunteer study found that paroxetine had no measurable effect on CFFT, tapping rate or a two-choice reaction time task, nor did it reverse deficits from alcohol or sedative drug treatment (Cooper et al., 1989).

The primary aim of the study was to determine whether the predicted increase in cortical arousal resulting from paroxetine treatment would increase selective attention and inhibition. To date no studies have assessed the effects of psychotropic medication on subjects' ability to inhibit representations of previously presented stimuli. The present experiment used a slightly simplified version of the spatial localisation task used to measure selective attentional processes described in detail in Chapter 1. The task involves repeated trials, each with a prime and probe display. In the probe display the colour cue is presented simultaneously with the probe. Three priming conditions are used rather than the seven used by Tipper et al. (1994); location (L), colour (C) and location-colour (LC), (Identity was not included as X shapes are used as the stimuli). In the L condition the target stimulus and the ignored distractor from the prime display share location, but not colour characteristics. In the C condition the prime target and the distractor share colour, but not location characteristics, while in the LC condition the target stimulus and the ignored distractor from the prime display share both colour and location characteristics. In the control condition the probe target stimulus does not share either location or colour with the prime distractor.

Evidence from animal studies (e.g. Flood and Cherkin, 1987), and studies carried out on healthy volunteers with alcohol induced cognitive deficits (Weingartner et al, 1983) have shown that the some SSRIs have memory enhancing properties. A measure of verbal memory was also

therefore included in the test battery. It is hypothesised that enhanced verbal memory scores may also be mediated by the cortical activation produced by paroxetine.

Method

Subjects

Three healthy female and six healthy male volunteers aged 21-40 years participated in the study. They were approximately matched on age and educational background with subjects in a comparison group. Experimental subjects underwent a full medical examination and gave written consent before entering the study. None of the experimental or control subjects were taking medication that was likely to interfere with their cognitive function. The subjects were paid £2.50 for each hour of testing. Approval for the study was obtained from the Gwynedd Health Authority Ethics Committee and the School of Psychology Ethics Committee.

Design

A single blind, placebo-controlled within-subjects design, with an independent comparison group was employed. All subjects in the experimental group took a placebo tablet each morning for seven days, followed by 20 mg of paroxetine on the subsequent seven mornings. As performance on the negative priming task and 20 Word Memory test (described below) are susceptible to practice effects (see Tipper and Watson, unpublished study and Watson, Pasteur, Hughes and Healy, 1994), the experimental subjects all received placebo tablets during the first week to provide the opportunity for baseline practice before the drug intervention. Any changes in performance during week two could therefore be more reliably attributed to the effect of paroxetine, rather than the effects of practice.

Subjects in the comparison group did not take any tablets. Both groups of subjects were tested on days 0, 1, 3 and 6 of both weeks at a consistent time each day to control for time of day effects.

Test materials and procedure

The test battery was made up of four measures of attention, a measure of episodic memory and a subjective mood measure. The 20 Word Verbal Memory test was described in Chapter 3.

Spatial Localisation Negative Priming Task

This task was carried out on a IBM type personal computer with a colour monitor. Subjects sat approximately 80 cm from the screen and made their responses using a Kraft KC30 joystick interfaced to the computer via a standard game port. Response times were computed using the method published by Bovens and Brysbaert (1990).

The screen display had four boxes (see Figure 4.1 in Appendix A). Subjects were instructed that a small coloured square would appear in the centre of the screen during each of the two displays that occur in each trial (prime and probe). The colour of this square would indicate the colour of a simultaneously presented target X which would appear in one of the four boxes. A distractor X of another colour would appear in another box. The subject was required to indicate the location of the matching coloured target X by making a spatially compatible movement with the joystick i.e. up, down, left or right. Subjects were told to respond as quickly and accurately as possible. A brief click was produced after each joystick response to indicate to the subject that their response had been recorded. A louder beep indicated an incorrect response.

Subjects began the session with practice trials in which they were required to complete at least three correct responses in each condition. They then completed 5 blocks of 50 trials with 30 second rest periods

between each block. Each trial comprised a prime and a probe display. Response times and errors were recorded automatically.

The Stroop Test

The Stroop test procedure had two components, a colour naming control task and an interference task. The task is described in detail in Chapter 7.

Continuous Attention Test

The Continuous Attention task is part of an Automated Psychological Test Programme (version 3.0.a) (Tiplady, 1992). It is a non-verbal development of the Continuous Performance Task and involves the brief presentation (100 msec.) of a series of 3x3 white-on-black random block patterns. The subjects task was to respond with a key press whenever two consecutive block patterns were identical. Identical patterns occurred once within every block of six trials, of which there were 40. The block patterns were presented at slightly irregular intervals (1-3 seconds) to prevent a regular anticipatory orientation of attention to the display.

Critical Flicker Fusion Threshold (CFFT).

Cortical arousal was assessed using the critical flicker fusion test of the Leeds Psychomotor Tester. The subject's task was to indicate the frequency at which he or she detected steadiness or fusion in a set of four previously flickering light emitting diodes (ascending frequency) and the frequency he or she detected flickering in lights that were previously steady (descending frequency). The mean of three flicker-to-fusion and three fusion-to-flicker thresholds was determined for each test session.

Subjective Mood Assessment.

Subjective mood was assessed using Visual Analogue Scales (Bond and Lader, 1974). The following dimensions were represented on 100 mm horizontal lines that the subjects marked to indicate how they felt at the

time: alert-drowsy, calm - excited, muzzy - clear headed, tense - relaxed, attentive - dreamy and interested - bored.

The Oxford -Liverpool Inventory of Feelings and Experiences

The schizotypy scores of the two groups were assessed using the Oxford-Liverpool Inventory of Feelings and Experiences (Mason, Claridge and Jackson, in press) as schizotypy has been found to affect negative priming performance (Watson and Tipper, unpublished study). The questionnaire comprised four scales containing items relating to the following scales; unusual experiences, cognitive disorganisation, introvertive anhedonia and impulsive non-conformity. Also included are a scale containing items from the schizotypal personality STA scale and a lie scale.

Results

A mixed repeated measures ANOVA with one between-subject factor and four within-subject factors was used to analyse the negative priming reaction time data. The between-subject factor was group (experimental vs comparison) while the within-subject factors were week (week 1 vs week 2), day (0, 1, 3, 6), colour and location. Each of the latter two priming condition factors had two levels, as the probe target item either shared or did not share that particular property with the prime distractor. The control condition was therefore described as location minus, colour minus, whereas the LC condition was location plus, colour plus. The size of the negative priming effect and all the other measures were analysed using a one between-subject and two within-subject factor repeated measures ANOVA in which the between-subject factor was the group and the within-subject factors were day and week. For a summary table of the ANOVAs see Table 4.1 in Appendix B. Scores on the Oxford-Liverpool Inventory of Feelings and Experiences in the two groups were compared using an unrelated t-test.

Spatial Localisation Task

The results of the spatial localisation task were examined in three stages. Firstly the overall response times on the task (irrespective of the negative priming condition) were analysed to determine whether paroxetine affected overall response speed. Figure 4.2 shows that the response times of the subjects in the experimental group were slower than those of the comparison group in week two with the most pronounced speed difference being on the last day of the study. Significant study week ($F=43.72$, $df=1,16$ $p<0.01$), study day ($F=26.81$, $df=3,48$ $p<0.01$) and study week by study day interaction ($F=9.26$, $df=3,48$ $p<0.01$) were found when the response times were analysed.

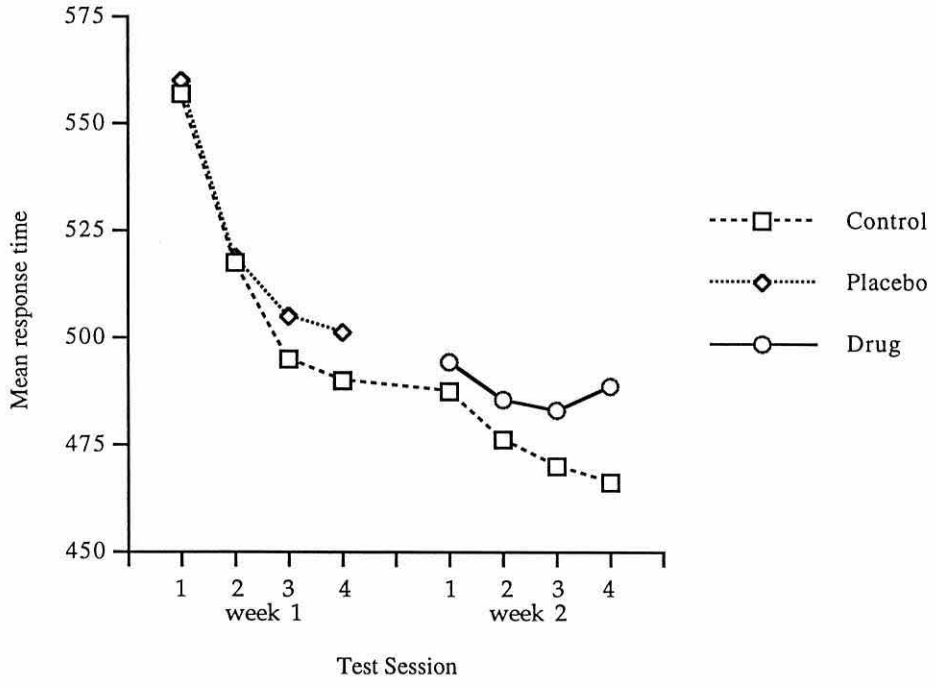


Figure 4.2. Mean response times on the negative priming spatial localisation task

Negative priming was then assessed by analysing probe display response times across the four negative conditions (L-C-, L+C-, L-C+ , L+C+). In this analysis negative priming was assessed by comparing L- conditions with L+ conditions and by comparing C- conditions with C+

conditions. These comparisons represent location and colour negative priming respectively. There was no significant colour effect. The location by colour interaction, which has been interpreted as a marker for the operation of perceptual review processes (Milliken et al., 1994), was also non-significant. Significant location, ($F=75.9$, $df=1,16$ $p<0.01$), study week by location ($F=11.26$, $df=1,16$ $p<0.01$) and study week by study day by location ($F=3.4$, $df=3,48$ $p<0.05$) effects were found.

The results of the spatial localisation task were also analysed more specifically in terms of the variations in the negative priming effect size. The three negative priming effect measures (L, C, and LC) were obtained by subtracting response time values for each of the three negative priming conditions from the control condition response times. No significant group x day x week interactions were found in the analysis of the colour negative priming effect, ($F=0.68$, $df=3,48$ $p=0.58$), the analysis of the location negative priming effect ($F=0.37$, $df=3,48$ $p=0.78$), or the analysis of the LC negative priming effect ($F=0.61$, $df=3,48$ $p=0.6$). Figure 4.3. shows that the location priming effect gradually decreased over the two weeks in both groups of subjects. The location analysis produced significant study day ($F=5.45$, $df=3,48$ $p<0.01$) and study week ($F=13.29$. $df=1,16$ $p<0.01$) effects. The two subject groups showed a similar, though less marked decrease in the LC effect over the fortnight (Figure 4.4). However the pattern of priming effects produced by colour alone were quite different in the two groups (Figure 4.5.). The experimental group data showed positive priming effects in both the placebo and drug week on some, but not all study days. The priming effects produced by the comparison group are much smaller and almost exclusively negative. No week x group interactions were significant in any of the priming conditions.

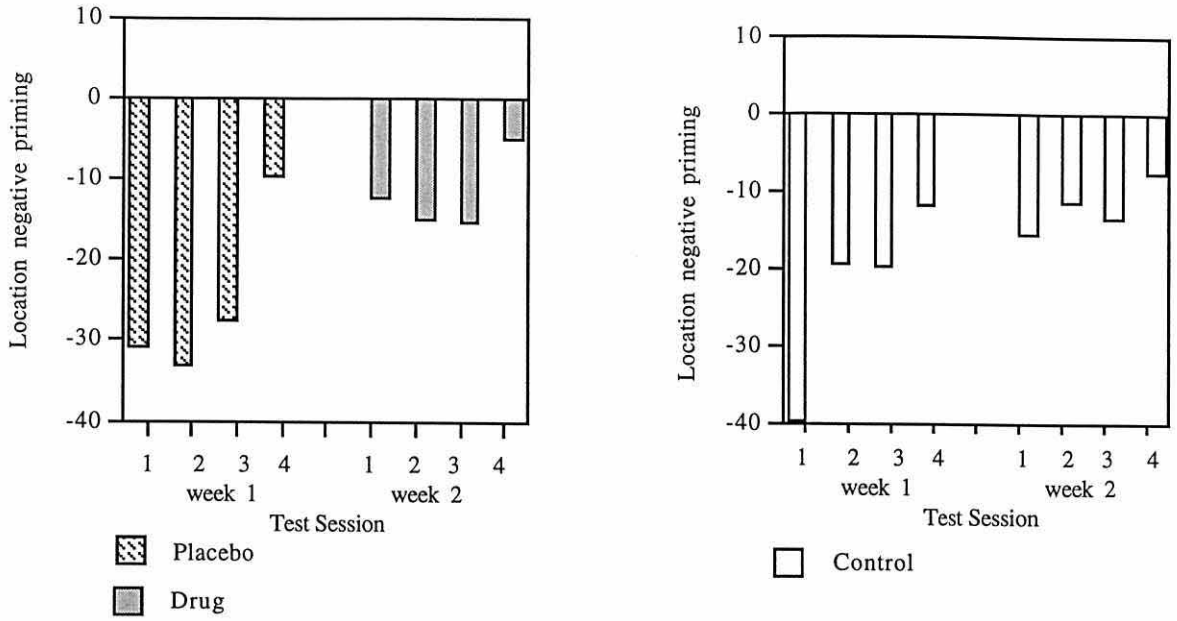


Figure 4.3. Changes in the location negative priming effect over the eight study days

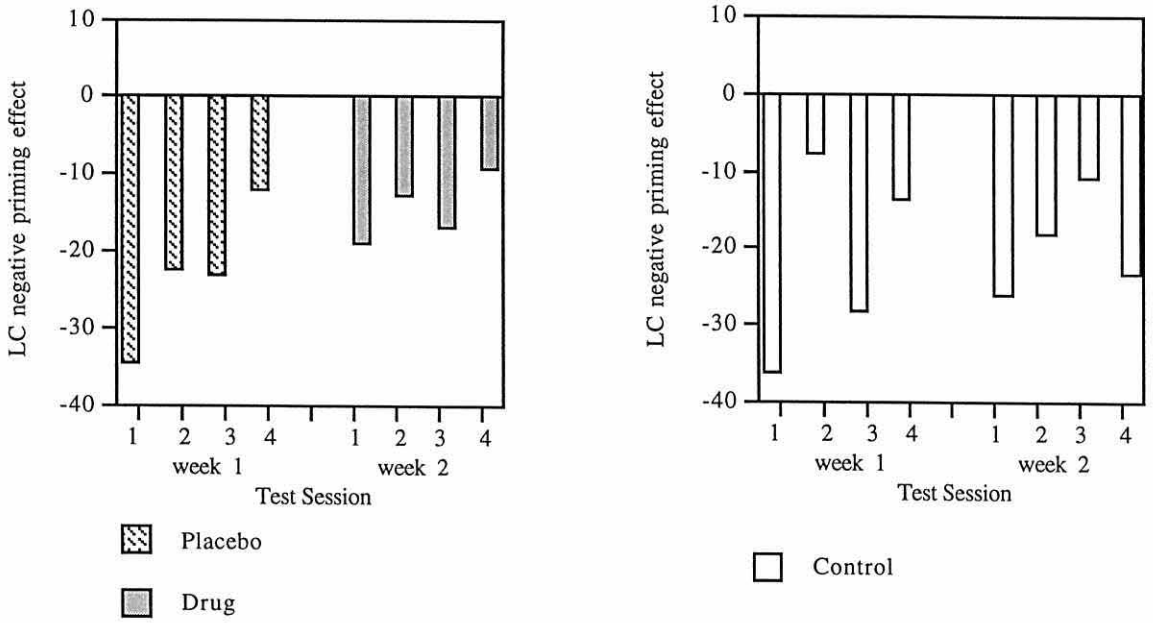


Figure 4.4. Changes in the location-colour negative priming effect over the eight test days

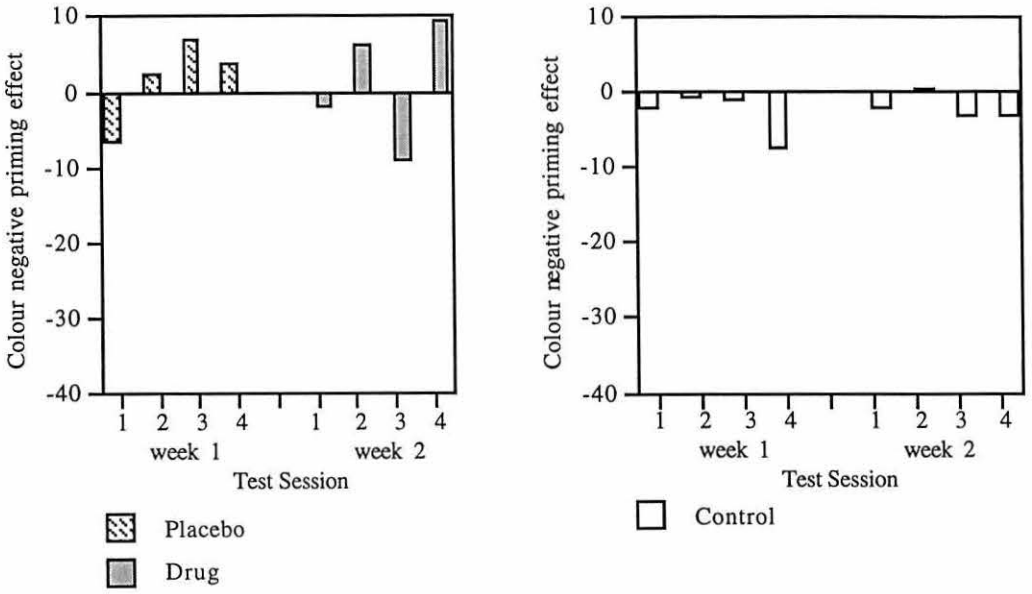


Figure 4.5. Changes in the colour spatial negative priming over the eight test days

An analysis of the error scores on the task indicated a significant group x day x week interaction ($F=3.0$, $df=3,42$ $p<0.05$). Figure 4.6. shows the experimental group made fewer errors than the control group during week one (with the exception of day 4), but more errors than the comparison group during the drug week. The interaction effect reflects changes in the performance within each of the two weeks rather than a drug effect causing differences between the two groups in week two. The week x group interaction was not significant ($F=1.3$, $df=1,14$, $p=0.3$)

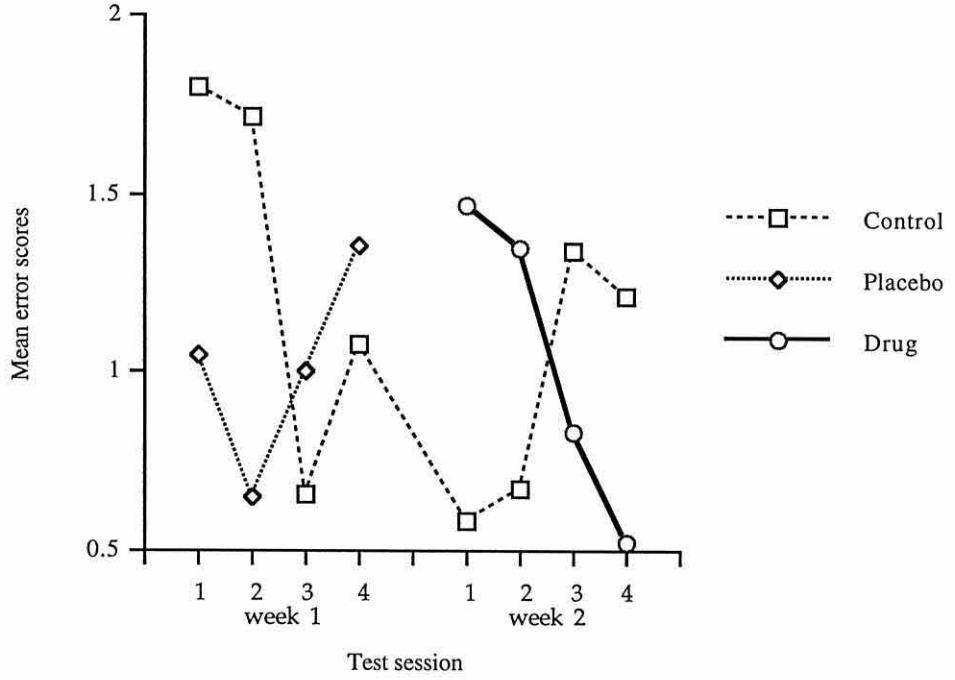


Figure 4.6. Mean error scores on the spatial localisation task.

The 20-word memory test

Immediate recall

Analyses were performed on the immediate recall, delayed recall, correct positive and correct negative scores of the 20-word memory test. All the experimental group data were analysed twice; once with the comparison group data from this experiment (comparison group 1) and again with the data of 10 randomly selected controls from a group of 27 students who participated in Experiment One (comparison group 2). The second analyses were carried out as the scores of the comparison group

collected in this experiment (comparison group 1), were higher than the experimental data in week one, when theoretically it should have been equivalent. Performance of comparison group 2 was the same as the experimental group in week one.

No significant week by day by group or week x group interactions were found in the immediate recall condition regardless of the control group used. Figure 4.7. highlights the differences in the pattern of performance of the two comparison groups in relation to the experimental group.

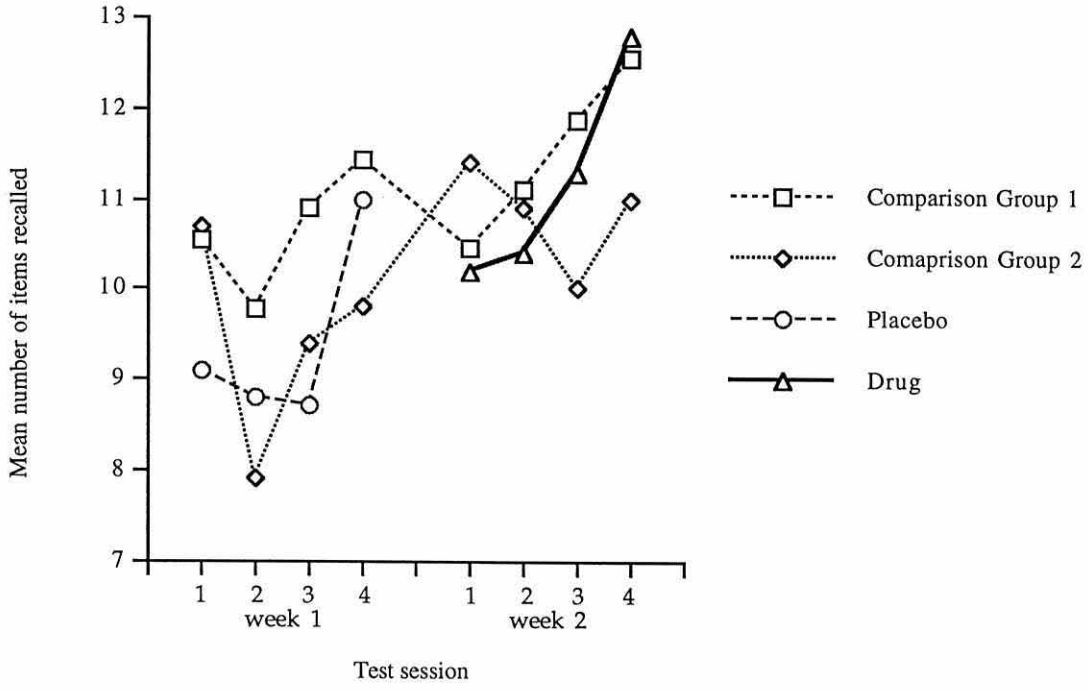


Figure 4.7. Mean immediate recall scores

Delayed recall

Analysis of the delayed recall data (using comparison group 1) shows a significant "week x day x group" interaction ($F=3.0$, $df=3,51$ $p<0.05$). It can be seen from Figure 4.8. that comparison group 1 scored at a higher level than the experimental group during both weeks 1 and 2. As there was no significant group effect the interaction is likely to reflect the different directions of effect between the two groups within week 1 only.

In week 2 both groups improve. The significant interaction effect described above was not found when the experimental data was analysed with the comparison group 2 data as the two groups' performance is similar in week 1. The week x group interaction was not significant.

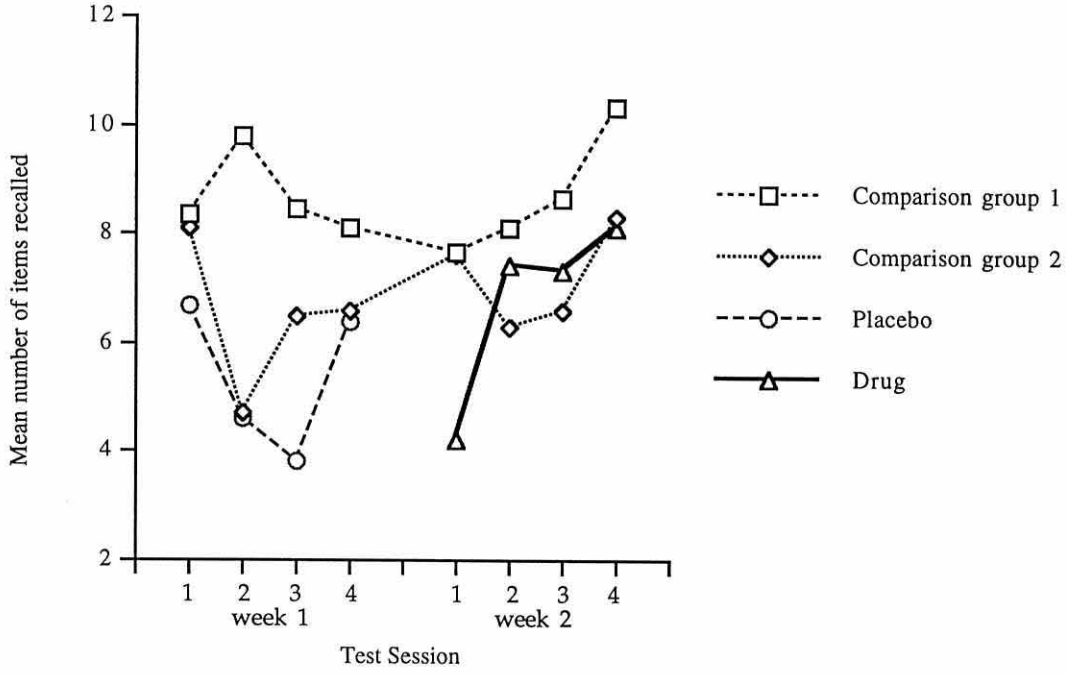


Figure 4.8 Mean scores on the delayed recall test

Analysis of the delayed recall experimental data alone showed a significant week by day interaction ($F=8.6$, $df=3,51$ $p<0.01$). Pair-wise comparisons of the means of the scores in week 1 and week 2 show that subjects remembered significantly fewer items on day one of week 2 compared to day one of week 1 ($t=2.7$, $p<0.01$). However, subjects performed significantly better on drug than on placebo on test days two ($t=-3.1$, $p<0.01$) and three ($t=-3.7$, $p<0.01$) although there were no differences between the weeks on the final test day.

Delayed recognition

Analysis of the delayed recognition hits showed no significant week x day x group or week x group interactions. There was a significant day by group interaction when the experimental data was compared with the

comparison group 1 data (F=2.9, df=3,51 p<0.05) but not when it was compared with the comparison group 2 data.

Analysis of the correct negative responses of the experimental group and comparison group 1 revealed a non-significant week x day x group interaction. However a significant week x day x group interaction was found when the experimental data was compared to the data of comparison group 2 (F=3.9, df=3,54 p<0.05). This interaction effect reflects changes in the direction of the scores of the experimental group within each of the two weeks separately.

Critical Flicker Fusion Threshold

No significant week x day x group or weekx group interactions were found on the task. However, Figure 4.9. shows that the mean ascending and descending CFFTs of the experimental subjects in week two were raised compared with week 1 (placebo week) and the comparison group. CFFTs appear to reach a peak in the drug group on the third test day of week 2.

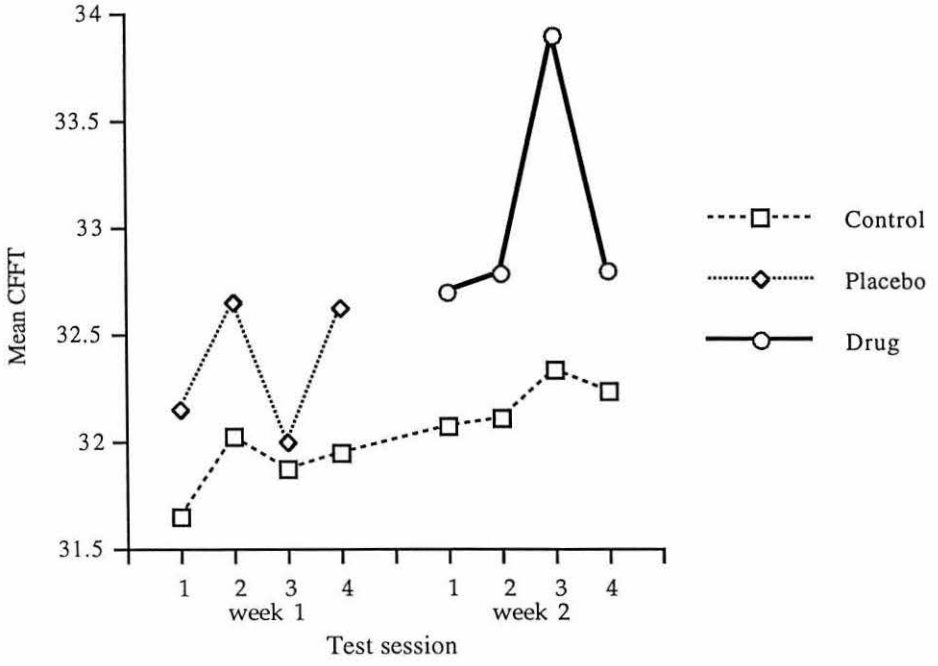


Figure 4.9. Mean CFFT scores

Continuous Attention Task

The results of the analysis showed no significant interactions or group differences between the experimental and control group. Table 4.1. shows that the control group were performing at a higher level than the experimental group in both weeks.

Table 4.1. Mean scores on the continuous attention task

	Week 1				*Week 2*			
test day	*day 1*	*day 2*	*day 3*	*day 4*	*day 5*	*day 6*	*day 7*	*day 8*
Expt. grp.	36.2	36.6	36.3	34.4	35.1	36.4	36.9	35.8
Comp.grp	36.9	38.4	38.7	37.3	37.8	38.8	38.0	38.3

The Stroop Task

Stroop interference was calculating by subtracting the control colour naming time from the Stroop colour naming time. Analysis of the Stroop colour naming and interference data showed a non-significant study week x day x group interaction and week x group interaction. Table 4.2. and 4.3. show that the performance of the two groups on the Stroop colour naming and interference task in weeks 1 and 2 were very similar. There was a significant improvement in the performance of the experimental group in the drug week when compared to placebo ($F=12.1$, $df=3,27$ $p<0.01$). However this improvement is also found in the comparison group ($F=5.09$, $df=3,24$ $p<0.01$).

Table 4.2. Mean scores on the Stroop colour naming test

	Week 1				*Week 2*			
test day	*day 1*	*day 2*	*day 3*	*day 4*	*day 5*	*day 6*	*day 7*	*day 8*
Expt. grp	54.7	45.6	44.0	43.9	44.6	40.9	42.4	40.9
Comp grp	48.4	45.7	43.4	44.2	43.2	43.6	41.9	41.6

Table 4.3. Mean scores on the Stroop interference test

	Week 1				*Week 2*			
test day	*day 1*	*day 2*	*day 3*	*day 4*	*day 5*	*day 6*	*day 7*	*day 8*
Expt. grp	86.2	74.4	71.0	68.9	63.8	63.7	61.8	63.1
Comp grp	82.8	72.2	67.1	65.3	65.6	62.9	61.1	59.9

Visual Analogue Ratings

Eight relevant measures of mood were analysed and no significant day x week x group interactions were found.

The Oxford-Liverpool Inventory of Feelings and Experiences

No significant differences were found in the scores of the experimental and control group on any of six sub-scales of the test.

Discussion

Spatial localisation task

It was predicted that paroxetine would increase response speeds and negative priming effects as a result of its general alerting effect. The reduction in overall response times observed in this study must be attributed to the effects of practice on the task as there were no significant group effects or interactions in the ANOVA. The performance of both groups' was similar in week one. In week two the paroxetine subjects were slower overall but followed the pattern of performance of the comparison group until the final test day. On the final test day the paroxetine groups' response times stopped decreasing and began to increase.

These small, non-significant differences in the pattern and level of performance of the two groups in the second week suggest that paroxetine may have had a retarding effect on performance. This effect was most marked at the end of week two which suggests the drug effect may be more potent at the end of the drug week.

The location negative priming effect was larger in week one than in week two and diminished over the study days. There was no evidence of a group interaction which suggests that paroxetine does not affect location negative priming. Analysis of the size of the location negative priming effect in the two groups produced a similar pattern of results with a week and day effect but no group interaction. The decrease in location effect size over the two weeks can be attributed to the effects of practice on the task.

The colour and LC conditions did not produce any negative priming effects. The absence of a significant LC interaction is consistent with Milliken et al. (1994) who found that the simultaneous presentation of the probe cue with the probe display prevents perceptual review processes operating. This in turn eliminates the facilitation in the LC condition that characterises the perceptual review process. The absence of a significant colour negative priming effect is also consistent with previous reported results of the procedure used in this experiment. It has been found that the prime-probe colour relation has little or no inhibitory effect as the property of colour does not compete directly for the control of action in the way location does. This is because the behavioural goal of the task is to locate the target and consequently the property of location is most likely to show priming effects. Thus, paroxetine did not affect the operation of location-based inhibition that this task demonstrates.

Paroxetine did not affect the number of errors made on the task. The significant group x day x week interaction was due to the differences between the experimental and comparison group performance within each week.

The 20-word memory test

Immediate recall

The results of Experiment One gave rise to an expectation of a particular performance pattern on the 20 Word Memory test. The 27 students who completed a different version of the test on nine study days showed that after an initial decline in task performance on day 2, there was a steady improvement until study day 5, when asymptote was reached. However, contrary to these expectations, the performance of comparison group tested in this experiment (comparison group 1) did not follow this pattern and there was no evidence of asymptote being reached on any of the measures. The comparison and experimental groups were also expected to perform at approximately the same level in week one as neither group was on active medication. However, in all the four conditions of the 20 Word Memory test the comparison group performed at a higher level than the experimental group during the first week (and often in the second week as well). As neither of these expectations were fulfilled it was considered appropriate to also compare the experimental data with data from a randomly selected group of 10 of the students who participated in Experiment One. The results are therefore discussed with reference to both comparison groups.

The immediate recall scores were not significantly enhanced or impaired by paroxetine when compared to placebo or comparison group 1. The scores of comparison group 1 were higher than the experimental group in week one, while in week two both the experimental and comparison group were performing at a similar level and improving gradually throughout the week. It is noteworthy that on the final test day, the paroxetine subjects had a mean score that was very slightly higher than the comparison group (scores on all the other days were considerably lower). However an improvement in performance on the final test day

could also be accounted for by the fact that the test version given on the last test day was the same as the one they were given on the first test day, as only 7 equivalent test versions were available.

When the immediate recall data from comparison group 2 was compared with the scores of the experimental group, both groups had similar scores in week one and asymptote was reached around day 5 in the comparison group. The performance of the subjects on paroxetine however continued to improve with the highest mean score being reached on the final test day. This could reflect a drug related trend in improvement in performance (see Figure 4.7).

Delayed recall

The significant interaction in the delayed recall condition was produced by the difference in performance of the two groups in week one. The control group was performing at a higher level with a slight upward trend in performance, whereas there was a downward trend in the scores of the experimental group. This interaction was not obtained when the experimental group data were compared to the comparison group 2 data.

Analysis of the delayed recall experimental data alone produced a significant week by day interaction effect which suggests that paroxetine was enhancing delayed memory recall. Pair-wise mean comparisons of placebo week and drug week scores showed that on test day one of the drug week drug scores were significantly poorer than placebo scores. This decline in performance on the first day of the drug week was also found in the immediate recall data and could have been caused by the paroxetine. The improvements on test day two and three of the drug week (the sixth and seventh test day of the study) may also have been drug related, rather than the result of learning and practice, as evidence from Experiment One suggests that asymptote on the task is reached around day 5.

Recognition memory

There was no evidence that paroxetine either facilitated or impaired delayed recognition memory scores. This is consistent with the differential effects of the SSRI, fluvoxamine, on recall and recognition in Korsakoff's Psychosis (Martin et al., 1989).

CFFT

Critical flicker fusion thresholds were not significantly raised or lowered by paroxetine. The scores of both groups were at the same level in the first week. In the second week there was a general upward trend in the scores of the experimental group with a peak in performance on the third test day which declined on the final test day (Figure 4.9.). This result fails to support the finding of Kerr et al (1991; 1992) that acute and chronic doses of paroxetine raise CFFT in both young and elderly healthy volunteers. However not all studies have reported that the SSRIs raise CFFT. Cooper et al. (1989) found that an acute dose of paroxetine did not raise CFFT or potentiate the sedative effects of other drugs.

Sustained attention tasks

Paroxetine did not have any significant effect on Stroop task performance. Both the experimental and control subjects were significantly faster at completing the task in week two than in week one, which would suggest that improvements were due to practice on the task. A chronic dose of 20 mg paroxetine in combination with alcohol was also found to have a neutral effect on Stroop performance in healthy elderly volunteers (Kerr et al., 1992).

Performance on the Continuous Attention task was unaffected by paroxetine. The comparison group scores were better overall but neither group showed practice effects on the task.

Mood measures

No significant changes in subjective mood ratings were found when subjects were taking paroxetine. However it is noteworthy that on some of the scales (happy-sad, tranquil -troubled, contented-discontented) the experimental subjects' subjective mood ratings worsened over the two weeks of the experiment. The experimental subjects may have had expectations about how they would feel when taking an antidepressant i.e. they may have expected to feel happier. As they did not know which week they were on active medication their subjective ratings may have been affected by their expectations during one or both of the weeks.

General Discussion

It was predicted from previous research that paroxetine would increase cortical arousal (as measured by CFFT) which would in turn lead to better performance on the selective attention test, sustained attention tasks and to a lesser extent, the verbal memory test. However, paroxetine did not raise CFFT significantly, although the experimental group subjects had raised CFFTs compared to the comparison group in week two. Paroxetine had no effect on performance on the Continuous Attention task and the Stroop test. These results suggest that a chronic dose of paroxetine has a neutral effect on arousal and attention.

The proposed alerting effect of the drug was predicted to reduce response times on the spatial localisation task. Contrary to expectation, it was found that the experimental subjects' reaction times were slightly slower than those of the comparison group which suggests that the paroxetine may have had a slight sedative effect. However there was no evidence of sedation from the CFFT or the subjective ratings of alertness. In terms of negative priming effects there was no evidence that paroxetine affected subjects' ability to inhibit representations that have previously been ignored.

The results of the present experiment suggest that subjects taking paroxetine obtained significantly higher delayed recall scores on test days two and three of the drug week than when they were taking placebo. As paroxetine did not raise cortical arousal, this improvement in delayed recall may not be attributed to any general alerting properties of the drug. This improvement must instead be mediated by some other process that affects delayed recall independently, as immediate recall and recognition memory were not enhanced by paroxetine. The tentative nature of this finding highlights the need to carry out further investigation into the possible verbal memory enhancing properties of paroxetine.

CHAPTER 5

Experiment Three; The effects of paroxetine on memory in healthy elderly volunteers: A single case study approach.

Introduction

Existing experimental evidence suggests that selective 5HT drugs can enhance memory performance in animals and humans with pre-existing deficits. A modest improvement in delayed recall performance was found in healthy young volunteers treated with a chronic dose of 20 mg paroxetine when compared with placebo (see Experiment Two). This evidence forms the basis of the prediction made here, that paroxetine will produce a greater improvement in the performance of healthy elderly humans on a range of cognitive tasks. It was assumed that paroxetine would be more likely to improve memory in elderly subjects than in young subjects, firstly, because a neurochemical deficiency that could be reversed by a selective serotonergic agent would be more likely in an aging human brain than in a young brain (e.g. Marcusson, Oreland, and Winbald, 1984), and secondly, because mild difficulties with episodic memory retrieval appear to be a feature of normal aging (White and Cunningham, 1982). As the elderly subjects' performance would be lower, any drug-related improvement in performance level would be more detectable.

As reviewed in Chapter Two, the SSRIs have been shown to enhance learning and memory in animals (Altman, Nordy and Ogren, 1984; Flood and Cherkin, 1987; Strek, et al., 1989). Human studies of SSRIs have assessed their effects either in healthy volunteers with an alcohol-induced memory deficit, or in patients with clinical memory deficits (such as organic alcoholic brain syndrome patients). Two healthy volunteer memory studies found that zimeldine reversed a dose-dependent alcohol-

induced impairment of free recall of verbal material (Weingartner et al., 1983; Linnoila et al., 1983).

Other volunteer studies reported the effects of SSRIs on memory in young healthy volunteers to be either neutral or inconclusive. Although the memory effects of paroxetine have not previously been examined, fluvoxamine (Curran, et al., 1986), and fluoxetine (Moskowitz and Burns, 1988) were found to neither impair nor improve verbal memory. The only human memory enhancement observed thus far with SSRIs are the improvements seen in volunteers pre-treated with alcohol (Weingartner et al., 1983) and in patients with alcoholic organic brain syndrome (Martin et al., 1989; Stapleton et al., 1989).

Theoretically a 5HT antagonist and a 5HT reuptake inhibitor should have opposing effects on cognitive performance as 5HT antagonists attenuate the activity of 5HT pathways, whilst SSRIs are assumed to increase serotonergic activity due to raised synaptic concentrations of 5HT (Feighner and Boyer, 1991). However, the evidence from animal and human studies suggests that both types of drug have an enhancing effect on memory performance. The selective 5HT3 receptor antagonist, ondansetron has been reported to produce a dose-related enhancement of baseline discrimination learning performance and a reversal of anticholinergic drug-induced learning deficits in animals (Barnes, et al., 1990). Crook and Lakin (1991) reported significant, dose-related positive effects of ondansetron, on both the acquisition and delayed recall of name-face associates and on face recognition performance in subjects with age-associated memory impairment. Thus, there is evidence that a reduction in the amount of available serotonin produced by a 5HT3 antagonist may cause human and animal memory enhancement, although the work reported by Barnes et al. (1990) gives a clear indication that the effect is mediated through the cholinergic system.

The object of the present study was to examine the effects of the SSRI, paroxetine, on the memory performance of healthy elderly subjects. Included in the test battery were measures of verbal, visual and spatial episodic memory as these memory systems are considered to be functionally distinct and may therefore be differentially affected by the drug. The Speed of Comprehension test (Baddeley 1992) was included to assess potential drug-related changes in semantic processing, while the digit span test evaluated any drug-induced changes in working memory function.

A single case approach was adopted in this study which involved daily baseline, placebo and drug test sessions. This design is more sensitive than a group design as changes in the trend of a subjects' performance in response to an intervention can be rigourously documented. Incorporated into the design was an initial seven session baseline testing period which allowed subjects considerable practice on the tests before the drug intervention was introduced. The tests employed in the present study were piloted on students and elderly subjects; asymptote was generally reached around day 4 or 5, although this did vary from test to test. The two post-intervention baseline measures also controlled for the effects of practice and allowed comparisons to be made between performance during a treatment phase (either drug or placebo) and a non-treatment phase.

It was predicted that paroxetine, like ondansetron, would improve baseline memory performance in healthy elderly volunteers and these improvements were most likely to be found on the two measures of verbal memory. This prediction was consistent with the tentative evidence of the delayed recall enhancing effects of paroxetine in young healthy subjects.

Method

Subjects

Five subjects (three male and two female) aged 55-75 participated in the study. The subjects were recruited through the subject panel of the School of Psychology , University of Wales, Bangor and were paid £2.50 for each hour of testing. Ethical approval for the study was obtained from Gwynedd Healthy Authority and the School of Psychology. Subjects underwent a full medical examination and gave written consent before entering the study. None of the subjects were taking medication that was likely to interfere with their cognitive function. The Geriatric Depression rating scale was administered to ensure that subjects were not depressed.

Design

A single subject, ABACA design was used in which phase A was baseline, and phases B and C were either 20 mg paroxetine followed by placebo or placebo followed by 20 mg paroxetine. During the two treatment phases (B and C) subjects were required to take a tablet each morning. Counter-balanced treatment orders were randomly assigned to the subjects. The experiment was conducted double-blind.

Each baseline and intervention phase lasted approximately seven days. Subjects were tested daily, at the same time each day (to control for time-of-day effects). Each intervention phase was followed by a washout period of 10-14 days, which was followed by a return to baseline testing. The study lasted eight to nine weeks in total. Seven parallel forms (A-G) of six memory tests were administered on consecutive days. Test administration order was determined by a Latin Square design.

Test Materials and Procedure

The test battery comprised six memory tests; the 20 Word Memory test, the Name-face-occupation associate learning test, an extended version of the Visual Retention Test (Benton, 1974), a spatial location memory test,

the digit span test and the Speed of Comprehension test (Baddeley, 1992). The effects of practice on all the tests had been evaluated in young and elderly volunteers in Experiment One. The multiple versions of the 20 Word Memory test, the Name-face-occupation associate learning test and the visual retention test were also evaluated for test-form equivalence.

The digit-span test materials and procedure were based on those used in the Wechsler Adult Intelligence Scale (Wechsler, 1981). The Speed of Comprehension test (Baddeley, 1992) required subjects to verify 100 written statements about the world (e.g. Nuns are made in factories) as quickly and as accurately as possible. The measure taken was the number of sentences verified in two minutes. As seven forms of the test were needed for the present experiment (only four were available), each set of sentences was divided into two, and the number of sentences verified in two minutes was estimated on the basis of the time taken to complete the adapted version. This method is recommended by the test author. Both the digit span test and the Speed of Comprehension test are described in detail in Chapter 7.

The tests were administered in a fixed order in the battery which took approximately 45 minutes to complete. Testing was carried out in the subjects' home. The subject's mood was also assessed during each testing session using visual analogue scales (Bond and Lader, 1974).

Results

The two female subjects withdrew from the study after experiencing adverse reactions to their first paroxetine dose. Only the results obtained with the three male subjects who completed the study are reported.

Baseline-treatment differences were initially assessed by visual inspection of the raw data (Kazdin, 1982). Kendall's tau was used to measure the trend in the mean of the data (Morley and Adams, 1989) and Wilcoxon's signed ranks test was used to compare drug and placebo

performance. As a large number of measures were analysed the critical level of significance was taken as $p<0.01$ to minimise the likelihood of making a type 1 error. Results at the level of $p<0.05$ were interpreted as being marginally significant. Each treatment condition (drug or placebo) occurred either in treatment week 1 (T1) or treatment week 2 (T2).

20 Word Memory Test

Immediate and delayed recall.

Subject 1. Immediate recall drug treatment (T2) performance gradually improved over the 7 days. Kendal's Tau showed a significant positive trend in the mean of the drug data with the lowest drug score being on day 1 and the highest overall score on day 7 ($tau=0.71$, $p<0.05$). However, Wilcoxon's signed rank test indicated that immediate recall performance in the drug condition was not significantly better than performance in the placebo condition (Figure 5.1.).

Figure 5.2. illustrates that delayed recall also gradually improved during the drug phase (T2) and that the improvement continued during the post-drug baseline phase. In this case, a Wilcoxon's signed ranks test revealed that delayed recall was marginally significantly better during drug treatment than during placebo treatment ($t=1$, $p<0.05$).

Subject 2. Neither recall measure varied significantly between the drug (T1) and placebo (T2) treatments (see Figures 5.1 and 5.2). Performance remained close to baseline levels throughout both intervention stages.

Subject 3. Immediate recall improved gradually over the five week study period. The scores were marginally significantly higher during placebo treatment (T2) than during the drug phase ($t=7$, $p<0.05$) (Figure 5.1.). In contrast, delayed recall remained stable over the five weeks of the experiment with little evidence of an overall learning effect (see Figure 5.2.).

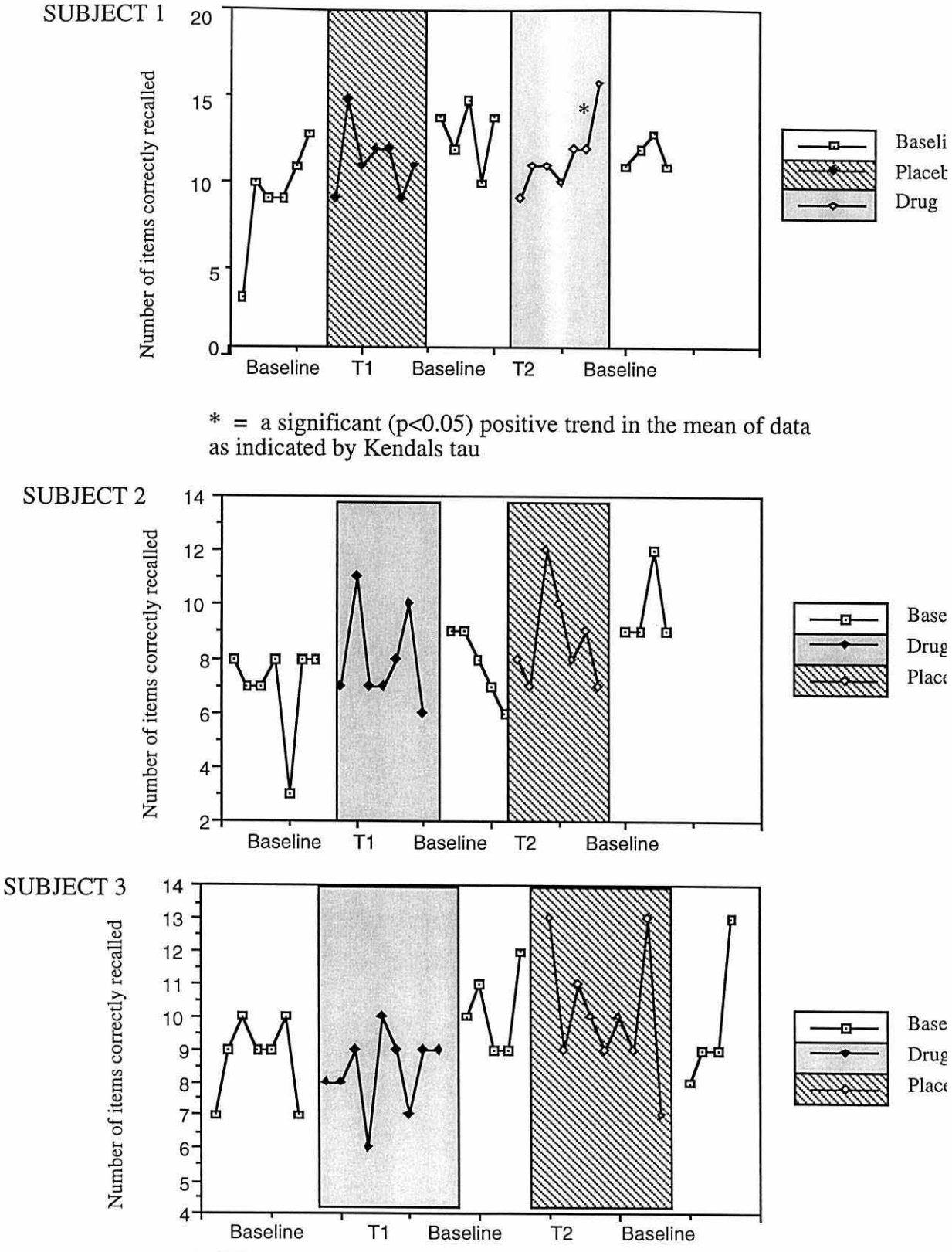
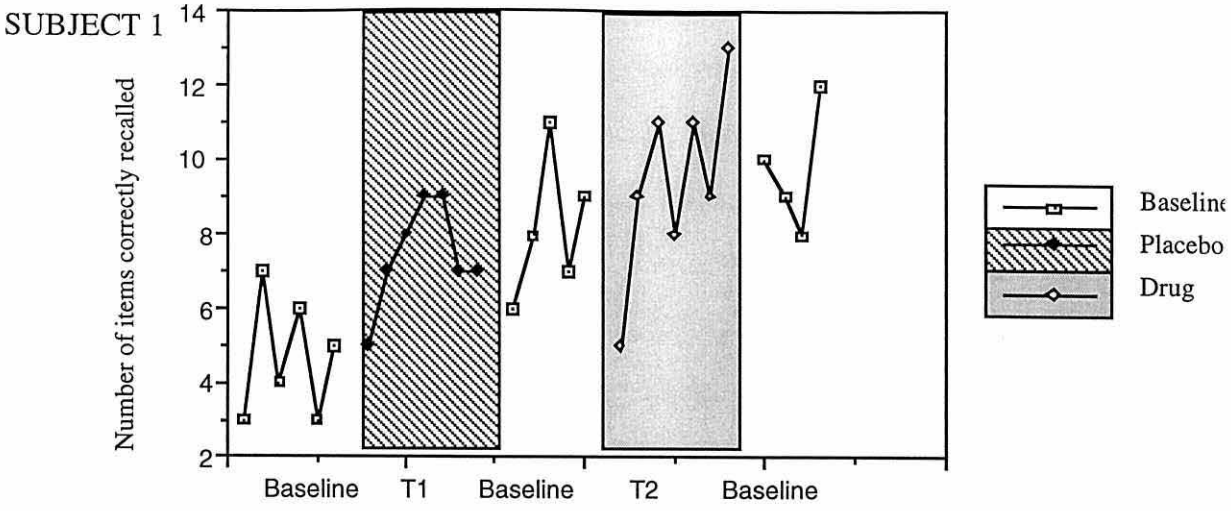
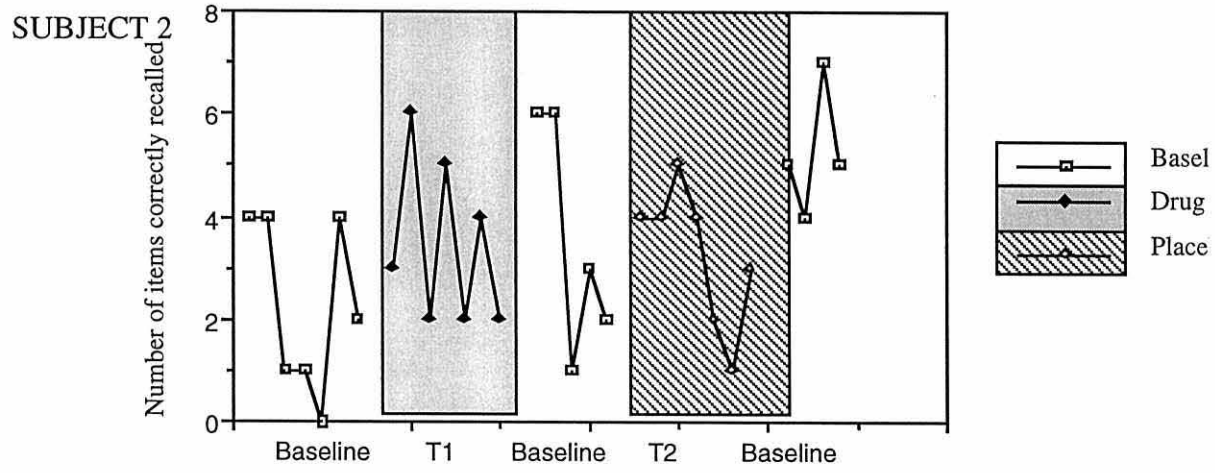


Figure 5.1. Immediate recall performance of Subject 1, Subject 2 and Subject 3.



A Wilcoxon's signed ranks test indicates that the drug scores were significantly higher than placebo scores ($p<0.05$)



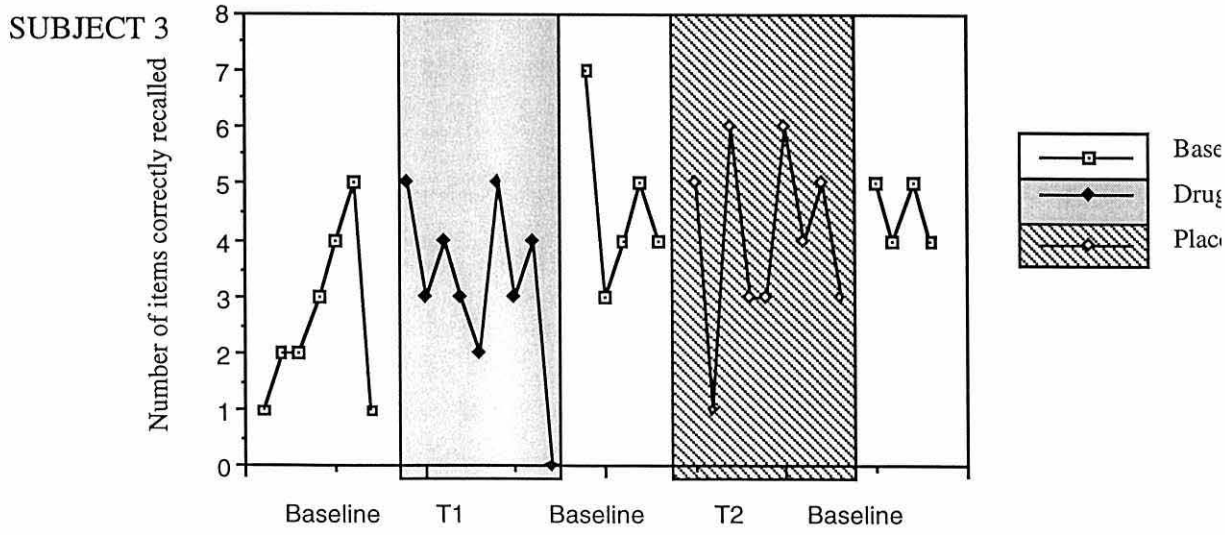


Figure 5.2. Delayed recall performance of Subject1, Subject 2 and Subject 3.

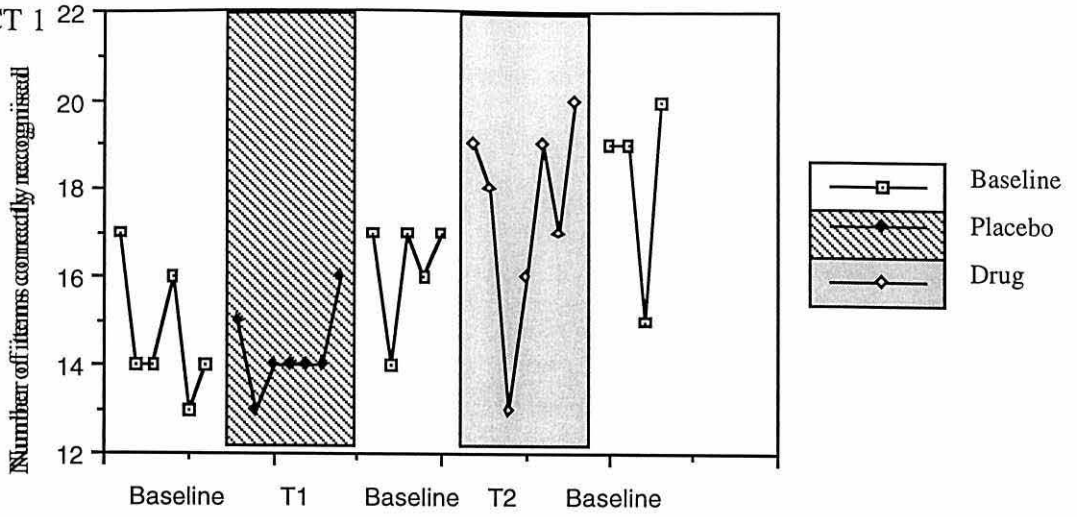
Delayed recognition

Subject 1. Figure 5.3 illustrates that the number of correctly rejected distractors showed a marginally significant increase during drug treatment (T2), compared with placebo ($t=1$, $p<0.05$) whilst the number of targets correctly recognised was unaffected by drug treatment. In keeping with this, the total number of 'yes' responses decreased throughout the experiment with marginally significantly more being made in the placebo week (T1) than in the drug week ($t=2$, $p<0.05$). Thus the drug-related improvement in correct negative scores may be attributable to an increase in negative responses overall.

Subject 2. There was no significant drug effect on the number of targets correctly recognised. Again, there was a steady increase in the number of correctly rejected distractors over the five weeks (see Figure 5.3.) with marginally significantly more being made in the placebo (T2) than the drug condition ($t=1.5$, $p<0.05$). The number of 'no' responses was marginally significantly smaller in the drug condition (T1) ($t=3$, $p<0.05$) than during placebo treatment (T2) and increased gradually throughout the testing sessions.

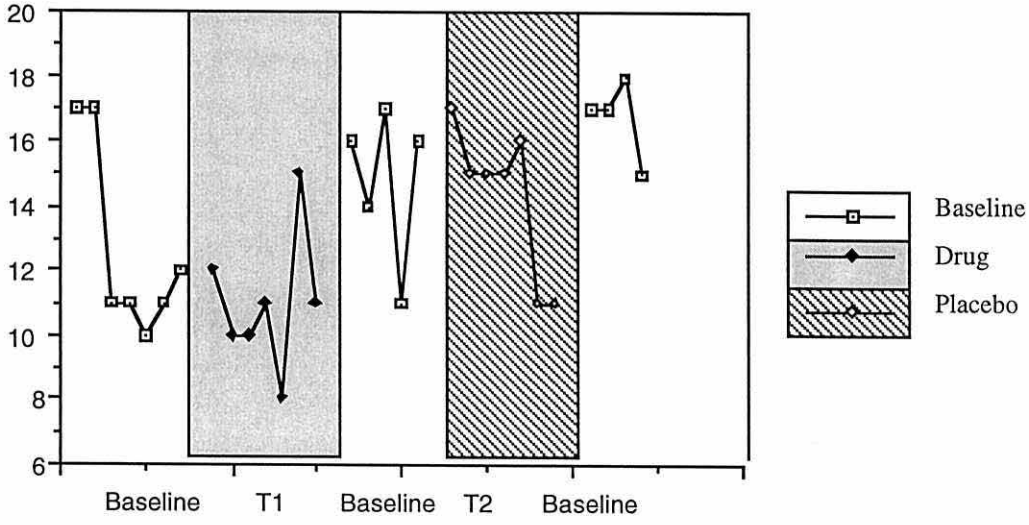
Subject 3. There was a steady increase throughout the experiment in the number of targets correctly recognised and positive ('yes') responses. There were marginally significantly more positive ($t=5.5$, $p<0.05$) and correct positive responses ($t=5$, $p<0.05$) made during placebo treatment (T2) than during drug treatment. Figure 5.3. shows that the number of correctly rejected distractors did not vary between drug and placebo conditions.

SUBJECT 1



A Wilcoxon's signed ranks test indicates that drug scores were marginally significantly higher than placebo scores, ($p<0.05$)

SUBJECT 2



A Wilcoxon's signed ranks test indicates that placebo scores were marginally significantly higher than drug scores ($p<0.05$)

SUBJECT 3

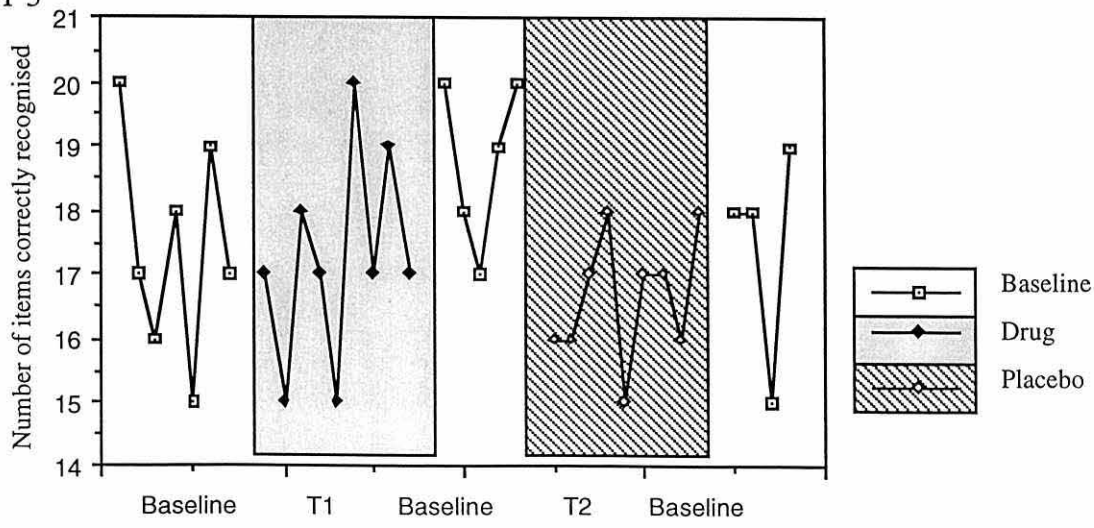


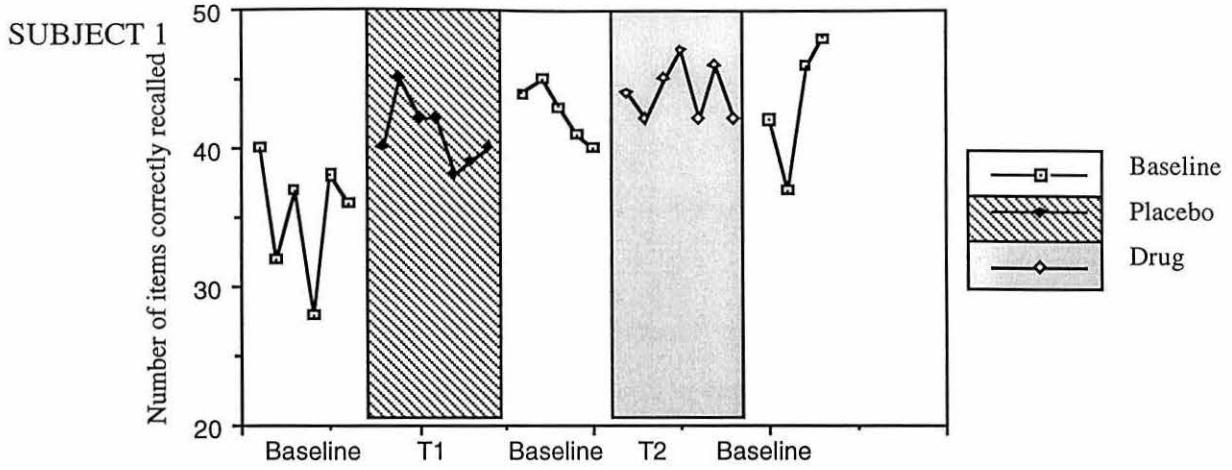
Figure 5.3. Correct negative performance of Subject 1, Subject 2 and Subject 3.

Name-face-occupation associate learning test

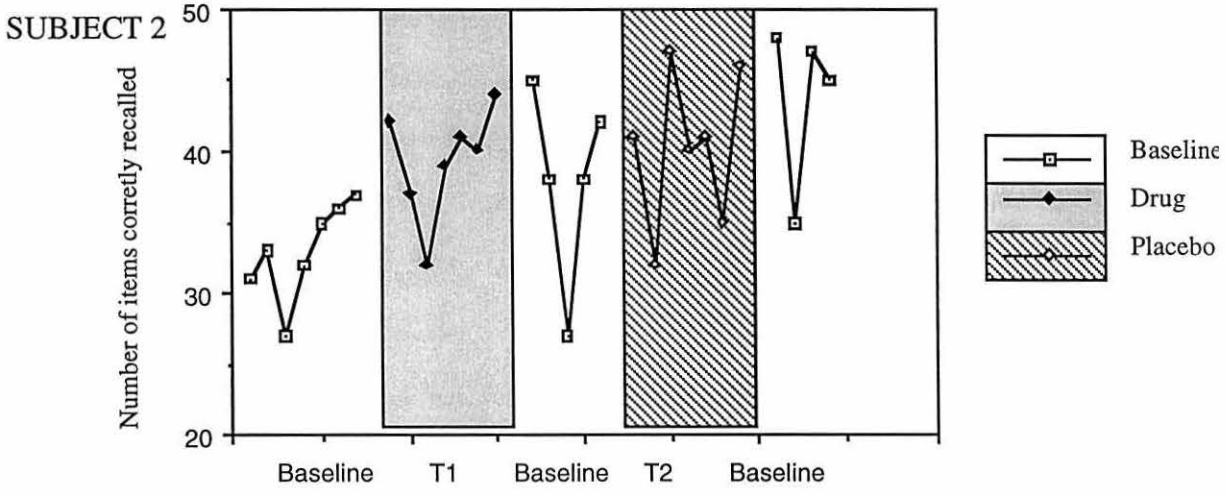
Subject 1. Figure 5.4. shows that scores were marginally significantly higher during the drug phase (T2) than during the placebo phase ($t=2.5$, $p<0.05$), but continued to improve during the final post-drug baseline phase.

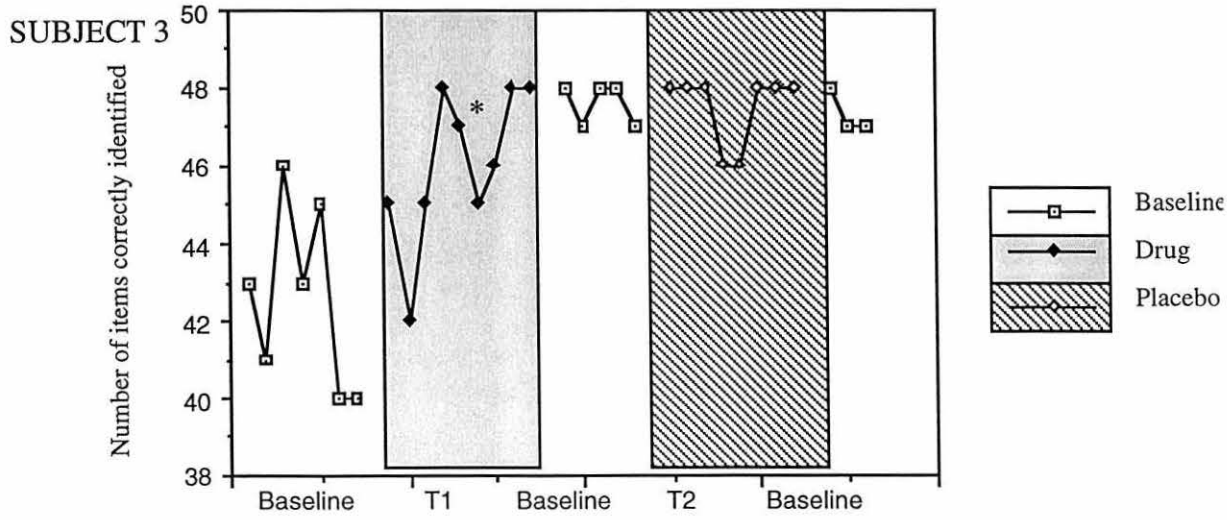
Subject 2. There was no significant difference between the drug (T1) and placebo (T2) phases (see Figure 5.4). There was a steady upward trend in the scores over the 5 week study period, with the highest score falling in the final baseline phase.

Subject 3. Figure 5.4 illustrates that although there was a marginally significant upward trend in performance during the drug phase (T1)($tau=0.528$, $p<0.05$), the placebo phase (T2) scores were marginally higher than drug phase scores ($t=3.5$, $p<0.05$), and performance peaked during the post-drug baseline phase.



A Wilcoxon's signed ranks test indicates that the drug scores were significantly higher than the placebo scores ($p<0.05$)





A Wilcoxon's signed ranks test indicated that placebo scores were significantly higher than thedrug scores ($p<0.05$)

* = a significant ($p<0.05$) positive trend in the mean of data as indicated by Kendals tau

Figure 5.4. Name-face-occupation associate learning performance of Subject 1, Subject 2 and Subject 3.

Speed of Comprehension test

Subject 1. Performance stabilised during the initial baseline, then marginally significantly improved during T1, the placebo phase (tau=0.8, $p<0.05$). Thereafter subject 1's performance stabilised and showed no drug effect.

Subject 2. After some initial improvement during the initial baseline week, performance stabilised, showing no difference between drug and placebo phases.

Subject 3. Performance stabilised during the initial baseline, then marginally significantly improved during T1, the drug phase (tau=0.528, $p<0.05$). The improvement continued over the 5 week study period, such that placebo (T2) performance was significantly better than drug phase performance ($t=1$, $p<0.01$), with scores peaking during the final baseline phase.

Digit Span Test

Subjects 1 and 2 showed very stable performances on both the digits forwards and digits backwards measures over the 5 weeks study period. Subject 3's forward digits scores remained stable but the digits backwards measure improved marginally significantly, such that placebo (T2) was superior to drug (T1) ($t=0$, $p<0.05$).

Spatial location memory test

There were no significant differences between drug and placebo related scores. Subject 1 and subject 2's scores remained stable after the initial baseline phase, while subject 3's scores were considerably more variable, particularly during the drug phase.

The Extended visual retention test

Subject 1. Scores were relatively stable following the initial baseline phase and there was no difference between performance during drug and placebo phases.

Subject 2. Scores improved gradually over the 5 weeks. The highest scores occurred during the placebo (T2) and final baseline phases.

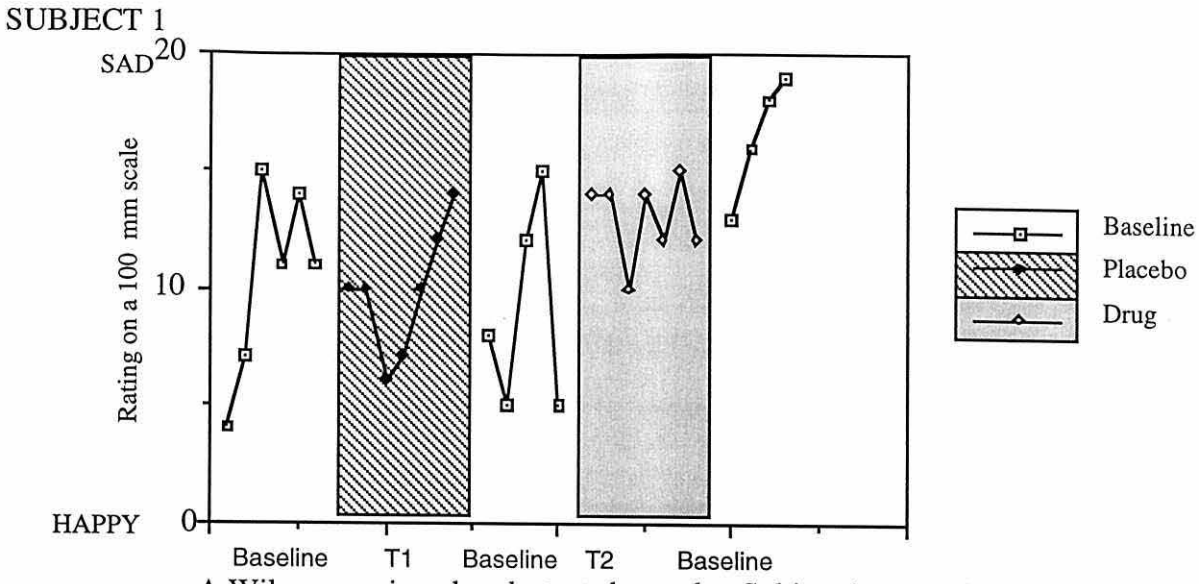
Subject 3. Following the initial baseline phase, performance was at ceiling.

Analogue Mood Ratings

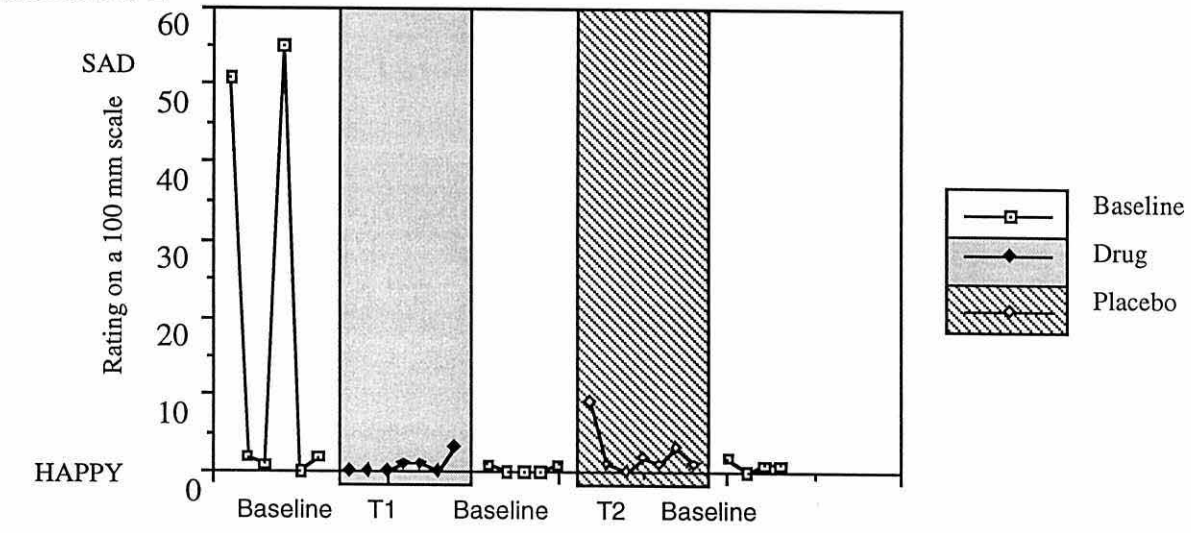
Subject 1. This subject rated himself as marginally significantly sadder (Figure 5.5) and more discontent on drug (T2) than on placebo ($t=1.5$, $p<0.05$, and $t=3$, $p<0.05$ respectively). His scores showed a gradual non-significant increase in discontentment, sadness and troubled feelings with the highest scores occurring in the final baseline stage. There were no changes in subjective alertness or clear-headedness.

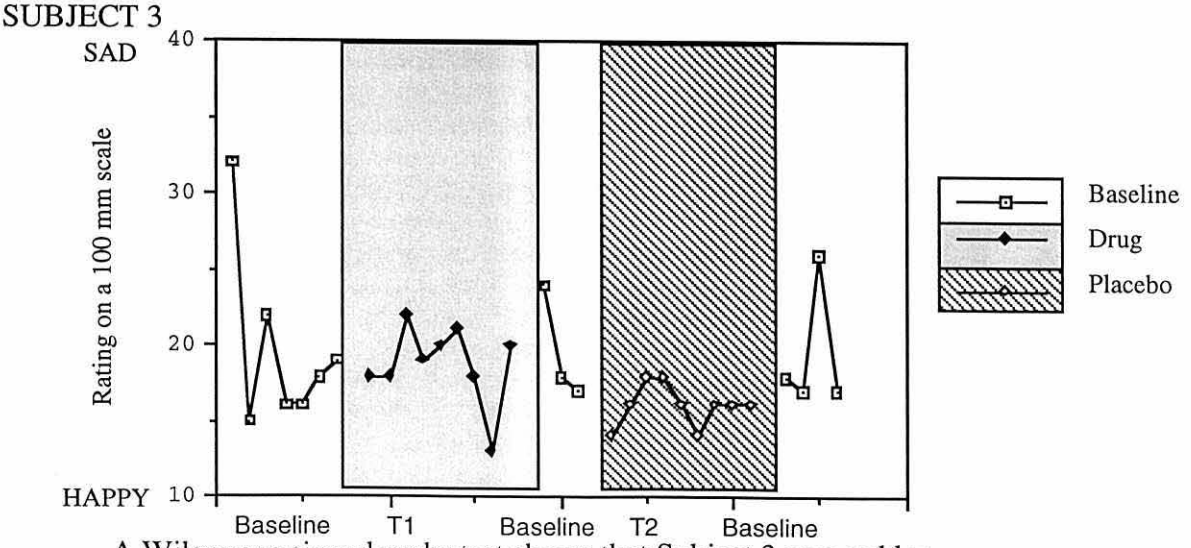
Subject 2. This subject rated himself as marginally significantly more drowsy ($t=0$, $p<0.05$), muzzy ($t=2.5$, $p<0.05$) and troubled ($t=1$, $p<0.05$) on drug (T1) than on placebo. His happy-sad and contented-discontented ratings were consistently around zero (i.e. he was happy and contented) in the drug (T1) and placebo phases, apart from one very high discontented score on the last day of the drug phase.

Subject 3. Figure 5.5 shows that this subject's mood was also negatively affected by the drug (T1) which made him marginally significantly more troubled ($t=5$, $p<0.05$) and less happy ($t=4$, $p<0.05$) than during the placebo phase. No subject showed a significant drug-placebo difference on the tense-relaxed or bored-interested scale.



A Wilcoxons signed ranks test shows that Subject 1 was sadder during the drug week than during the placebo week $p<0.05$





A Wilcoxons signed ranks test shows that Subject 3 was sadder during the drug week than during the placebo week $p<0.05$.

Figure 5.5. Scores of Subject 1, Subject 2 and Subject 3 on the Happy-Sad item of the Visual Analogue scales.

Table 3.1. A summary of the significant drug phase differences.

Measure	Subject	Superior condition	Superior phase
Immediate recall	S3	Placebo	T2
Delayed recall	S1	Drug	T2
Recognition correct 'no'	S1	Drug	T2
Recognition correct 'no'	S2	Placebo	T2
Recognition correct 'yes'	S3	Placebo	T2
Face-name-occupation	S1	Drug	T2
Face-name-occupation	S3	Placebo	T2
Speed of Comprehension	S3	Placebo	T2
Digit span	S3	Placebo	T2

Discussion

Verbal memory test performance

It was predicted that paroxetine would enhance cognitive performance in the three elderly subjects. The most prominent result obtained in this study was the finding that Subject 1's delayed verbal recall scores were higher during the drug phase (T2) than during the placebo phase. The scores improved significantly during the drug phase, but, critically, this improvement did not continue following the return to baseline. Therefore, the improvement seen in the drug phase may tentatively be attributed to paroxetine rather than to practice on the task. This interpretation is strengthened by the observation that neither Subject

2 nor Subject 3 showed evidence of strong practice effects on delayed recall performance (see Figure 5.2.)

Subject 1 also showed a marginally significant drug-related improvement in the number of distractors correctly rejected in the delayed recognition task (Figure 5.3.). However as this improvement continued in the post-drug baseline phase and was also found in Subject 2, who took placebo in T2, it was likely to be due to the effects of practice on the task. This effect may have been caused by his tendency to make more negative responses overall during the second treatment phase, which in turn may be related to the poorer subjective mood reported by this subject during the drug phase.

Name-face-occupation associate learning test

Subject 1 showed a further marginally significant improvement during the T2 drug phase on the name-face-occupation associate learning task. However, as his performance on this task continued to improve during the post-drug baseline phase, it would be difficult to attribute this apparently drug-related effect to paroxetine. Given that Subject 3 showed five significant placebo-related improvements in memory performance during T2, it is clear that practice was an important determinant of performance on many of the tasks used in this study, and that evidence of a reduction in scores following a return to baseline is required before any of these effects can be attributed to paroxetine.

Previous research by Crook and Lakin suggested that the $5HT_3$ receptor antagonist, ondansetron improved the name-face associate learning and recall of subjects with AAMI. A comparable effect of paroxetine may not have been found for a number of reasons. It may be that the pharmacological differences between SSRIs and $5HT_3$ reuptake inhibitors result in the agents having differential effects on verbal memory processes. It is also posssible that the test was not sensitive enough to the

potential effects of the drug. As the task involves immediate recall rather than delayed recall, working memory processes are involved and it is consequently not such a pure measure of episodic memory as the delayed recall test. The considerable learning effects on the task and the fact that one of the subjects was performing at ceiling suggests that the task was not sufficently difficult for use on so many repeated occasions.

In general, verbal memory test performance was superior in T2 compared with T1, regardless of whether the treatment was drug or placebo (see Table 5.1.). For example, Subjects 1 and 3 showed a significant increase in name-face-occupation associate learning during T2, whilst Subject 2 showed a steady improvement in performance over the study period (T2 was the placebo phase for subjects 2 and 3).

Speed of Comprehension test

The performance of all the subjects improved dramatically on the Speed of Comprehension task during the initial two phases of the experiment (regardless of whether they were taking drug or placebo). Subject 3 showed a T2 placebo-related improvement on the task which confirms that the faster processing times were not due to paroxetine. These results suggest that paroxetine does not affect processing speed or the ability to retrieve information from long-term semantic memory.

Spatial location memory test and extended visual retention test

Neither the spatial location memory test nor the extended visual retention test showed any significant phase or treatment effects. Both subjects 1 and 3 were performing at or near ceiling on the extended visual retention test, so any potential improvements on the task may have been masked. Despite the use of the most difficult of the four different administration procedures suggested by Benton (1974), the results indicate that the test and its administration procedure were not difficult enough to be used repeatedly without ceiling performances being reached in some

subjects. A more difficult visual memory task would be necessary to establish whether or not visual episodic memory is facilitated by paroxetine.

Digit span test.

Paroxetine did not impair or enhance digit span performance which suggests that it has no effect on working memory processes. The immediate recall condition of the verbal memory test, the Speed of Comprehension test and the name-face-occupation associate learning test all involve the use of the articulatory loop component of working memory, as well as episodic memory. The involvement of working memory on these tasks may explain why they are less sensitive to the effects of paroxetine than a more specific measure of episodic memory such as delayed recall.

Mood measures.

The measures of mood showed that paroxetine had a negative effect on the mood of all the subjects. It was also found to cause drowsiness in one subject. This is inconsistent with the effects it has on mood when it is used as an antidepressant in patients and with the reported effects on mood, well being and expressed personality in healthy individuals taking Prozac, another SSRI. SSRI's are not generally associated with sedative properties in patients or healthy volunteers and paroxetine produced an alerting effect as measured by critical flicker fusion (Kerr, et al., 1991). However, Hindmarch and Bhatti (1988) found that while objective measures of the effects of the SSRI, sertraline, showed it to have an alerting effect, many of the subjects reported feelings of drowsiness. It may be that subjective reports are not a reliable indication of subjects' levels of arousal and an objective measure should also be made.

Drawbacks of the single-case approach

Single case design is traditionally used in behavioural studies where the target behaviour is monitored during a baseline phase until that behaviour becomes stable i.e. there is an absence of trend or slope and a minimum of variability in the data (Kazdin, 1982). The behaviours being monitored are generally infinitely measurable as they are not affected by learning or practice. The present study was constrained by the fact that there were only seven versions of each memory test, and thus testing was not infinitely repeatable without learning occurring. The baseline phase was thus limited in length to 7 testing sessions which did not allow for the possibility that different subjects may reach asymptote on different tests at different times. The first intervention was rigidly set to start on day 8 of the study whether or not the baseline scores were stable, as it would have been impractical to wait until a stable baseline on all the memory measures was achieved before introducing the intervention. However the pattern of performance of subjects who completed the tests on nine consequetive occasions (see Experiment One) showed that asymptote was reached by day 7.

A further drawback of the design is that comparisons between the drug and placebo phases were confounded by the effects of increasing test familiarity and practice, given the frequency with which performance was superior in T2. Consequently, if the two subjects who received paroxetine in T1 had experienced a genuine T1 drug-related improvement, the effect could have been masked by a subsequent and more marked practice-related improvement in the T2 placebo phase.

General discussion

It was predicted that paroxetine would improve the performance of subjects on the cognitive tasks. However the only significant effect of paroxetine on memory was found in the delayed recall performance of one

subject. As a single case design was used, this result can theoretically be viewed as independent of the other subjects. However the lack of any similar trend in performance of the other two subjects seriously weakens the claim that paroxetine enhances episodic verbal memory in elderly subjects. It may be that higher doses of paroxetine (e.g. 30 mg) would have produced similar results in the other subjects. Further research into the effects of varying doses of paroxetine on measures of delayed recall is needed to establish whether or not the SSRIs, and specifically paroxetine, improve episodic memory. There is no indication from these results that paroxetine has any effect on semantic memory, visual episodic memory, short term memory or spatial memory. The verbal memory tasks are more sensitive measures than the visual tests, as only the verbal tests responded to practice and increased familiarity, placebo-induced arousal and possibly, the effects of paroxetine.

The absence of positive drug effects in this experiment highlights the difficulties of investigating cognitive enhancement. Thus healthy elderly subjects may not be the best group for the assessment of potentially cognitive enhancing drug effects. It was assumed that elderly healthy volunteers would have experienced some decline in memory ability since their early adulthood, and that paroxetine might enhance their current performance by increasing 5HT activity/availability. The absence of a positive drug effect (in all but one measure observed in one subject) could be interpreted in several ways. The subjects may not have experienced any age-associated memory decline (in which case, they would be as unlikely as young subjects to show an improvement) or their age-related memory deficit may not stem from a 5HT deficiency and could not therefore be reversed by an increase in available serotonin. A clinical patient group with cognitive deficits that are related to serotonin depletion may

therefore be more likely to show cognitive improvements resulting from treatment with paroxetine.

CHAPTER SIX

The Effect of Depression on Cognitive Processes.

Introduction

Conflicting research evidence surrounds the question of whether depression causes significant impairments in cognitive function. Many depressed people claim to have significant memory and concentration problems. However, a number of studies suggest that depression may be linked more closely to subjective reports of memory impairment rather than objective measures, particularly in the elderly. An association has been identified in some studies between elderly depressed subjects' self assessment of memory skills and depression, but not between depression and their actual memory performance (e.g. West, Boatwright and Schleser, 1984). Williams, Little, Scates, and Blockman (1987) found that despite older depressed subjects' complaints of greater memory problems, and the fact that they were significantly impaired on verbal memory measures compared to controls, both depressed and control subjects performed in the average to superior range on the Wechsler Memory Scale. In a group of subjects over 75 years old it was found that depression was generally associated with impaired concentration and indecisiveness rather than memory deficits, though depressed subjects were impaired on some recall measures (O'Connor, Pollitt, Roth, Brook and Reiss ,1990) .

Kahn, Zarit, Hilbert and Niederehe (1975) attempted to clarify the question of whether memory impairment in the aged is a normal or psychopathalogical phenonmenon. One hundred and fifty-three people over the age of fifty were assessed for depression and brain function. Their memory complaints were evaluated using a rating scale and their memory performance was tested using a wide variety of tests. Little correlation was found between actual memory function

and memory complaints. Memory performance deficits were strongly associated with brain dysfunction, but not with depression. Depression, by contrast, seemed to be strongly linked to memory complaints. The experimenters suggested that the relationship between depression and exagerated memory complaints may stem from the fact that depressed people tended to be pessimistic when judging their own abilities and their discrepant reporting could be related to personality factors.

Many studies have attempted to document the nature of objective cognitive changes that occur as a result of clinical depression. However, the results of these studies have not provided any clear consensus as to the effects of depression on cognition. Some studies report that depression leads to no overall impairment in objective memory performance (e.g. Friedman, 1964; Miller and Lewis, 1977; Niederehe and Camp, 1985), while other studies have found significant impairments on some measures of memory (e.g. Cronholm and Ottosson 1961; Sternberg and Jarvik, 1976; Kopelman, 1986). The precise nature of these cognitive impairments remains unclear, with some investigators reporting deficits in short term memory, others in long term memory, while others consider that the transfer of information from short-term to long term memory is disrupted (Henry, Weingartner and Murphy, 1973). Several factors could explain the lack of consistency in the results of these studies. Firstly, a wide range of methodologies have been employed to investigate many different cognitive processes e.g. short-term and long-term memory, visual and verbal memory.

A second source of discrepancy is the age of the subjects. As aging is known to affect memory independently, the effects of depression may be magnified in older adults. The combined effect of

old age and depression may interact and produce a different cognitive performance profile when compared with younger depressed subjects (see Jorm 1986). In support of this, Raskin (1982, 1986) found that cognitive deficits in a group of 277 depressed adults were more severe in subjects aged over 40 than those under 40. The effects of old age were also more likely on tasks involving the ability to solve problems and shift cognitive sets than on measures of recall and recognition.

A third source of inconsistency in the results of studies assessing the effect of depression on cognitive processes lies in the sampling of depressed patients. In some studies, depressed subjects were medicated, while other studies they were unmedicated. Many studies fail to specify the medication status of the subjects used. There is considerable evidence that treatment with tricyclic antidepressants and benzodiazepines results in cognitive impairments which may confound the effects of depression on cognitive performance (e.g. Lamping et al., 1984).

Other variables that confuse the issue further are the nature and severity of the depression, and whether or not the subjects are in-patients or out-patients. The nature of the control group used in these studies also varies widely. Some studies used other clinical groups as comparitors e.g. dementia patients, while other studies used the depressed group as their own controls, comparing performance before and after treatment with ECT or anti-depressants. Some studies have attempted to match the controls with the experimental subjects, while others failed to control for confounding variables such as age, education and dementia. In the following section the work on the effect of depression on different measures of cognitive processing is reviewed.

Evidence for impairments in verbal learning.

A number of studies have found that depression affects performance on verbal learning tasks. An early, influential study by Cronholm and Ottosson (1961) compared a sample of matched depressed subjects and physically ill controls. Measures of immediate and delayed recall and forgetting (after 3 hours) were taken on a test of 30 word pairs, 20 simple figures and a 30 item test of personal data about fictitious people. Subjects were tested twice, once before ECT and again one week after treatment had finished. The depressed patients were impaired on immediate and delayed recall measures compared to controls, but there was no difference in their retention ability as measured by forgetting (immediate recall minus delayed recall). The 42 patients who recovered as a result of ECT were found to have improved learning but impaired retention. The experimenters conclude from this that the memory deficit experienced by the depressed subjects was a result of impaired 'registration' of information rather than retention. Stromgren (1977) studied performance on the Wechsler Memory Scale in 152 unmedicated depressives before and after ECT, and found impairments on the measures of mental control, verbal learning and visual reproduction before ECT treatment but not after. However, as he did not use a control group his results must be viewed with caution.

Sternberg and Jarvik (1976) examined the verbal memory ability of hospitalised patients with endogenous depression before and after treatment with anti-depressants. They also assessed control subjects using the same tests as Cronholm and Ottosson (1963) which were validated and checked for reliability. The results suggested that depression was associated with impaired encoding of information as measured by immediate recall, though retention was unaffected.

Testing after 26 days indicated that the greater the recovery from depression, the greater the improvement in patients' ability to encode information effectively, although there was no change in their ability to retain information in long term memory.

These and other studies have found fairly consistent impairments on episodic verbal memory as measured by list learning (immediate and delayed recall) and paired associate learning in groups of depressed patients (Coughlan and Hollows, 1984; Kopelman, 1986). Williams, et al. (1987) found depressed older (over 40 years) subjects were impaired on tasks that involved verbal learning and recall such as list acquisition and recall. Two studies have found that depression caused impairments on short story recall (Kopelman, 1986, Watts and Sharrock, 1987), although other studies have found short story recall to be unimpaired (Coughlan and Hollows, 1984; Williams et al., 1987).

The majority of the studies described above did not assess elderly subjects. As the experimental work in this thesis was carried out on elderly subjects and aging is thought to cause cognitive deficits irrespective of depressive state, it is important to consider the effects of depression in the elderly. Niederehe (1986) compared groups of young and elderly unmedicated depressed subjects (each with a control group) on verbal episodic involving free recall, cued recall and recognition. Subjects were shown a list of 40 words that contained groups of ten taxonomically related words, the superordinate names of which were used to cue recall. Two encoding conditions (using two equivalent lists) were also employed; one in which encoding was spontaneous, and one in which subjects were prompted to encode by being asked to assign each item to one of the taxonomic categories. All subjects were found to perform less well in the prompted encoding condition which suggests that the prompts interfered with, rather than

facilitated encoding. Although the depressed subjects in both groups scored below the control groups on free recall and cued recall, no significant overall depression-related differences or interactions between age and depression were found. The results of this study suggests that young and elderly depressed subjects do not have different performance profiles on a test of verbal episodic memory.

Table 6.1. Summary of the results of experiments assessing the effects of depression on verbal episodic memory.

Author	Tasks	Medicated or unmedicated	Control	Result
Cronholm et al., 1961	Verbal memory	Medicated	Matched	Impairment
Sternberg et al., 1976	Verbal memory	Both	Matched	Impairment
Stromgren, 1977	WMS	Unmedicated	None	Impairment
Coughlan al., 1984	Verbal learning Story recall Word recognition	Not specified	Unmatched	Impaired on et verbal learning only
Kopelman et al., 1986	Verbal learning Story recall	Medicated (13 out of 16)	Matched	Impairments
Niederehe, 1986	Verbal memory	Not specified	Matched	No impairments
Williams et al., 1987	Verbal memory Story recall	Not specified	Matched	Impaired on verbal memory only
Watts et al., 1987	Story recall	Medicated	IQ matched	Impairments

The effect of depression on attention and working memory

A review of studies examining the effects of depression on attentional measures indicated that significant deficits have been identified on some, but not all tasks (Cassens, Wolfe and Zola, 1990). Impairments have been found on measures of trailmaking (part A and B), but not on measures of continuous performance or visual apprehension span (see review by Cassens et al., 1990). Performance on the Stroop task was found to be impaired in a group of depressed subjects with mixed diagnoses of depression and unspecified medication status compared to controls (Raskin, et al., 1982). In another study a group of unmedicated patients with depression were found to be unimpaired compared to controls on the Stroop task (Rush, Weissenburger and Visson, 1983).

Immediate recall from working memory has been widely assessed in depressed patients using the digit span test. When reviewing these studies, Cassens et al. (1990) found the vast majority of depressed patients were unimpaired on digit span performance compared to controls. Colby and Gotlib (1988) found that memory for digits was unimpaired one second after presentation but impaired after delays of 20 and 30 seconds. This suggests that depressed individuals may encode information effectively but have difficulty retaining and rehearsing it in short term memory. A short delay in recall may make the task considerably more effortful and therefore more difficult for depressed individuals.

Evidence of impairments in visual memory

Research into the effects of depression on visual episodic memory is relatively sparse. However, there is enough evidence to suggest that depressives are impaired on some measures of visual

memory. Shipley, Kupfer, Spiker, Shaw, Coble, Neil and Cofsky (1981) compared the performance of a mixed group of unmedicated depressives with normative data and found them impaired on form A (immediate reproduction) of the Benton visual retention test. However, no impairments were found on the Benton visual retention test in a group of mixed unmedicated depressed patients compared with schizophrenics and patients with coarse brain disease (Taylor, Redfield and Abrams, 1981). Coughlan and Hollows (1984) compared depressed patients with controls on a design learning task, a complex figure recall task and forced choice face recognition (Warrington, 1984). The depressed group were impaired on the design learning task, but not on the other two measures. These results indicate that depression may cause selective visual memory deficits. However, there is a further need to assess visual memory performance in depressed subjects in order to clarify whether or not depression causes deficits.

The effect of depression on semantic memory

Previous studies have found that access to previously acquired knowledge is unaffected by depression. Niederehe (1986) investigated the effects of depression on semantic memory in groups of elderly and young depressed subjects and controls. The semantic memory test they used comprised 40 real-world knowledge items e.g. Which cowboy had a horse named Silver?, and subjects were tested on their immediate recall, cued recall and recognition of information. The depressed groups performed slightly less well than their respective control groups, and both the elderly groups performed better than the young groups. This suggests that depression does not affect retrieval of information from semantic memory or old episodic memories.

The results of the studies reviewed above indicate that cognitive deficits resulting from depression have been found most reliably on

measures of verbal episodic memory. Studies exploring the effects of depression on episodic visual memory and attention have yielded inconclusive results and there is no evidence to suggest that depression causes cognitive deficits on measures of working memory or semantic memory. As the majority of these studies involve medicated subjects, or subjects whose medication status is not specified, it is difficult to establish whether the deficits found on the verbal and visual memory and the attention tasks are due to the medication or the effects of depression. It is therefore important to examine performance on these tasks in unmedicated depressed subjects.

Theories of the effect of mood state on memory.

A number of theories have been put forward to account for the findings described in the previous section. The most influential theory is the processing resource theory proposed by Ellis and Ashbrook (1987). The theory is based on Kahneman's (1973) capacity theory of attention, which assumes that there is a limited pool of capacity that can be allocated to any given task. In the case of a depressed individual this capacity is depleted as resources are devoted to depressive thoughts. Some theories attribute cognitive impairment in depressed people to mood congruency effects, whereby negative materials that match the subjects mood are learned and retained best, while the learning of neutral and positive material is impaired (e.g. Beck, 1967; Bower, 1981). Another hypothesis posits that psychological deficits in depression can be explained by the inability of depressives to initiate the use of strategies (Hertel and Hardin, 1990).

Ellis and Ashbrooks' model is based on a number of assumptions. Firstly it assumes that emotional states regulate the capacity that is allocated to a task, and that in depression the amount of

capacity available for task-processing is reduced. Secondly, it assumes that the encoding of information required in memory tasks requires some allocation of capacity or cognitive "effort", and that memory performance is positively correlated with the degree of effort allocated to a task. The model would therefore predict that depressed subjects are more likely to be impaired on tasks requiring them to remember relatively unorganised, poorly structured materials that require considerable cognitive "effort" and processing resources, while they should perform at the same level as control subjects on less demanding tasks.

Ellis and Ashbrook (1987) cite a number of studies to support their theory. They used a mood induction procedure in three studies to examine mood effects on elaborative encoding, semantic processing, and cognitive effort. The first experiment showed that depressed mood subjects, unlike controls, were more likely to recall a word if it was embedded in a simple sentence than if it was embedded in an elaborate sentence. According to the resource allocation theory, this is because they do not have the additional resources to process an elaborate sentence. In the second experiment, subjects were required to recall semantic information after they had either been given a semantic orienting task (rating the word as pleasant or unpleasant), or a control orienting task (counting 'e's in the word). Subjects with a depressed mood were found to profit less from the semantic orienting task than controls. According to the theory, this is because using a semantic orienting task demands more cognitive "effort" than the control orienting task. In the third experiment, subjects were presented with sentences with missing words and asked to select a filler word in two conditions. In the low effort condition the selection was obvious (e.g. if the missing word was dream "The girl was awakened by a

frightening....."), while in the high effort condition it was less obvious ("The man was alarmed by the frightening .....). At recall, the subjects were required to write down the target words. Depressed mood subjects displayed poorer recall than the neutral mood subjects. This performance decrement was found to be almost entirely attributable to poorer performance on the high effort sentences resulting from the subjects' inability to make use of the complicated mnemonic connections offered by the difficult sentence.

Weingartner and Silberman (1984) carried out a number of similar experiments on clinically depressed subjects (as opposed to subjects with induced depressed mood). Using a methodology similar to that used in Ellis and Ashbrooks' second experiment (described above), they compared the ability of depressed people to process and recall lists of words that were semantically related and words that were acoustically related in response to a stimulus word. Twenty four hours later they were required to recall the stimulus words and the response words. The depressed subjects did not manifest the normal advantage of semantic processing on recall. It was surmised from this that impairment in learning and recall only occurs in conditions requiring more elaborate and effortful encoding.

Weingartner and Silberman (1984) also investigated the effect of structure and organisation on the learning and recall of information. Subjects were required to learn and remember different lists of 32 words. The four different types of word lists were used;- 32 unrelated words, 2 clusters of 16 (semantically) related words, 4 clusters of 8 related words, or 8 clusters of 4 related words. Depressed patients recalled significantly fewer words than controls overall. However, depressed patients were indistinguishable from controls at recalling the lists that were highly organised, and the largest difference between

the two groups was found on the recall of lists of unorganised, unrelated information. The results of these two experiments lend support to the resource allocation theory and suggest that findings in subjects with an induced depressed mood can be generalised to clinically depressed subjects.

Ellis and Ashbrook (1987) observed that depression is less likely to affect memory performance when relatively structured materials such as sentences and passages of prose are used. However, Watts and Cooper (1989) demonstrated that depression is also associated with deficits on prose recall. They tested medicated severely depressed individuals' memory for a story comprising 37 units. The items in the story were rated on gist (high-gist and low-gist) and imageability. The results showed that unlike the controls, depressed patients were not biased towards recalling high-gist units that are central to the structure of the story. These results suggest that the depressed individuals are unable to structure material as efficiently as non-depressed people. Imageability was not found to interact with depression and this was attributed to the notion that imageability of materials is an automatically controlled processes and therefore unaffected by depression (Hasher and Zacks, 1979).

Other researchers have obtained results that condradict the processing resource theory. Levy and Maxwell (1968) carried out an experiment in which they varied the structure of approximation-to-text word lists; at one extreme was a normal sentence and at the other, a random series of words. They found that unmedicated depressed subjects benefited less than normals from the increasing structure. This anomaly in results lead Watts, Dalgleish, Bourke and Healy, (1990) to investigate the relationship between the type of information structure and deficits further. The approximation-to-text condition comprised

materials similar to those used by Levy and Maxwell (employing three levels of approximation), while lists of 20 semantically clustered words (at three levels of structure) comprised the other condition. These materials were presented to 18 unmedicated depressed patients and 18 controls. As predicted by resource allocation theory, depressed subjects showed better recall of high level of structure materials than medium level structure materials. However, post hoc analyses of the results indicated that, contrary to the prediction based on resource allocation theory, the relative memory deficit of depressed patients was greater for medium than low structure material. The experimenters suggest that very unstructured materials are relatively insensitive to the amount of resources deployed and would therefore show less of a depression-related memory deficit than medium level structure materials. The results of the studies described above suggest that depressed patients have difficulty spontaneously using an inherent organizational task structure.

In an attempt to accommodate these findings, Hertel and Hardin (1990) proposed that memory deficits in depression are not due to a reduction in cognitive capacity but rather to an inability to initiate the use of cognitive strategies. They postulated that depressed patients are most likely to be impaired on tasks where the use of appropriate strategies is not well controlled by the task itself. This possibility was investigated by comparing the performance of subjects with induced depressed mood and clinically depressed subjects with control subjects in two conditions. In one condition subjects were guided towards using appropriate cognitive strategies, and in the other condition the strategies were concealed. The provision of instructions regarding strategy use improved the performance of clinically

depressed subjects, though it was less beneficial to subjects with induced depressed mood.

Processing resource theory also fails to shed much light on why and how cognitive processing capacity is reduced in depression. It has been proposed that depressed people use up resources on depressive thoughts or are unable to concentrate. However, there has been surprisingly little research into the automatic thoughts of depressed individuals during task performance. Seibert and Ellis (1991) demonstrated that although all the subjects they tested on a memory task reported irrelevant thoughts, the levels were higher when they were in either an induced happy or sad mood condition than when they were in a neutral mood condition. Increases in irrelevant thoughts lead to poorer performance on the task in all subjects. Thus, people have more irrelevant thoughts during both positive and negative emotional mood states, and these thoughts have a detrimental effect on memory task performance.

Watts, MacLeod and Morris (1988) explored depressive thoughts in terms of the nature of the lapses in concentration experienced by clinically depressed medicated individuals. They made a phenomenological distinction between task-irrelevant thoughts ("mind wandering") and an inability to concentrate on the task or think about anything else ("blanking"). They did this by obtaining a self-report measure using a questionnaire. Subjects were then tested on their memory for a passage of prose, and on the "Tower of London" planning task. The questionnaire results indicated that "mind wandering" was significantly more common than "blanking" and was associated with poor prose recall, while blanking was associated with a longer planning time on the "Tower of London" task. The experimenters concluded that there are at least two distinct kinds of lapses in

concentration in depressed patients that affect different tasks. Not all performance deficits in depression can therefore be explained by the fact that cognitive capacity is being taken up by competing thoughts. An alternative explanation is that cognitive resources are not being appropriately allocated to the task being carried out.

A number of studies have indicated that memory impairments in depression occur in situations or tasks where the information encoding requires effort rather than being automatic. The conceptual differences between automatic and effortful processes is that automatic processes always function at a constant level under all circumstances and do not make significant demands on cognitive resources. Automatic processes show limited developmental trends and are resistant to practice. Information encoded in this fashion includes spatial location, temporal order and frequency of occurrence (Hasher and Zacks 1979). In contrast effortful processes require considerable processing resources and include operations such as imagery organisation of information and mnemonic techniques. Hasher and Zacks (1979) propose that effortful processes are disrupted in depression, while automatic ones remain undisrupted.

Roy-Byrne, Weingartner, Bierer, Thompson and Post (1986) tested this theory by presenting depressed and control subjects with lists of categorically similar words in which some words were presented twice. Subjects were asked to raise their hand when they heard a word repeated. Depressed subjects were impaired on the effortful free recall component of the task, but they performed as well as controls on the automatic repetition monitoring component. In a similar experiment involving word production, Calev, Nigal and Chazan (1989) found depressed subjects were more impaired on the effortful task of producing words from a semantic category than on a

more automatic task involving the production of words beginning with a common letter. Cohen, Weingartner, Smallberg, Pickar and Murphy (1982) found that unmedicated depressed subjects showed the greatest impairments on tasks that required sustained effort. It can be concluded from the results of these studies that depression-related deficits are more likely to be found on tasks that require effort and elaborative encoding procedures.

Noncognitive factors associated with memory deficits in depression.

Several non-cognitive factors may influence depressed patients performance on memory tasks. Johnson and Magaro (1987) raise the possiblity that depressed patients perform less well than controls on memory tasks because they lack confidence in their ability to remember information. This lack of confidence leads to a conservative response style which may be responsible for their apparent memory deficits, rather than their inability to access memories. Signal detection analysis can be used in recognition memory tasks to identify response bias (ß) and observer sensitivity or ability to discriminate (d'). Low levels of hits may be indicative of cautious responding. In such a case signal detection analysis would indicate differences from controls in ß scores rather than d'. One problem with investigating response bias on recognition memory tests is that the tests have been found to be less sensitive to memory impairments than tests of recall even when the recall and recognition conditions have been matched for difficulty (Calev and Erwin, 1985).

A number of studies have attempted to explore the possiblility that memory deficits are the result of response bias. Miller and Lewis (1977) compared the performance of a group of elderly depressed, elderly dementia patients and controls on a recognition memory test of geometric designs. Signal detection analysis provided no evidence of

differences between depressed and controls on d' scores indicating that the depressed subjects overall memory sensitivity was no different from controls. The ß scores indicated that the depressed subjects had a more conservative response bias than the controls. A similar pattern of recognition memory response was found by Dunbar and Lishman (1984), using words with varying hedonic tone and Neiderehe and Camp (1985) who tested elderly subjects on word lists made up of high and low imagery words.

Watts, Morris and Mac Leod (1987) employed a different procedure and found contradictory results to those described above. Depressed patients and controls were matched on IQ and presented with words for recognition in two conditions; silent and vocal. Signal detection analysis showed that depressed subjects had lower d' scores than the controls but there were no differences between the two groups' ß scores. This suggests that their ability to recognise previously presented words was impaired, but they were not responding any more cautiously than the controls. This conclusion was supported by the observation that the depressed group made more false alarms than controls in the vocalisation condition. Watts et al. (1987) suggest that the vocalisation of materials by depressed subjects gave them more confidence when it came to responding. The results of this experiment show that there are conditions in which depression is associated with a memory deficit that is not caused by cautious responding.

All the studies described above investigated the response style of medicated depressed patients or subjects whose medication status was not specified by the experimenters. As medication may also affect memory sensitivity and response bias, it is desirable to investigate these two factors in unmedicated patients as proposed in Experiment Four.

Another possible influence on the memory performance of depressed patients is the psychomotor retardation associated with depression that may interfere with their ability to rehearse information sufficently fast and output responses. Analysis of the kinds of errors that depressed people make has lead to the suggestion that they may not perform well simply because they do not make the effort to produce responses. Henry et al. (1973) and Whitehead (1973) have both found that the errors made by depressed subjects tend to be ones of omission rather than comission. This suggests that their poor memory performance may be due to the poverty of their depressed subjects' output.

However there is considerable evidence to suggest that poor performance in depressed subjects is not due entirely to poor productivity. Leight and Ellis (1981) used a forced recall paradigm on subjects with an induced depressed mood and found they showed memory impairments despite the fact that they were forced to respond. Watts and Sharrock (1987) tested depressed memory for prose using a free recall and cued recall condition that required very little output (one word or a short phrase). If the memory deficit was due to poor productivity, depressed subjects would have performed as well as controls in the cued recall condition. However the difference in performance between depressed and controls was greater in the cued recall condition than in the free recall condition which suggests that the effects of depression on memory are not explicable solely in terms of poverty of output.

Summary

There is a wide range of evidence to suggest that depression is associated with deficits on verbal memory tasks. There is also evidence that depression affects visual episodic memory, attention and short

term memory though the nature of these deficits is not yet clearly defined. In order to be able to further characterise the cognitive profile of depressed subjects it is necessary to control for the effects of medication on cognitive processes by assessing unmedicated depressed subjects with matched controls on a range of tasks. Processing resource theory predicts that depressed subjects are likely to show deficits on 'effortful' tasks such as list learning and perform at the same level as controls on less demanding tasks. Performance on tasks requiring varying degrees of effort will therefore be assessed.

CHAPTER 7

The Clinical Trial

Introduction

Data for Experiments Four and Five and Studies One and Two were collected as part of a multicentred drug trial carried out by the pharmaceutical company, SmithKline Beecham, comparing the SSRI, paroxetine with the tricyclic, lofepramine. The clinical trial will be described in this chapter in some detail. The chapter will also explain how the data for experiments and studies described in this thesis was collected. Groups of patients were selected from the clinical trial data set and matched with control data collected independently of the clinical trial. This control data allowed additional, more elaborate analyses of the clinical trial data to be carried out.

The primary aim of the clinical trial for the drug company was to compare the efficacy and tolerability of the selective serotonin reuptake inhibitor, paroxetine (20-30 mg daily) with the tricyclic lofepramine in depressed elderly in- and out-patients. The secondary aim for the drug company, which was the primary aim of this thesis, was to compare the effects of paroxetine with the tricyclic antidepressant lofepramine on cognitive function.

Data was collected in 10 centres around Britain by psychiatrists and psychologists. One hundred and one subjects completed the study country-wide. Complete sets of data for fifteen patients (3 withdrew due to adverse reactions to the drug) were collected in North Wales. Ethical approval for the study was obtained from Gwynedd and Clwyd Health Authorities.

Subjects

Depressed subjects aged 65-85 years were recruited at ten centres in Britain by psychiatrists through psychiatric clinics and hospitals where they were either in-or out-patients. Cognitive testing was carried out by trained psychologists and psychiatrists. To be included in the study subjects were required to meet the DSM-III-R diagnostic criteria for major depression and have a minimum score of 20 on the Montgomery Asberg Depression Rating Scale and a total score of 23 or more on the Folstein Mini Mental State Examination.

Subjects were excluded from the study for the following reasons: failure to meet diagnostic criteria for major depression; presence of a clinically significant co-existing disease such as dementia, mania or bipolar disorder, schizophrenia, epilepsy, Parkinsonism; known hypersensitivity to tricyclic anti depressants; treatment with ECT or one of the investigational compounds during the three months prior to entering the study; treatment with other psychotropic medication e.g. monoamine oxidase inhibitors during the two weeks before entering the study; treatment with oral or depot neuroleptics in the past two months (see protocol in appendix C for full exclusion criteria). At the outset of the study subjects were excluded if they were being treated concomitantly with temazepam or beta-blockers. The protocol was later amended to include these subjects. Subjects that agreed to take part in the study were required to give informed written consent.

Experimental Design

A between groups, repeated measures design was used. The experimental subjects were randomly assigned to each treatment group and the study was conducted double-blind.

Procedure

The study lasted nine weeks and began with a one week placebo run-in period (day -7 to day 0) during which the background tests and the baseline measures on the cognitive tests were made. This was followed by an eight week period of active drug treatment. During the first week of active medication patients received paroxetine 20 mg once daily in the morning or lofepramine 70 mg in a divided daily dose (morning and evening). On day 7 patients receiving lofepramine had the dose increased to 140 mg while patients receiving paroxetine continued taking a 20 mg dose. If at day 21, the investigator considered that the response to the study medication was not adequate, the dosage was inceased to 30 mg paroxetine or 210 mg lofepramine.

The cognitive tests were divided into two sets, set A and set B, and administered three times each on alternate testing sessions. On day -7 subjects completed the background and set B tests (baseline) and on day 0, more background tests and set A tests (baseline). On day 7 they completed set B tests for a second time and on day 21 set A tests for a second time. Set B tests were administered for a third time on day 35 and set A tests were administered again on day 56. Each set of tests was made up of different forms of the same test, with the exception of the Stroop Test. Details of the cognitve tests and their administration are given below. Clinical assessments and laboratory observations were carried out regularly by the psychiatrists (see page 19 of protocol in appendix C for full details).

Analyses

The clinical trial data was analysed by calculating differences in the changes from baseline in the paroxetine and lofepramine treated groups (i.e. treatment minus baseline) and comparing them. The results of this analysis are not included in this thesis.

Experiments and studies using the clinical trial data

Control subjects

Complete sets of cognitive data were collected from fifteen non-depressed control subjects aged between 65 and 85 years old independent of the clinical trial. Three other control subjects only completed baseline testing. The control subjects were recruited by advertising in sheltered housing for the elderly. Potential subjects were screened for depression. None were taking psychotropic medication. The control subjects were used in Experiments Four and Five.

Experiment Four.

The baseline data from the clinical trial was used to investigate the effects of depression on cognitive function. Eighteen depressed patients were selected from the complete group of subjects who entered the clinical trial and matched with 18 non-depressed controls. Differences between the cognitive performance of the two groups were analysed.

Experiment Five.

The effects of the paroxetine on cognitive function was assessed by selecting 15 subjects treated with paroxetine and comparing them with 15 subjects treated with lofepramine and 15 control subjects. The groups of paroxetine and lofepramine treated subjects were selected from the clinical trial data. Subjects in the all three groups were matched on age, gender and NART IQ. The performance of the three groups on the two sets of tests was compared over the time course of the trial.

Two further studies were carried out on different sub-groups of patients from the clinical trial. In one study the cognitive performance of nine paroxetine treated subjects who made a full clinical recovery was compared with eight subjects who were resistant to treatment with paroxetine. In a second study, a comparison was made between all the

subjects in the clinical trial who had been depressed previously with all the subjects who were depressed for the first time.

Cognitive test materials and administration procedure

General Procedure

The cognitive tests used in the study were divided into two sets; set A and set B. Set A consisted of the short story recall test (Wechsler, 1987), the Fuld Object Evaluation Test (Fuld, 1981), the digit span test (Wechsler 1981) and the Stroop Test (Stroop, 1935) and were administered in that order. Set B was made up of the Verbal Memory test, the Benton Visual Retention Test (Benton 1974) and the Speed of Comprehension test (Baddeley, 1992), administered in that order. The background tests used were the Recognition Memory Test (Warrington, 1984) and the NART (Nelson, 1982) and Schonell Graded Reading Test (Schonell, 1942) as measures of pre-morbid IQ. The former was administered on day -7 together with set B while the word reading tests were administered on day 0 together with set A. The tests were administered in a fixed order and took 30-40 minutes to complete. Subjects were tested either in their own home or at the clinic they attended.

Individuals were tested by the same experimenter over the nine weeks. However, as matching the subjects with controls involved the subjects in the experimental groups being drawn from the pool of subjects from centres all over Britain, they were not all tested by the same experimenter.

Background Tests

The Schonell Graded Word Reading Test

This consists of 50 words of increasing difficulty printed on a card. Subjects were instructed to read slowly down a list of words and wait for the experimenter to say "next" before reading the next word. The number

of errors was recorded. The results of the Schonell were only used if subjects made more than 40 errors on the NART. In these cases the NART and Schonell scores were combined to calculate the subject's FSIQ.

The National Adult Reading Test (NART)

This test comprises a list of 50 words printed in order of increasing difficulty. The words in this test are all irregular with respect to the common rules of pronunciation and can therefore only be read correctly if they are known and recognised by the subject. Subjects were instructed to read slowly down the list of words and wait until the experimenter said "next" before moving on to a new word. Subjects were warned that there may be words that they would not know. The responses were recorded by the tester and the number of errors made taken as the score. This reading error score was then used to calculate the WAIS Full-Scale IQ on the basis of normative data.

The Warrington Recognition Memory test

The ability to recognise recently presented information was assessed by two separate subtests, one using words as stimuli and one using faces. As only one form of this test is available it was chosen as a background test to provide a measure of subjects' visual and verbal memory at the outset of the study.

In the word recognition subtest subjects were required to look at a pack of 50 words printed on cards and instructed to say 'yes' if their associations withthe word were pleasant and 'no' if they were not so pleasant. They were told that there is no right or wrong answer but they were required to make a judgement about each word. Immediately after this they were given a sheet with 50 pairs of target and distractor words printed on it and instructed to tell the experimenter which word they had just seen and to guess if they were unsure.

In the face recognition condition subjects were shown a pack of 50 male faces and told to say 'yes' if they thought the face looked pleasant and 'no' if it was not so pleasant. They were then shown another pack of faces with two photographs on each page-a target photograph and a distractor and instructed to point to the face they had just seen in the pack.

The test is scored by awarding a point for each correctly identified word and face. Each subtest thus produced two scores out of 50. A percentile score was calculated using normative data from a group aged 55 years and upwards.

Main Measures-Set A

Short Story Memory test

The stories for this test were taken from the Revised Wechsler Memory Schedule. Each story contains 25 "idea units" which can be scored independently. In the standard testing procedure two stories are told together in sequence before a recall task. Scores are calculated on the basis of the recall of both the stories. Normative data for this procedure was available, but as there were not enough stories available to carry out three testing sessions using the standard procedure, only one story was used in each session, thus compromising the normative comparison.

Prior to each story being read out loud, subjects were instructed to listen carefully and try to remember the story as exactly as possible. After the story had been read, the subjects were asked to recount it and their were responses recorded. They were then told that they would be asked to recount the story again later. After subjects had completed the Fuld Object Evaluation Test and the digit span test i.e.approximately 15-20 minutes later, they were asked to recall the story again.

The stories were divided into units for scoring purposes. Each correctly reproduced unit was worth one point. Guidelines as to what constitutes an acceptable response were available from the WMS to help

standardise the scoring procedure. Only delayed recall scores were analysed.

The Fuld Object Memory Evaluation

This test was designed specifically for use with elderly subjects and consequently has norms based on two groups of controls, community resident and institutionalised 70-79 and 80-89 year olds. As there are only two published forms of the Fuld Object Memory Evaluation available, a third form was compiled using object familiarity norms.

Each form of the test comprised a black bag containing ten common objects. Subjects were instructed to identify each of the ten objects by touch, without looking using alternating hands. The object-name or description that the patient gave and the order of naming was recorded. If the patient was unable to name the object a suggestion was made. All the objects were replaced in the bag and the bag remained closed but within sight for remainder of the test. Immediately after the objects were replaced in the bag subjects were required to do a verbal fluency task which involved them producing as many different girls' /boys' (same sex as patient) names as they could in 60 seconds. Their responses were recorded. The patient was then asked to recall the things from the bag a second time. Recall was timed and the items ticked off as they were recalled. When the subjects had recalled all the words that they could in 60 seconds, they were reminded of the objects that they had left out at the rate of one word every 5 seconds. They were then told that they would be given more chances to recall all the objects.

There were four further rapid verbal retrieval trials of thirty seconds each, alternated with four object recall trials lasting 60 seconds, followed by the selective reminding procedure. The rapid verbal retrieval trials involved subjects listing names of foods, names of vegetables, things that make people happy and things that make people sad, respectively.

After a five minute filled delay (during which the digit span test was administered) subjects were asked to recall all the items from the bag again. Items that were not recalled were probed for using a recognition task. Subjects were asked to choose the correct item from a list of three similar items.

The test produced several different memory measures. The total retrieval score was calculated by counting the number of items recalled on the first trial and then adding any additional items recalled on subsequent trials thus providing a cumulative total for each trial. The scores from each trial were then totalled to provide a score out of 50.

The retrieval estimate was calculated by counting the number of items recalled in each trial. These values were considered to be measures of long term retrieval on each trial as the rapid verbal retrieval task prevents rehearsal from immediate memory. The scores from each trial were then added to provide a score out of 50. Repeated retrievals were calculated by marking each repeated recall of an item on two successive trials with a "+" sign. The plus signs between each trial were then added together to provide four between trial scores. These were then totalled to give a score out of 40. Ineffective reminders were calculated by marking each occurrence of a failure to recall an item on two successive trials with a "-" sign. The minus signs between each trial were then added together to provide four between trial scores which were then totalled to give a score out of 40. The rapid verbal retrieval task scores were calculated by adding the number of different items produced on each verbal retrieval task. The delayed condition of the test provided a recall and recognition score, which when added together provide a crude measure of how many of the items had been remembered.

As this test yielded so many measures only the total retrieval score, repeated retrieval score and total delayed recall were analysed.

Digit Span test

This task is based on the Wechsler Adult Intelligence Score (WAIS) procedure. Digit strings of increasing length were presented verbally by the experimenter and the subject was required to repeat them back. The first part of the task was terminated when the subject failed on two trials of the same digit length. The subject was then presented with further progressively lengthening strings and required to repeat them back the reverse order. The task terminated after failure on two trials of the same digit length.

The test was scored by awarding two points if both trials were passed, one point if one trial was passed and no points for failure on both trials. A maximum score of 14 points on the forward test and 14 points on the backwards test was possible. The total of these two scores was analysed. Age-related scaled scores were only available for subjects up to the age of 74 years so they were not used.

The Stroop test

The full Stroop test procedure described below comprises four subtests, a word naming control and interference task and a colour naming control and interference task. The full procedure was used at the outset of the clinical trial, but was found to be too time consuming and demanding for the subjects. It was therefore decided to drop the word naming control and interference task and concentrate on the more attentionally demanding colour naming subtests of the task.

Three separate stimulus sheets were used each with words (printed in lower-case) or colour patches arranged in four columns on an A4 sized piece of paper. The colours used were "red", "blue", "green" and "brown". All subjects were checked for normal colour vision before starting the task.

In the word naming control task subjects were required to read colour words printed in black ink. This was followed by the word naming

interference task in which they were asked to read a list of colour words printed in incongrously coloured ink. In the colour naming control task subjects were required to name colour patches. In the interference colour naming task subjects were instructed to name the ink colour of incongrously coloured words. In all conditions subjects were instructed to read aloud the words or name the colours as quickly possible, starting at the top of the first column reading down each of the four columns in turn. They were told to correct themselves and keep going if they made a mistake. The four subtests were administered in the order described above.

The primary measure recorded for each subtest was the number of seconds taken to read or name all the words or colours on the sheet. The tester recorded the time taken to complete each sheet using a stop-watch and also recorded any breaks the subject had as a result of difficulties they encountered. Responses were noted on a record sheet; a correct response with a tick, an incorrect response with a cross and a self-corrected error with "s/c" next to the cross. Two measures were analysed: the control naming time and the interference colour-naming measure which was calculated by subtracting the control naming time from the time taken to name the ink colour of incongruously coloured words.

Main Measures-Set B

Verbal Memory test

This test comprised an immediate recall, delayed recall and delayed recognition condition. The target and distractor word lists used for the task were made up of concrete nouns matched for word frequency and imageability (Kucera and Francis, 1967-see appendix A). The words were printed in bold on separate cards and bound in a fixed random order into booklets.

In the immediate recall stage of the task a booklet of sixteen target words were read aloud to the subject as they were presented for three seconds each. Subjects were then asked to recall as many of the words as they could. The free recall period was timed to last no longer than 90 seconds. The subject was then told that they would be asked to remember the word list later in the testing session. After the Benton Visual Retention Test and Speed of Comprehension test had been completed, the examiner asked the subject to recall as many of the words in the list as possible for a second time.

In the delayed recognition condition a pack of 32 word cards, containing the 16 target words and 16 distractor words, was presented. Subjects were told that half of the words in the list were words that they had seen before, but the other half were words they had not seen that day. They were instructed to say 'yes' if they thought they had seen the word earlier in this testing session, 'no' if they thought that they had not seen the word before and to guess if they didn't know. The recognition task was not paced. The "yes" and "no" responses were recorded next to the corresponding word on the record form.

Subjects scored one point for each word correctly recalled at the immediate and delayed recall stage of the test. The recognition memory test results were scored by assigning responses to one of the following four categories:-a hit (a target which was correctly identified); a miss (a target which was not recognised); a correct negative (a distractor which was correctly rejected); a false alarm (a distractor which was incorrectly identified as a target).

The Benton Visual Retention test.

This published test (Benton 1974) has three separate forms (C, D and E) that can be administered on different occasions and compared with each other. Each form of the test comprises ten cards of abstract

geometrical designs of increasing complexity. Administration D of the test was used which involves the subject viewing each of the cards for 10 seconds and then reproducing it after a 15 second unfilled delay.

Each card was presented without comment, except Card III (which is the first to include two major figures and a peripheral minor figure). When this was presented the subject was reminded to remember to draw everything they see. If the patient omitted the peripheral minor figure in his reproduction of Card III, the examiner made the same statement before he or she introduced Card IV.

Two possible scoring systems are available for the Benton. The one chosen for the present experiment involved each design being objectively assessed on an "all-or-none" basis with no credit given for a partially correct reproduction. One point was scored for each correctly reproduced design. Guidelines to the principles underlying the scoring and specific scoring samples standardised the scoring procedure.

The Speed of Comprehension test

This test has four parallel forms (A,B,C,and D), three of which were used. Each version of the test is made up of a list of one hundred sentences about the world, half of which are true and half false. The false sentences were made up by pairing the subject half of one true statement with the predicate half of another true statement. These sentences were then checked to ensure that they were grammatically correct and unambiguous.

The sentences were presented on response sheets with 25 sentences on each page. Subjects were instructed to work down the list of sentences and write a tick or a cross next to each sentence, depending on whether it was true or false. They were told to work as quickly as possible and to complete as many sentences as they could in two minutes. They were told that there were no trick sentences, even thoughsome of the sentences may

look wrong or like trick questions because of the words that had been used. Before beginning they worked through a few practice sentences to make sure that there were no problems with the procedure.

The total number of sentences completed in the two minute period was taken as the subject's score on the test. The number of errors was also recorded. However, as there were no scaled or percentile score tables available for the over 65 age group, corrected scores could not be calculated from the error scores. In the unlikely event of a subject completing all 100 items in less than two minutes then it was possible to extrapolate from the time taken to complete 100 to calculate how many items would have been completed in the two minutes.

CHAPTER 8

Experiment Four: The effects of clinical depression on cognitive function in unmedicated elderly patients.

Introduction

The studies reviewed in Chapter 6 indicate that depression is associated with cognitive deficits, although the reported findings are not consistent. One possible source of these inconsistencies is that some of the studies assessed cognitive function in depressed subjects who were taking psychotropic medication. In many of the studies the medication status of the subjects was not specified, and in these cases it was assumed that they were medicated. It is known that treatment with tricyclic antidepressants causes impairment on a variety of cognitive measures, in particular those assessing verbal episodic memory (e.g. Lamping et al, 1984; Curran et al., 1988). Impairments resulting from medication could therefore be confounding and compounding impairments due to the depression per se. The primary aim of the present experiment was therefore to specify the nature of cognitive deficits in a group of unmedicated depressed elderly patients.

Cognitive deficits in depression have been widely documented on measures of list learning and recall, although it remains unclear which stage of processing is affected by depression. Some studies have found impairments on measures of learning and immediate recall of information, but not retention of information (Cronholm and Ottoson, 1961; Sternberg and Jarvik, 1976), while other studies have found subjects impaired on both measures (Kopelman, 1986; Coughlan and Hollows, 1984). Determining the measures that are affected by depression is an important step in understanding more specifically which memory processes are being influenced. For example, deficits on measures of immediate verbal

recall suggest an encoding or retrieval deficit, while impaired delayed recall performance indicates interference at the retention or retrieval stage of processing. The second aim of the study was to assess the memory performance of depressed patients with particular reference to verbal memory. In order to investigate which verbal memory processes are affected by depression, measures of the immediate and delayed recall of word lists were assessed.

One explanation of memory deficits in depressed subjects' is that they respond more cautiously than control subjects due to a lack motivation or confidence in their memory (Johnson and Marago, 1987). This possibility has been assessed using signal detection theory on recognition memory scores. Two studies have found that medicated depressed elderly subjects respond more cautiously than controls (Miller and Lewis, 1974; Neiderehe and Camp, 1985). However Watts, Morris and MacLeod (1987) found that when young subjects vocalised the words they were learning, they showed no response bias. Thus, the third aim of the present experiment was to use signal detection measures to determine whether or not unmedicated depressed elderly subjects responded more cautiously than control subjects on a recognition memory test.

The fourth aim of the study was to compare the performance of depressed and control subjects on further measures of verbal episodic memory obtained from the Fuld Object Memory Evaluation. The Fuld OME was designed for use with the elderly and is successful in characterising and differentiating memory impairments in elderly subjects. La Rue (1989) found that 44% of the depressed inpatients she tested on the Fuld OME scored within normal limits on all the measures, 37% had selective deficits and 20% had generalised deficits. The Fuld OME is a less effortful task than the Verbal Memory test as it incorporates a selective reminding procedure. The Verbal Memory test, on the other

hand, is more demanding as the materials are unstructured and recall therefore requires more explicit use of memory strategies.

Processing resource theory (Ellis and Ashbrook, 1987) predicts that depressed subjects will not be impaired when required to recall material presented in a structured way, as it is less effortful than recalling unstructured material such as word lists. The fifth aim was therefore to examine the effects of depression on patients' ability to recall structured prose and compare it with their ability to remember lists of unrelated words. To this end, the test battery included stories from the Logical Memory subtest of the Wechsler Memory Schedule (1987). Previous assessments of the effects of depression on short story recall have produced some conflicting results, with some finding subjects impaired (Kopelman, 1986; Watts and Sharrock, 1987), while others found depressed subjects unimpaired (Coughlan and Hollows, 1984; Williams et al., 1987). Subjects in these studies were either medicated or their medication status was unspecified.

The sixth aim was to test whether, and to what extent, depression reduces cognitive processing speed. Two measures in the test battery were intended to measure processing speed. The colour naming measure of the Stroop provided a list reading speed measure, while the Speed of Comprehension task (Baddeley, 1992) measured the rate at which subjects read, retrieve and process information from long-term memory.

Equivocal evidence has suggested that depressed patients experience contextual and attentional impairments as measured by the Stroop test. For example, Raskin et al. (1982) found that a group of depressed patients with mixed diagnoses were impaired on the Stroop task compared to controls. Conversely, Rush et al. (1983) found no Stroop performance decrements in a group of unmedicated patients with endogenous depression when they were compared to an age-matched

population of control subjects. The seventh aim was to follow up this evidence by providing more conclusive evidence of the effects of untreated depression on attentional control and the ability to make use of contextual information.

The digit span test was included to ensure that working memory was not affected by depression as suggested by existing evidence (Cassens et al., 1990). This is important as a depression-related working memory deficit could contribute to poor episodic memory performance.

The final aim of the study was to explore the effect of depression on visual episodic memory. In their review, Cassens et al. (1990) found considerable evidence of impairments on a variety of immediate visual memory measures and they suggest that a decrement on this measure is a reliable indicator of endogenous depression and pseudo-dementias. To date, research in this area has focused on immediate visual memory with scant attention paid to more delayed episodic visual memory. Impairments have been identified in depressed subjects on the immediate reproduction version of the Benton VRT, compared to normative data for the test (Shipley et al., 1981). It was therefore predicted that depressed subjects would be impaired on the more effortful version of the Benton VRT (form D) which was included in the test battery as it involves retrieving visual information after 15 second delay.

The aim of this study was to assess the performance of a group of unmedicated elderly depressed subjects on a range of cognitive tasks. Patients were assessed on three different measures of verbal episodic memory; an 'effortful' word list memory test, a less demanding object-name memory test (with selective reminding) and a memory test for structured prose. It was predicted that subjects would be most impaired on the task requiring the most effort and spontaneous structuring of the materials. Visual episodic memory, short-term memory, attention and

speed of semantic processing were also assessed. The objective was to characterise the breadth and nature of the predicted depression-related memory impairments and assess the contribution of other possible deficits (e.g. attentional control) to the predicted verbal memory impairment.

Method

Subjects

Eighteen unmedicated depressed subjects (ten female, eight male) aged 65-85 years who met criteria for entry in the antidepressant clinical drug trial (described in Chapter 7), were selected from the trial data and matched on age, sex and pre-morbid IQ with eighteen control subjects. The control subjects had been satisfactorily screened for depression using the MADRS. None of the subjects were taking psychoactive medication.

Design

A matched group design was used with subjects matched on measures of age, gender and NART IQ.

Procedure

The depressed subjects were tested on two separate occasions during the placebo run-in week of the clinical trial. Prior to the placebo week subjects had been drug-free for a two week wash-out period. On the first testing occasion, subjects were required to complete the Set B tests (the Verbal Memory test, the Benton visual retention test, the Speed of Comprehension task). On the second testing occasion they were assessed on the NART and the Schonell and set A tests (short story recall, Fuld Object Memory Evaluation, digit span, and the Stroop test). The tests are described in detail in Chapter 7. The control subjects' testing schedule followed the same pattern. All subjects were tested in their own homes.

Results

Patients and control group differences were analysed using paired t-tests. Some measures had skewed distributions and were transformed using a logarithmic transformation (Fuld total scores and the Stroop control times) or a square-root transformation (Fuld repeated retrievals). The skews were satisfactorily reduced by the transformations. Transformation of delayed recall and recognition hits and false alarm data did not reduce the skew in these variables, so Wilcoxon's signed rank test was used as parametric analyses could not be justified.

NART and MADRS scores

The depressed and control subjects' mean NART scores were equivalent: 116.1 (sd=8.54) and 116.9 (sd=7.4) respectively. The mean age of the depressed subjects was 76.5 years (sd=5.1) and the control subjects 77.2 (sd=5.9). The mean MADRS score of the depressed group was 30.6 (sd=4.1) and the mean score of the control group was 2.9 (sd=2.4). Subjects scoring more than 20 points on the MADRS are considered to be depressed.

Immediate and delayed recall

Depressed subjects were significantly impaired on the immediate recall measure of the Verbal Memory test ($t=2.3$, $p<0.05$). Wilcoxon's signed ranks test showed no difference between the two groups' delayed verbal recall performance ($z=-1.14$ $p=0.26$). There was no significant difference between depressed and control subjects in the number of words they could successfully retain ($z=-1.54$, $p=0.12$).

Table 8.1. Mean scores on the recall measures of the VMT.

	Depressed		Control	
	Mean	SD	Mean	SD
Immediate Recall	**6.3**	3.2	**8.7** *	3.2
Delayed recall	**3.2**	2.8	**4.6**	3.6
Forgetting (IR-DR)	**3.1**	2.3	**4.2**	2.7

*p<0.05

Delayed recognition memory

Wilcoxon's signed ranks test indicated that depressed subjects made significantly more false alarms than controls (z=-2.1, p<0.05) , but there was no significant difference between the two groups in the number of hits scored (z=0.76, p=0.45).

Signal detection analysis was carried out to calculate memory sensitivity, d' and response bias, ß. Depressed subjects were significantly impaired on the measure of memory sensitivity (t=1.8, p<0.05), but not on the measure of response bias (t=-0.02, p=0.5).

Table 8.2. Mean scores on the recognition measures of the VMT

	Depressed		Control	
	Mean	SD	Mean	SD
Recognition 'hits'	**12.2**	2.3	**12.5**	3.2
False alarms	**3.2**	3.0	**1.3** *	1.5

*p<0.05

Fuld Object Memory Evaluation

The mean scores of the depressed subjects were considerably lower than the controls on all measures of the Fuld OME (see table 8.3). Depressed subjects recalled significantly fewer objects on the delayed recall measure of the Fuld OME than the control subjects (t=2.0, p<0.05).

However, a paired t-test performed on transformed data showed no significant difference between depressed and control subjects' total retrieval scores (t=1.5, p=0.08) or their repeated retrieval scores (t=1.1, p=0.14).

Table 8.3. Mean scores on the measures of the Fuld OME.

	Depressed		Control	
	Mean	SD	Mean	SD
Total retrieval	**33.8**	19.8	**41.5**	5.3
Repeated retrieval	**22.9**	21.5	**28.6**	6.8
Delayed recall	**8.1**	2.8	**9.3 ***	1.0

* $p<0.05$

Delayed short story recall

The mean scores of the two groups were almost identical (see table 8.4). There was no significant difference between depressed and control subjects on the measure of delayed short story recall (t=0.32, p=0.62).

Table 8.4. Mean delayed short story recall scores.

	Depressed		Control	
	Mean	SD	Mean	SD
Delayed story recall	**6.6**	3.4	**6.2**	4.0

Benton visual retention test

The control subjects mean score was slightly higher than the depressed subjects (see table 8.5). However, there were no significant differences between depressed and control subjects on the Benton visual retention task (t=0.7, p=0.24).

Speed of Comprehension test

Depressed subjects processed significantly fewer sentences than the control subjects on the this task (t=2.37, p<0.05) (see table 8.5).

The Stroop test

The mean scores on both the control and interference condition of the Stroop test indicate that the depressed subjects were slightly slower than the control subjects (see table 8.5). Stroop interference was calculated by subtracting the control colour naming time from the Stroop colour naming time. No significant difference was found between depressed and control subjects' performance on the colour naming task ($t=1.4$, $p=0.19$) or the Stroop interference task ($t=1.6$, $p=0.14$).

Digit Span Test

The mean score of the depressed subjects was slightly higher than the control subjects (see table 8.5). There were no significant differences between the depressed and the control group on the test ($t=0.6$, $p=0.53$).

Table 8.5. Mean scores on the Benton, Speed of Comprehension, Stroop measures and the digit span test.

	Depressed		Control	
	Mean	SD	Mean	SD
Benton VRT	**3.9**	2.9	**4.5**	2.0
Speed of Comp.	**41.6**	17.4	**54.2** *	19.0
Stroop control	**80.0**	21.4	**70.5**	37.9
Stroop interference	**100.1**	51.4	**81.5**	43.1
Digit span	**14.3**	5.0	**13.4**	2.5

*$p<0.05$

Correlations between cognitive tests.

Pearsons correlations were computed on the complete variable set of the depressed and control subjects together. The pattern of intercorrelation between the tasks provided information about the degree to which different tasks were measuring the same processes. The correlations that were significant at the critical level of $p<0.01$ are summarised in Table 8.6. As expected, different measures on the same task

were highly correlated e.g. Fuld total retrieval with repeated retrieval, as were different tasks measuring verbal memory e.g. Fuld delayed recall scores correlated with Verbal Memory test immediate and delayed recall. Intercorrelation were also found between the Benton VRT, and digit span, delayed short story recall and both the colour naming and interference conditions of the Stroop. One further notable intercorrelation was found between the colour-naming task and the Speed of Comprehension test.

Table 8.6. Summary of intercorrelations between the memory test.

TEST	Correlation -r
FULD total, FULD repeated	0.99 *
FULD total, FULD delayed	0.54 *
FULD repeated, FULD delayed	0.47 *
FULD delayed, Stroop Interference	-0.47 *
FULD delayed, VMT immed. recall	0.49 *
FULD delayed, VMT delayed	0.51 *
Short story, FULD delayed recall	0.45 *
Short story, VMT delayed recall	0.53 *
Short story, Benton VRT	0.49 *
VMT, immediate, VMT delayed	0.77 *
VMT, immediate, Speed of Comp.	0.61 *
Stroop control, Stroop interference	0.5 *
Stroop control, VMT immediate	-0.59 *
Stroop control, VMT delayed	-0.53 *
Stroop control , Benton	-0.53 *
Stroop control, Speed of Comp.	-0.71 *
Stroop interference, Benton	-0.56 *
Digit span, Benton	0.62 *

* $p<0.01$

Discussion

Verbal memory performance

It was predicted that unmedicated depressed subjects would exhibit performance deficits on demanding cognitive tasks that required them to recall unstructured verbal materials. Verbal episodic memory was assessed using three measures which required varying degrees of effort; the verbal memory test, the Fuld OME and delayed short story recall test.

Only the immediate recall component of the depressed subjects' verbal memory performance was impaired on the Verbal Memory test. Delayed recall performance was equivalent in the two groups indicating that they did not differ in their ability to retain the information for delayed recall. These results support the proposition that deficits in depression occur at the acquisition stage of the memory process and do not affect retention of information (Cronholm and Ottoson, 1961; Sternberg and Jarvik, 1976). However, the apparently neutral effect of depression on the delayed recall measure may be due to a floor effect on the task as one third of the depressed and control subjects failed to recall any of the words. This floor effect reflects a methodological problem with the measurement of recall and recognition in the elderly. Recall tasks require subjects to retrieve responses with very little support from external cues, whereas in a recognition task the target stimulus itself serves as a retrieval cue. Recognition memory tests therefore tend to be less sensitive to depression related memory deficits than free recall tests and must therefore be relatively difficult in order to detect differences between groups (Calev and Erwin, 1985). While the test used in this experiment may have been difficult enough (but not too difficult) to differentiate the two groups on

both immediate recall and delayed recognition, it was too taxing to discriminate delayed recall differences.

The unmedicated depressed subjects scored as many 'hits' but more 'false alarms' than the control subjects. Thus, depressed subjects made more positive 'yes' responses than controls and were therefore responding less cautiously, although there was no quantitative difference in response bias between the two groups. Signal detection measures indicated that the depressed patients exhibited a reduction in memory sensitivity. This contrasts with the findings from a series of studies in which medicated depressed subjects responded more cautiously than control subjects, but did not differ on measures of sensitivity (Miller and Lewis, 1984; Dunbar and Lishman, 1984; Niederehe and Camp, 1985). The pattern of recognition memory performance in this sample of unmedicated depressed subjects appears to differ from the pattern reported in other studies. As the depressed subjects in previous studies were either medicated or did not have their medication status specified, it is possible that the differences in performance were due to the medication.

Depressed subjects showed no significant deficits on either the total retrieval or the repeated retrieval measure of the Fuld OME, although they had considerably lower mean scores than controls on both these measures. The depressed patients may not have been significantly impaired on these measures of the Fuld OME because they required less effort than the Verbal Memory test for a number of reasons. Firstly, there were only 10 objects to be remembered (compared with the 16 words in the VMT). Secondly, the objects were identified by touch and sight at the beginning of the test, which may have aided encoding. Thirdly, the selective reminding procedure provided the subject with additional opportunities to encode the object names, whilst in the Verbal Memory test, the subject has only one opportunity to encode each word.

The delayed recall impairment of the depressed subjects on the Fuld OME suggests that retention of information may be affected by depression. The results of the Fuld OME and the Verbal Memory present a paradox in terms of the effects of depression on acquisition, retention and retrieval. Contrary to the results of the Verbal Memory test, the delayed Fuld results suggest that depressed subjects are able to encode information effectively, but not retain and retrieve it. This paradox can be explained to some degree by the possibility that the effective encoding may be a direct result of the extensive support provided by the selective reminding procedure in the Fuld OME. This support was not provided in the delayed recall phase which thus required more effort and was consequently more difficult for depressed patients.

The results of the Verbal Memory test and the Fuld OME support one of the underlying assumptions of Ellis and Ashbrooks' resource allocation model (1987) which posits that depressed subjects are more likely to be impaired on tasks that require a high degree of cognitive 'effort', than on less cognitively demanding tasks. Related to this is the second assumption of the model that depression has a less impairing effect on recall of structured materials than on unstructured lists of unrelated words. The depressed subjects in the present experiment recalled as many units of a highly structured short story as controls which would suggests that they made spontaneous and effective use of the prose structure. This is contrary to Watts and Sharrocks' (1987) finding that severely depressed, medicated subjects were impaired on free recall and cued recall of a complicated passage of prose. However the passage of prose they used in their study was relatively complicated and the subjects were severely depressed and on medication, which may account for the impairments they found.

Benton visual retention test

Depressed subjects correctly reproduced as many designs as the control subjects on the Benton VRT. This contradicts previous research into the effects of depression on visual memory which predicted that depressed subjects would show decrements on the Benton VRT. For example, Cassens et al. (1990) claim in their review that decrements in immediate visual memory are reliable indicators of depression. In accordance with this claim, Shipley et al. (1981) found unmedicated depressed subjects were impaired on the immediate reproduction version of the Benton VRT. The failure here to detect impairments on the most taxing version of the Benton VRT suggests that visual memory remains intact in elderly depressed subjects who are not taking psychotropic medication. Channon, Baker and Robertson (1993) found that medicated depressed subjects were also unimpaired on a visual working memory task which suggests that medication is unlikely to alter performance on the Benton VRT.

Performance on the Benton correlated highly with performance on the digit span test. Assuming that the articulatory loop and visuo-spatial scratch pad normally produce correlated performance, this suggests that performance on the Benton is dependent upon the visuo-spatial scratch pad component of working memory. As scores on tasks that depend on the components of working memory are correlated, it can be concluded that neither verbal short-term memory nor visual short-term memory are compromised in depression.

Speed of Comprehension

Depressed subjects were impaired on the Speed of Comprehension task. Performance on the task involves two elements that could be affected by depression; general psychomotor speed and semantic retrieval. An impairment of either or both of these could underlie the deficit in the

patient group. Performance on the Speed of Comprehension task was found to correlate highly with performance on the Stroop control measure. Both tasks measure psychomotor speed, but the depressed subjects were no slower at naming the colour patches than the controls. This suggests that the component of the Stroop control time that predicts Speed of Comprehension is unlikely to be the 'automatic' colour naming and general psychomotor component, but rather the more effortful task of retrieving information from semantic memory. Previous studies have reported that performance on an unpaced semantic memory task is unaffected by depression (Niederehe, 1985). The present task required subjects to sustain their performance for the duration of two minutes. The pacing of the task may therefore be the factor that made the task more difficult for depressed patients than controls.

The Stroop test

Depressed patients were found to be unimpaired on the control and interference measure of the Stroop test, although their mean scores show that they took slightly longer to complete the task than controls. This is contrary to the finding of Raskin et al. (1984) who tested 277 medicated depressed patients and 112 controls aged 16-70 years and found impairments in the patients on measures of the Stroop (control, interference and the number of errors). Rush et al. (1983) found unmedicated patients to be unimpaired on the task which raises the possibility that impairments on the task may be caused by medication.

Digit span test

The finding that digit span performance is unaffected by depression is consistent with results from similar studies indicating that tasks which involve working memory are fairly robust to the effects of depression.

General Discussion

This study provides further insight into the pattern of cognitive deficits in unmedicated elderly depressed patients. As predicted on the basis of previous studies, deficits were identified on measures of verbal episodic memory that require effort and the spontaneous use of organisational strategies to structure unrelated words. Unfortunately, the effect of depression on retention and delayed retrieval were not reliably assessed as both the measures of delayed recall were subject to either floor or ceiling effects. Memory deficits were not found when the learning of materials was less demanding as on the immediate recall measures of the Fuld OME task or when the verbal material was presented as structured prose. Depressed subjects' impairments on the Speed of Comprehension task may have resulted from the demands imposed by the pacing of the task.

Visual memory was unimpaired in the depressed subjects which suggests that verbal memory tests are more sensitive to the effects of depression than visual tasks. Visual and verbal memory may also be differentially affected by depression. Performance on the Stroop and the digit span was unimpaired in unmedicated depressed subjects which indicates that verbal encoding deficits may not be attributed to attentional limitations or working memory deficits.

The performance of unmedicated depressed subjects in the present study differed from that of medicated patients in previous studies on a number of measures, particularly the measures of verbal recognition memory. The Stroop test result replicated previous findings using unmedicated subjects, but were contrary to those using medicated subjects. These inconsistent results between groups of medicated and unmedicated patients stress the importance of investigating the effects of depression on cognitive processes in drug-free subjects.

CHAPTER 9

Experiment Five: The effects of paroxetine and lofepramine on cognitive function in depressed elderly patients.

Introduction

Evidence from animals studies (e.g. Flood and Cherkin, 1987) and studies of humans with pre-existing cognitive deficits (e.g. Martin et al., 1989) have indicated that the SSRIs have potential as cognitive enhancers. Slight improvements in delayed episodic memory were also found in a group of young healthy volunteers (Experiment Two) and in one of the three elderly healthy volunteers (Experiment Three). The tentative nature of these findings necessitates their replication. Previous to these findings, SSRI-related improvements had only been found in subjects with deficits induced by alcohol or alcoholic organic brain disorders, although none of these studies involved paroxetine (Weingartner et al., 1983; Martin et al., 1989). In the light of previous findings, it was proposed that if paroxetine genuinely enhanced memory, the effects of the drug would be manifested more clearly in depressed elderly subjects than in healthy volunteers. This prediction was based on the assumption that improvements may be more detectable in depressed elderly subjects as they have pre-existing deficits resulting from the combined effects of depression and old age.

To date, the results of previous studies assessing the effects of the SSRIs on memory in healthy volunteers suggest that they neither impair, nor improve performance (Curran et al., 1986; Moskowitz and Burns, 1988). Previous studies of paroxetine had focused only on the drugs' psychomotor and alerting properties in young healthy volunteers. The findings were conflicting; Kerr et al. (1991) found paroxetine raised CFFT, while Cooper et al. (1989) found that paroxetine did not improve

performance on a range of tasks including CFFT. The results of Experiment Two failed to identify raised CFFT or improvements on attentional tasks in young healthy volunteers.

This study was designed to compare the cognitive performance of elderly depressed patients treated with either paroxetine or lofepramine for seven weeks. Experiment Four showed that elderly depressed patients have cognitive deficits compared to healthy elderly controls; the objective of this study was to determine whether paroxetine and lofepramine would have differential effects on these existing impairments.

Lofepramine was chosen as the comparison drug for the clinical trial because it has relatively weak anticholinergic properties compared with other tricyclics, e.g. imipramine and amitriptyline. Lofepramine was nevertheless predicted to have less favourable cognitive side-effects than paroxetine (Brown and Watson, 1991).

As the subjects were assessed on three parallel versions of the same tests during the clinical trial period, practice-related improvements in performance were predicted. In an attempt to control for these practice effects, the performance of subjects from both drug groups was compared to a group of unmedicated non-depressed elderly subjects. The inclusion of a control group permitted the comparison of data reflecting the combined effects of drugs and practice with data reflecting the effects of practice alone.

The cognitive effects of paroxetine and lofepramine were investigated in elderly patients rather than in young patients for a number of reasons. Firstly, there is a higher incidence of depression in the elderly than in the young, such that age-related biochemical changes in the brain may cause late-onset depression. Secondly, as cognitive deficits are independently associated with both old age and depression, any drug that exacerbates either of these deficits may be counter-therapeutic. Healthy

volunteer studies have shown that some tricyclic antidepressants cause cognitive impairments (Lamping et al., 1984; Branconnier et al., 1982). It has also been suggested that old age is a risk factor for central nervous system toxicity associated with tricyclic antidepressant treatment (Preskorn and Jerkovic, 1990). It is therefore particularly important to consider the cognitive side-effects of antidepressant drugs when treating elderly patients.

The primary purpose of this study was to determine the effects of paroxetine on verbal episodic memory. Previous SSRI studies have demonstrated improvements in this aspect of memory e.g. Martin et al. (1989), and Stapleton et al. (1989) found that the SSRI, fluoxetine, improved verbal recall but not recognition performance in patients with alcoholic organic brain syndrome. Episodic memory impairments have also been documented in depression (e.g. Sternberg and Jarvik, 1976). The results of Experiment Four indicated that depression impaired performance on effortful tasks, such as the Verbal Memory test, but not on tasks that require less effort such as the Fuld OME. Another reason for focusing on episodic memory is that drugs with anticholinergic side-effects have been found to impair episodic memory (Branconnier et al., 1982; Curran et al., 1988). Lamping et al. (1984) found that treatment with the tricyclic, amitriptyline, did not alter immediate and delayed verbal learning scores or false alarm scores when compared with clovoxamine (a serotonin and noradrenaline reuptake inhibitor), although the number of recognition hits was significantly reduced during the 28 days of the trial. Previous research has shown that a list learning task such as the Verbal Memory test, provides recall and recognition measures which are sensitive to the effects of depression, 5-HT reuptake inhibitors (Martin et al., 1989) and anticholinergic effects caused by tricyclic antidepressants (Branconnier et al., 1982). The Fuld OME was included in the battery as it was designed

specifically for testing elderly subjects and is known to be sensitive to memory impairments in the elderly (La Rue, 1989). It was also predicted to be sensitive to the effects of the drugs.

A second aim of the study was to explore the effects of paroxetine on memory for structured material using the Wechsler Logical Memory test (the short story recall test). To date, the effects of the SSRIs on memory for structured material have not been explored. However performance on the Logical Memory test was unaffected by clovoxamine and the tricyclic amitriptyline (Lamping et al., 1984). Evidence from Experiment Four suggested that depression does not affect recall of highly structured verbal material so any improvements or impairments in performance found on this task are likely to be due to the effect of the drugs rather than their depression ameliorating properties.

There is a small amount of evidence to suggest that SSRIs improve visual memory. Improvements were found on the visual memory component of the Wechsler Memory Scale in patients with alcoholic organic brain syndrome treated with fluvoxamine (Martin et al., 1989). Performance on a figure matching task was unaffected by paroxetine in healthy volunteers (Deijen et al., 1989). A third aim of this study was therefore to assess of the effects of paroxetine on visual episodic memory in a group of depressed patients using the Benton VRT. Lamping et al. (1982) found that amitriptyline did not affect performance on the Benton VRT when compared with clovoxamine, which suggests that visual memory is not susceptible to anticholinergic side-effects. The results of Experiment Four indicated that performance on the Benton VRT is unaffected by depression.

A fourth objective of the study was to appraise the effects of paroxetine and lofepramine on general cognitive processing speed and retrieval of information from semantic memory using the Speed of

Comprehension test (Baddeley, 1992). To date no studies have evaluated the effects of the SSRIs on this task. Tricyclic antidepressants with varying sedative and anticholinergic side-effects had no effect on semantic retrieval ability in healthy volunteers (Curran et al., 1988). The findings of Experiment Four indicated that depression caused impairments on the Speed of Comprehension task, so this deficit must be taken into account when considering the effects of the drugs.

A number of studies exploring the effects of SSRIs on cognitive processes in healthy volunteers have included measures of attention in their test batteries. The results of these studies suggest that SSRIs have a neutral effect on some measures of attention e.g. the continuous performance task was unaffected by acute doses of fluvoxamine and alcohol (Eckardt et al., 1986) and zimeldine (Linnoila et al., 1983). Other studies have shown improvements on attentional tasks e.g. finger tapping (Saletu el al., 1980). The task included in this test battery is the Stroop test which is a complex measure of attention that reflects several processes. The colour naming test assesses cognitive processing speed while the interference task measures attentional control ability. A further reason for including the Stroop task in the battery is that interference on the Stroop task has been found to increase when cholinergic activity is reduced by the administration of the muscarinic antagonist, scopolamine (Wesnes and Revell, 1984) .

The final aim of the study was to establish the effect of paroxetine on short term memory using the digit span test. Cooper et al. (1989) found that paroxetine did not potentiate the impairments on digit span performance produced by alcohol and a variety of sedative and psychomotor-impairing drugs. Fudge et al. (1990) found that neither of the SSRIs, fluoxetine or trazadone, affected digit span performance in a group of depressed outpatients. There exists conflicting evidence that

short-term memory capacity is sensitive to anticholinergic effects. Curran et al. (1988) showed that it was the sedative, rather than anticholinergic effects of anti-depressant drugs lead to short-term memory impairments. Rusted and Warburton (1988) explored the effect of the muscarinic antagonist, scopolamine on a digit span and mental rotation task and found that performance was unaffected by scopolamine when the task was completed alone or with secondary tasks that were unrelated to the primary task. However both tasks were selectively sensitive to task-specific interference (concurrent articulation in the case of digit span and concurrent spatial tapping in the case of the mental rotation task). This suggested that scopolamine selectively impairs the central executive component of working memory while leaving the two "slave" systems intact. Thus, the anticholinergic effects of lofepramine may produce impairments of digit span performance.

It was predicted that cognitive performance on the tasks described may improve in both groups of elderly depressed patients as a result of the anti-depressant action of paroxetine and lofepramine. Treatment with paroxetine was expected to confer an additional advantage due to its possible cognitive enhancing properties and its lack of anticholinergic effects. Subjects treated with lofepramine were expected be comparatively impaired on some tasks as a result of the drug's anticholinergic effects. It was predicted from the results of previous studies that measures of verbal episodic memory would be most sensitive to the effects of the two drugs.

Method

Subjects

Fifteen subjects who had been treated with paroxetine were selected from the clinical trial sample and matched with fifteen subjects who had been treated with lofepramine and fifteen healthy control subjects.

Subjects were matched on age, sex, and pre-morbid IQ measured by the NART. Nine of the subjects in each group were female and six were male. The patient groups were different from the group selected in Experiment Four, although the control subjects were the same. Details of the test materials used and the procedure are described in Chapter 7.

Results

The results of the Benton, Digit Span Test, delayed Short Story recall test and both measures of the Stroop Test were analysed using a repeated measures ANOVA with one between subject factor i.e. subject group (paroxetine, lofepramine, control) and one within subject facor, i.e. testing occasion (baseline, T2 and T3). Some of these measures had skewed distributions and were transformed using a logarithmic transformation (Stroop interference) or a square root transformation (Short Story test and digit span test). Data from all the other cognitive tests were analysed using non-parametric measures as the data were not normally distributed and logarithmic transformations did not reduce the skew variables. The scores from the three groups were analysed using Friedmans' test (the non-parametric equivalent of a repeated measures ANOVA) as the groups were matched. Summary tables of parametric analyses of all the data are in Table 9.0, Appendix B.

Cognitive assessments on Set A and Set B test were made in the placebo week of the clinical trial (baseline). Each set of tests was then administered on two further occasions, T2 (day 7 for Set B and day 21 for Set A) and T3 (day 35 for Set B and day 56 for Set A). In order to assess change in performance the groups were compared on baseline scores, on baseline minus T2 difference scores and on baseline minus T3 difference scores. Difference scores at T2 and T3 were calculated by subtracting the baseline scores from the T2 and T3 scores respectively. Where differences between the three groups were found, the Wilcoxons signed ranks test was used to identify which of the groups differed significantly. As a large number of measures were analysed the critical value for significance was adjusted to $p<0.01$ and results at the level of $p<0.05$ were interpreted as being marginally significant. Table 9.1. shows that there were no

significant differences between the ages or NART scores of the three groups of subjects.

Table 9.1. Mean ages and NART scores.

		Paroxetine Group	Lofepramine Grp	Control Group
NART	Mean	**118.6**	**116.3**	**118.2**
	SD	7.2	5.6	5.7
AGE	Mean	**75.8**	**75.5**	**76.2**
	SD	5.9	5.2	5.8

Figure 9.1. shows that there is a considerable improvement in depression as measured by the MADRS scores once active treatment had begun (day 1). After 3 weeks active treatment, mean MADRS scores had been reduced to the critical level for depression (i.e. 20). No significant differences were found between the paroxetine and lofepramine group on MADRS scores on any of the six testing occasions.

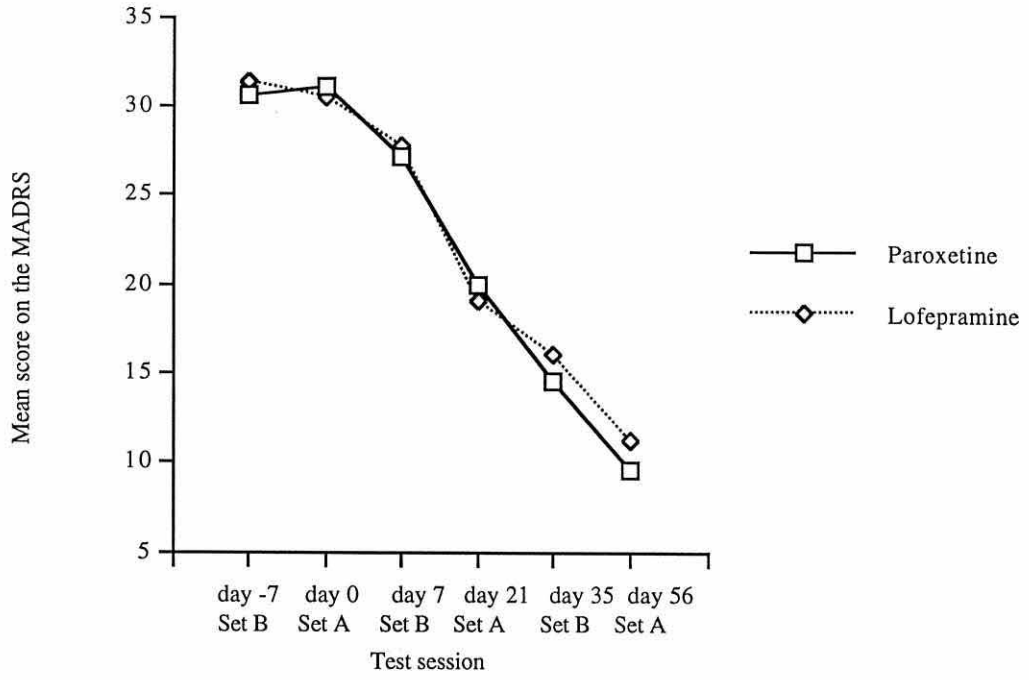


Figure 9.1. Mean scores of the paroxetine and lofepramine groups on the MADRS.

Verbal Memory test (Set B)

Immediate Recall

Figure 9.2. shows that the scores of the paroxetine group at T3 had more of an upward trend from baseline and T2 than the scores of the lofepramine group, which did not change between T2 and T3. The scores of the control group decreased at T2, and were lower at T3 than at baseline indicating that there were no overall practice effects on the task. Friedman's ANOVA revealed a marginally significant difference between the immediate recall performance of the three groups at baseline (χ=9.79, $p<0.05$). Wilcoxon's signed ranks test identified significant differences between the lofepramine group and the control group at baseline ($z=-3.19$, $p<0.01$) and a marginally significant difference between the paroxetine group and the control group ($z=-2.05$, $p<0.05$). This confirms the differences between depressed and control subjects reported in Experiment Four. Freidman's ANOVA identified a marginally significant difference between the T2 scores (χ=8.19, $p<0.05$) which Wilcoxon's signed

ranks test showed to be signifcant between the lofepramine and the control group (z=-2.72, p<0.01). There were no differences between the T3 scores of the three groups (χ=1.04, p=0.61) or between the lofepramine group and the paroxetine group on any of the three testing occasions.

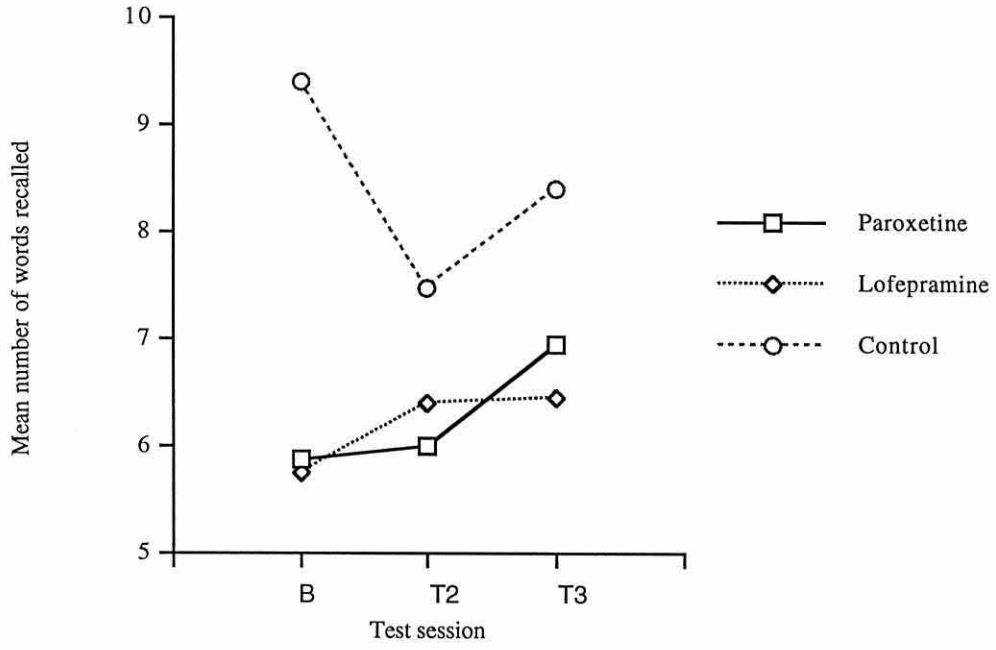


Figure 9.2. Mean immediate recall scores on the Verbal Memory test

Delayed recall

Both the paroxetine and the control groups' performance declined at T2 but all the groups show an improvement at T3 compared with baseline (see figure 9.3.). Friedman's ANOVA showed no significant differences were found between the groups at baseline (χ=1.4, p=0.5), or T2 (χ=3.2, p=0.3) or T3 (χ=2.1, p=0.4) on delayed recall performance.

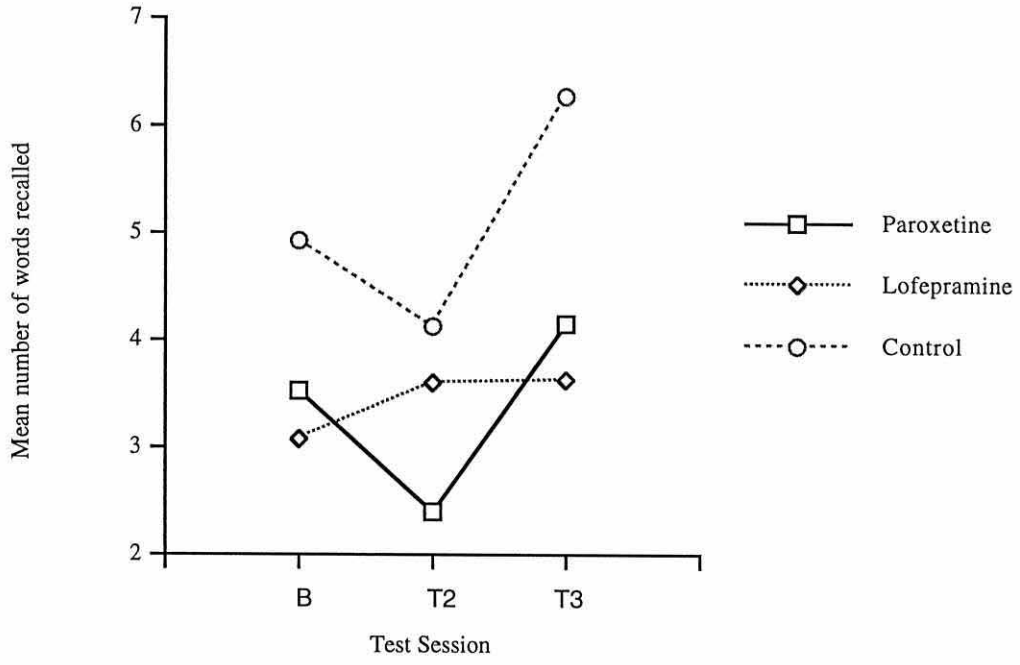


Figure 9.3. Mean delayed recall scores for the paroxetine, lofepramine and control groups

Recognition hits

Figure 9.4. shows that the performance of the paroxetine group was superior to the lofepramine group on all testing occasions but that neither group improved during the clinical trial. The control group's scores were superior at baseline but decreased to the level of the lofepramine group at T2 and despite improving at T3 they did not regain baseline levels of performance. Friedman's ANOVA showed the number of 'hits' made on the recognition phase of the VMT did not vary significantly between the three groups at baseline (χ=2.6, p=0.3), or T2 (χ=1.1, p=0.6) or T3 (χ=0.4, p=0.8).

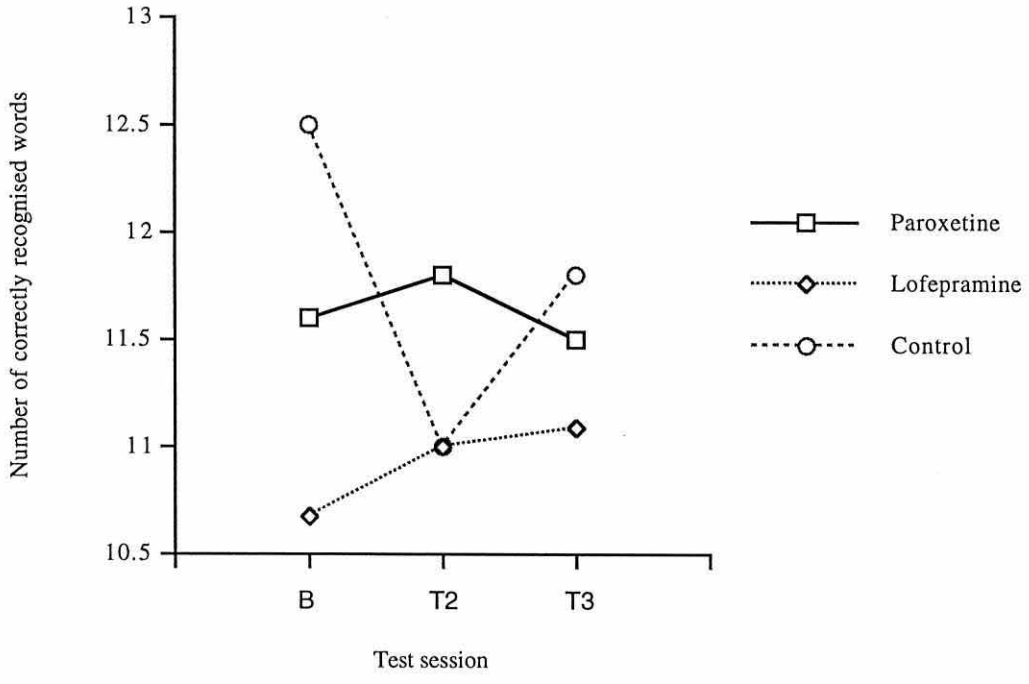


Figure 9.4.Mean recognition 'hit' scores on the Verbal Memory Test

Recognition false alarms.

The paroxetine-treated group showed a very slight downward trend in the number of false alarms scores, while the lofepramine group showed an upward trend at T2. The performance of the control group was superior throughout and showed little change over the three testing sessions (see figure 9.5.). Friedmans' ANOVA indicated no significant difference between the three groups in the number of false alarms responses made at baseline (χ=4.6, p=0.1) T2 (χ=0) and T3 (χ=1.5, p=0.5).

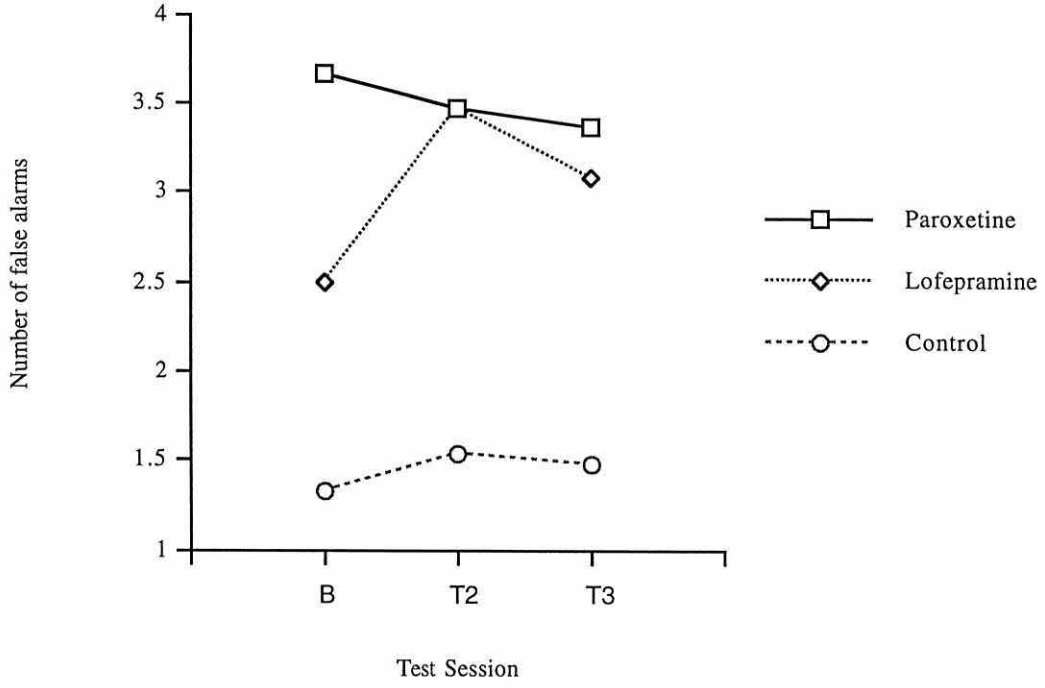


Figure 9.5. Mean false alarms scores on the Verbal Memory test

FULD Object Memory Evaluation (Set A)

Fuld total retrieval scores

Both the paroxetine and lofepramine scores were lower at T2 than T3 and baseline. The paroxetine group demonstrated more of an upward trend in performance between T2 and T3 than the lofepramine treated subjects (see figure 9.6.). The control groups' scores were better on all testing occasions. They showed no decrease at T2 and a slight increase at T3.

Friedman ANOVA showed no significant difference between the three groups of subjects either at baseline (X=4.2, p=0.2), or T2 (X=2.7, p=0.3) or T3 (X=5.7, p=0.06) on the Fuld total retrieval scores.

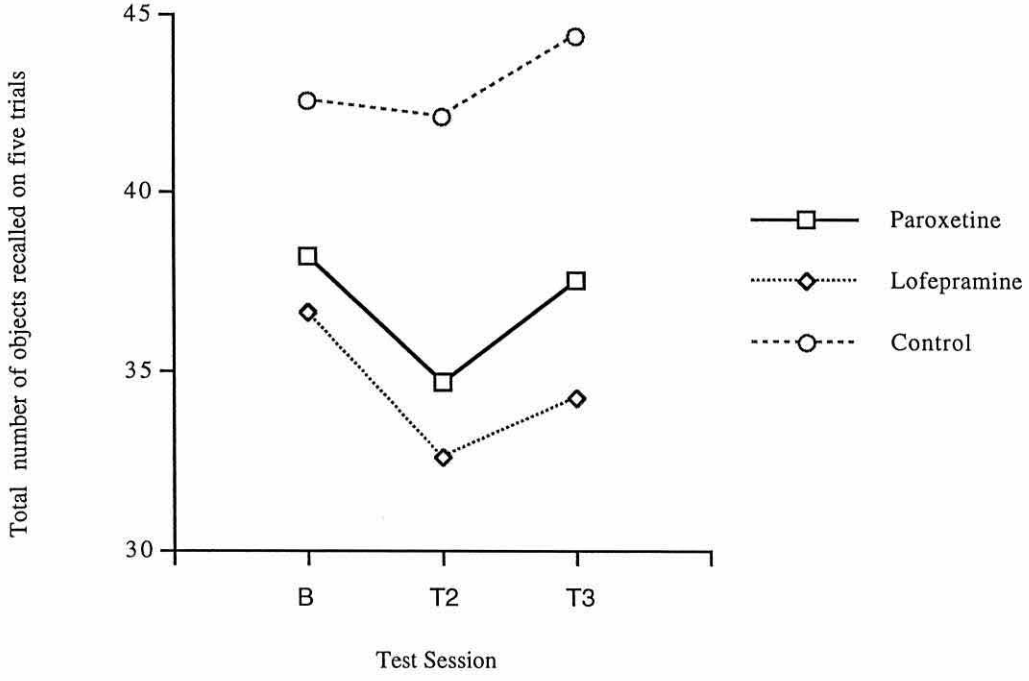


Figure 9.6. Mean total retrieval scores on the Fuld OME

Fuld repeated retrieval

As with the Fuld total retrieval scores, there was a decline in repeated retrieval scores at T2 from baseline, although there was an improvement at T3 in all the groups. The paroxetine group improved slightly more than the lofepramine group at T3 (see figure 9.7.). The pattern of the control groups' performance followed that found on the Fuld total retrieval scores. There were no significant differences between the three groups at baseline (X=2.1, p=0.4), or T2 (X=1.1, p=0.6) or T3 (X=3.4, p=0.2).

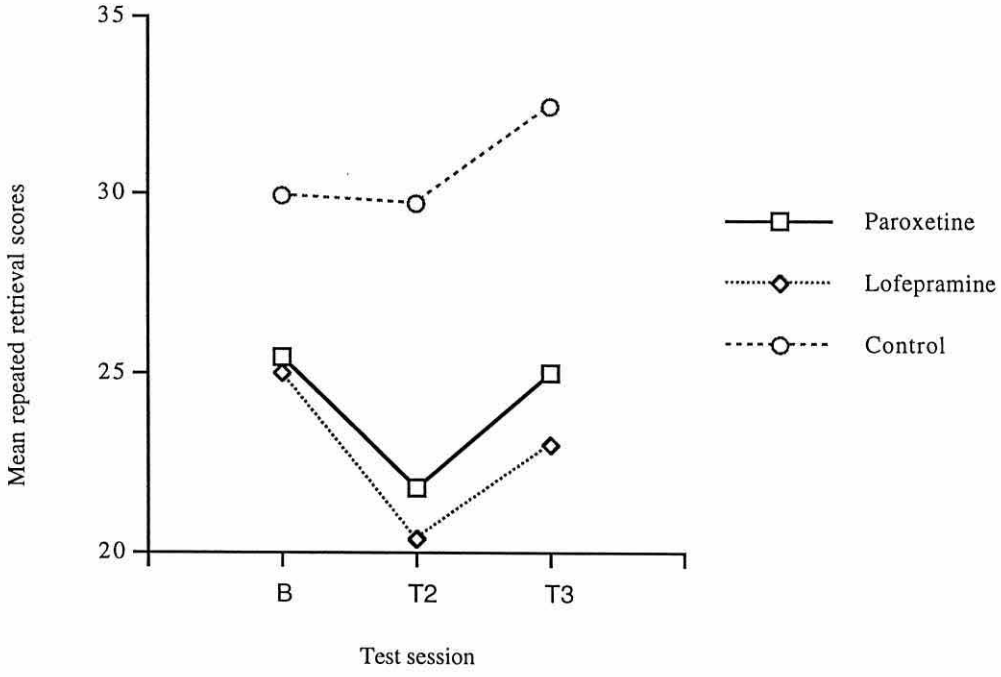


Figure 9.7. Mean repeated retrieval scores on the Fuld OME

Delayed Fuld OME

Figure 9.8. shows that the paroxetine group scored more highly than the lofepramine group at baseline and maintained a higher level of performance over the testing sessions, while the lofepramine groups' performance declined. The performance of the control group was superior on all testing occasions.

Friedmans ANOVA showed a marginally significant difference between the performance of the three groups at baseline on the delayed recall measure of the Fuld OME (χ=6.86, p<0.05), but there were no differences at T2 (χ=4.3, p=0.1) or T3 (χ=0.14, p=0.9). The differences at baseline were analysed using Wilcoxon's signed ranks test and found to be marginally significant between the control group and the lofepramine group (z=-2.15, p<0.05). There were no differences between the paroxetine group and the control group (z=-1.8, p=0.07) or between the paroxetine and lofepramine groups (z=-0.36, p=0.7). The differences between the patients groups and the control group confirms the findings of Experiment Four.

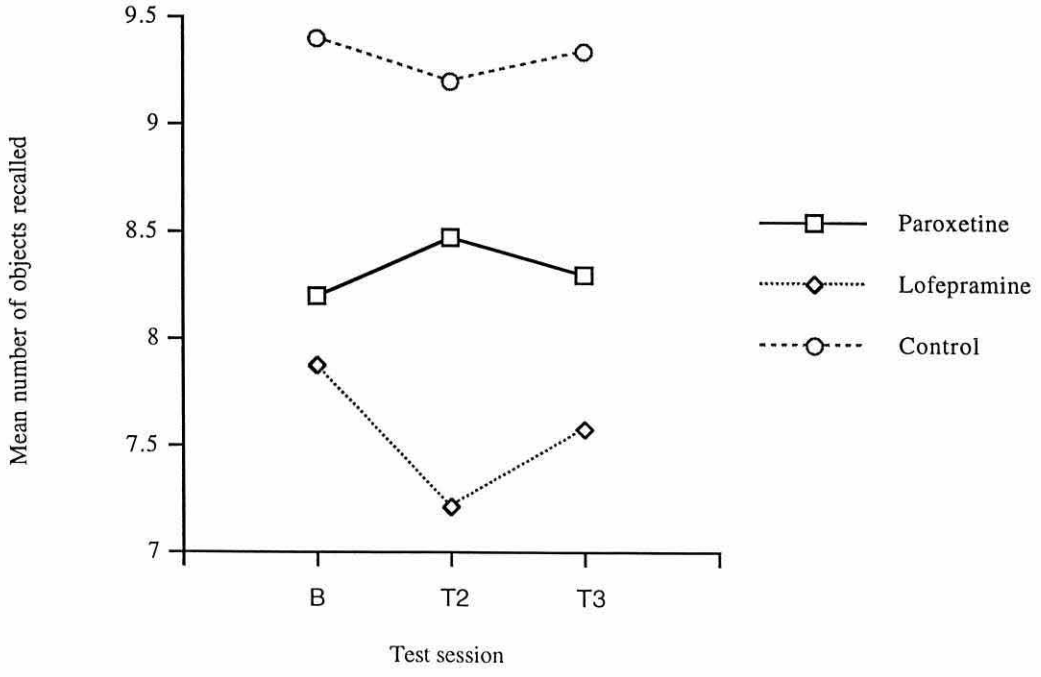


Figure 9.8. Mean delayed recall scores on the Fuld OME

Short story recall (Set A)

Figure 9.9. illustrates that the performance of the paroxetine group improved dramatically from baseline at T2 but then returned to baseline levels at T3. Both the lofepramine and the control groups performance picked up over the three testing sessions.

A repeated measures ANOVA revealed that there was no significant interaction between subject group and test day on delayed short story recall (F=0.2, df=4,48 p=0.95).

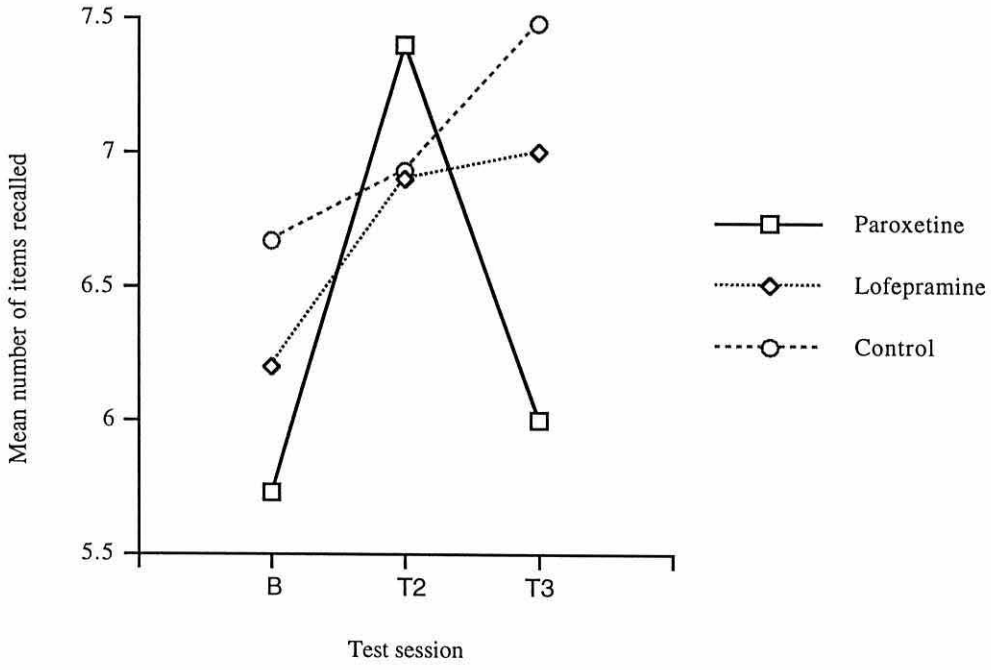


Figure 9.9. Mean number of items recalled on the short story recall test

The Benton Visual Retention Test (Set B)

Figure 9.10. shows that the performance of all three groups followed a similar pattern, apart from a decline in the lofepramine groups performance at T2. The control group's performance was superior and showed no sign of practice on the task. Scores were analysed using a repeated measures ANOVA. No significant interactions were obtained (F=0.88, df=4,48 p=0.48).

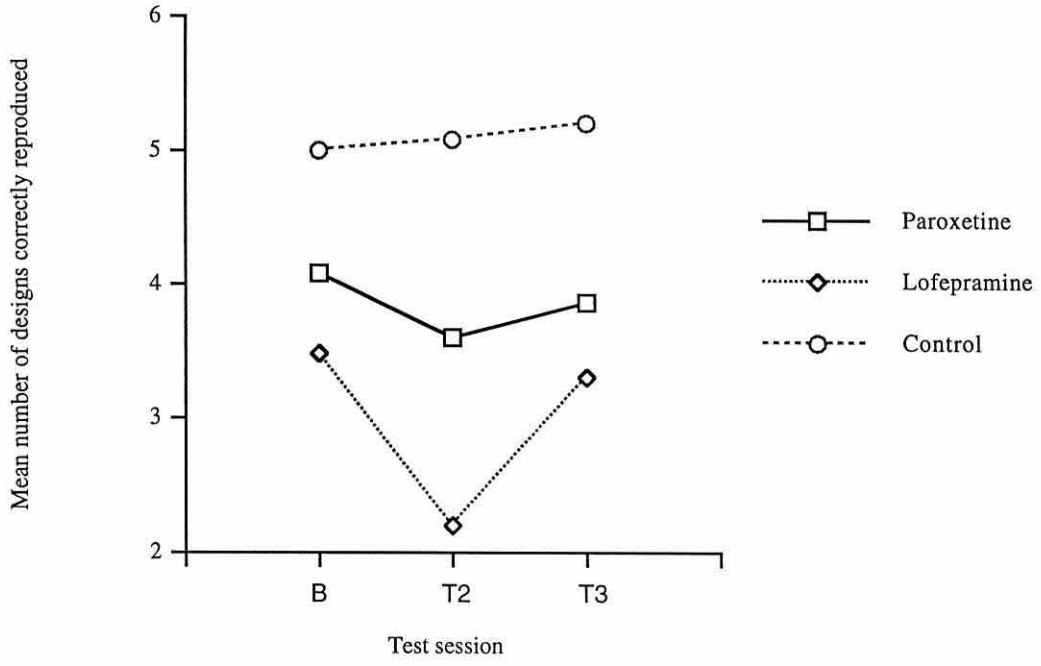


Figure 9.10. Mean number of designs correctly reproduced on the Benton VRT

Speed of Comprehension Test (Set B)

Figure 9.11. illustrates that the performance of the paroxetine and lofepramine groups was almost identical while the control groups performance was markedly superior. All three groups improved over the three testing sessions indicating that the task is susceptible to the effects of practice.

Friedman's ANOVA revealed significant differences between the three groups on the Speed of Comprehension test at baseline (χ=10.2, p<0.01) but not at T2 (χ=0.4, p=0.82) or at T3 (χ=1.2, p=0.55). Wilcoxons signed ranks test showed a significant difference at baseline between the lofepramine and control group (z=-2.98, p<0.01) and a marginally significant difference between the paroxetine and the control group (z=-1.99, p<0.05). No significant differences were found between the lofepramine and the paroxetine group at baseline (z=-0.3, p=0.8). The baseline differences between the patient groups and the control group confirm the findings of Experiment Four.

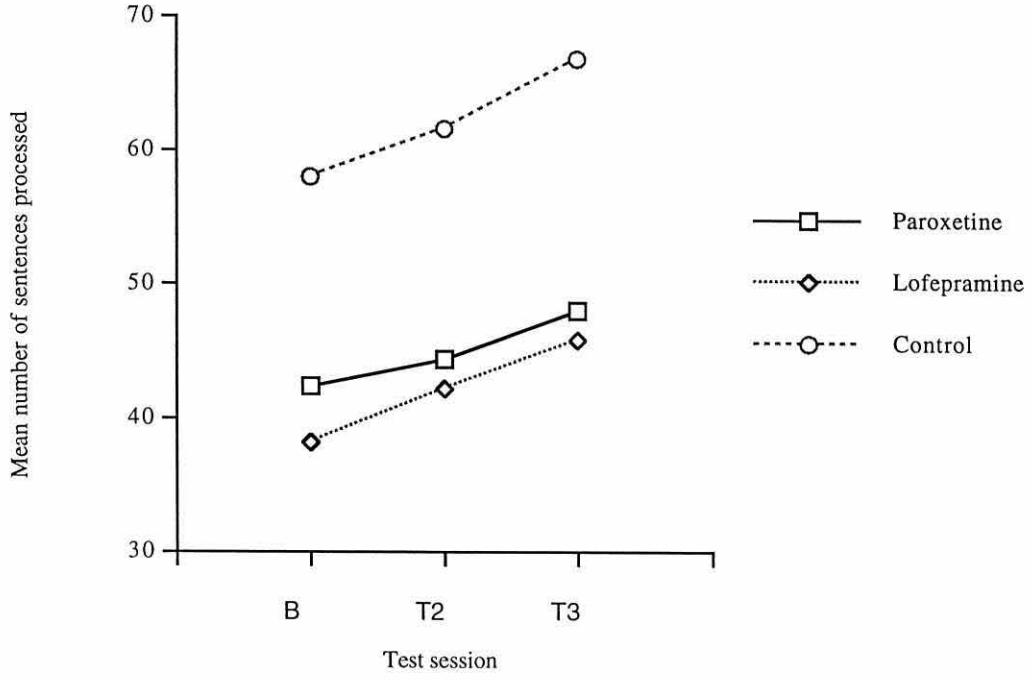


Figure 9.11. Mean number of sentences processed in 2 minutes on the Speed of Processing test

Stroop Task (Set A)

Colour naming task

Figure 9.12. shows that the paroxetine treated group showed a trend toward improvement at both T2 and T3, while the lofepramine treated group improved at T2 but then returned to baseline levels at T3. The control groups' scores were faster than both the drug groups but showed little effect of practice.

A repeated measures ANOVA revealed a group effect (F=6.7, df=2,16, p<0.01), but no significant interaction between the group and testing occasion (F=0.7, df=4,32, p=0.6).

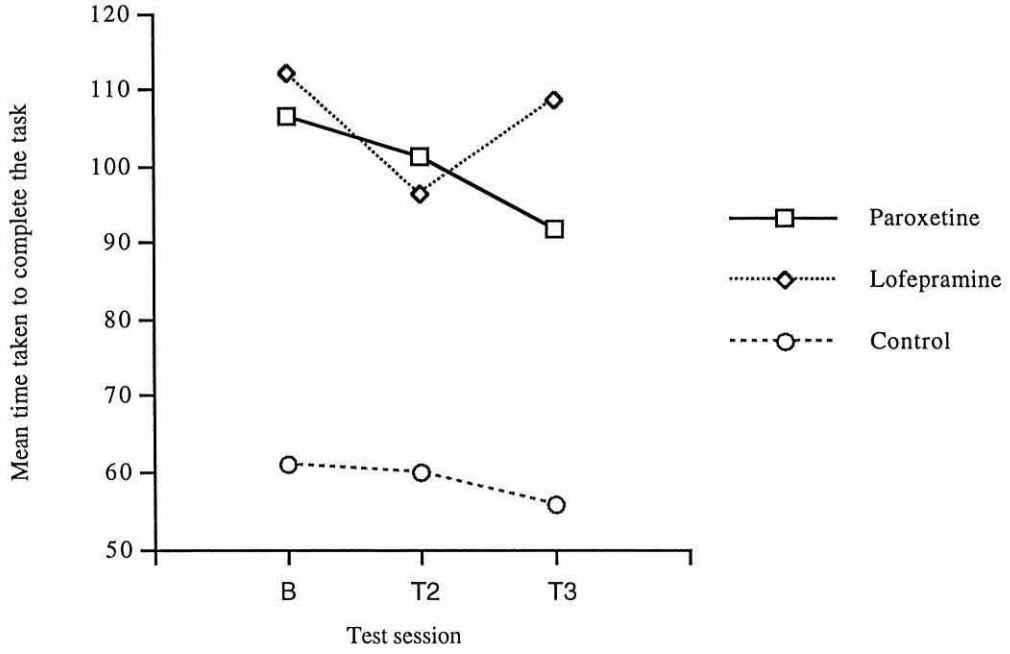


Figure 9.12. Mean times taken to complete the colour naming task

Stroop Interference

Stroop interference was calculated by subtracting the control colour naming time from the Stroop colour naming time. Figure 9.13. shows that the paroxetine group times decreased at T2 but that at T3 they took longer than at baseline to complete the task . The lofepramine and the control group made faster responses over the three testing sessions with most improvement occuring in the control group, which suggests that the task is affected by practice. A repeated measures ANOVA showed that there was a non-significant interaction between group and testing occasion(F=0.95, df= 4,32, p=0.45).

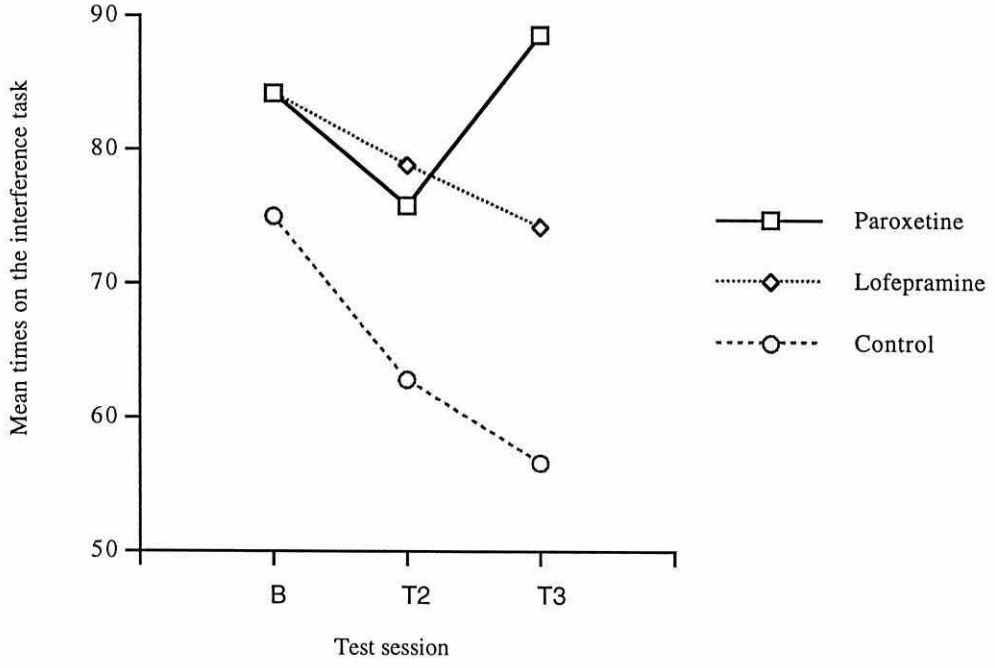


Figure 9.13.Mean times taken to complete the Stroop interference task

Short Term Memory (Set A)

Figure 9.14. shows that the paroxetine group performed poorly at baseline compared to the lofepramine and control groups, and despite improving more that the other two groups, their scores remain lower at T3. Both the lofepramine and control groups scores increase slightly over the three testing sessions. A repeated measures ANOVA revealed no significant interaction between group and testing occassion (F=1.12, df=4,48, p=0.34).

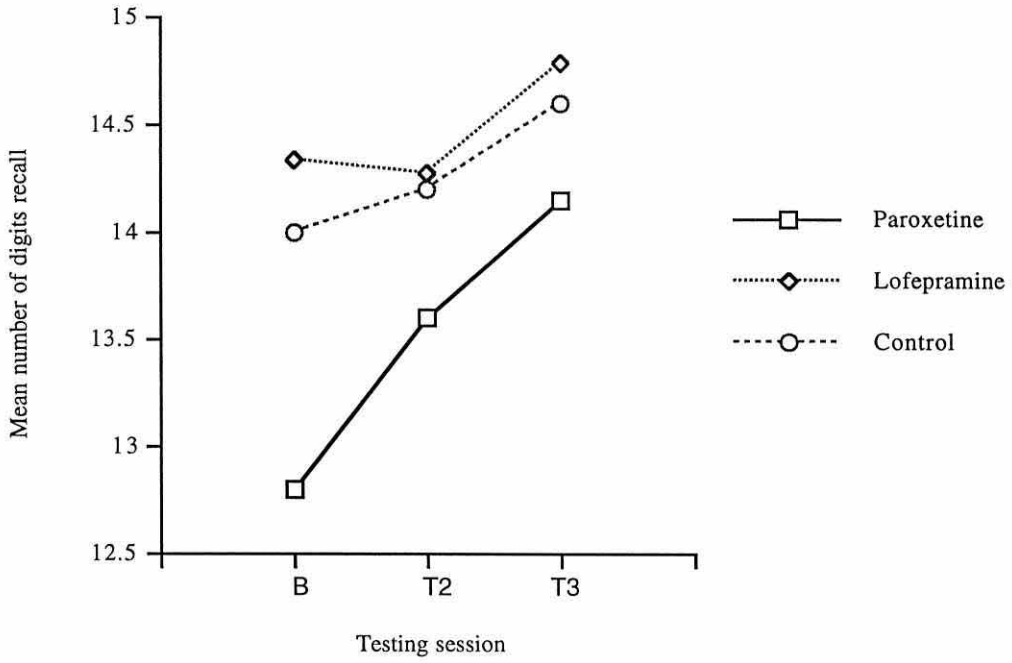


Figure 9.14. Mean scores on the digit span test

Discussion

It was initially predicted that while both paroxetine and lofepramine would be efficacious in treating depression, paroxetine would enhance performance on cognitive measures relative to lofepramine. This prediction was based on prior research, the results of Experiments Two and Three which demonstrated SSRI-related improvements on a measure of verbal episodic memory and the results of Experiment Four which demonstrated depression -related cognitive impairments in elderly patients. Contrary to this prediction, patients treated with paroxetine and lofepramine did not show significantly different changes over time on any of the cognitive measures assessed. The data must therefore be discussed in terms of the trends toward improvements that were found in the data.

The pattern of performance of patients treated with paroxetine and lofepramine was very similar on most of measures. The tentative delayed recall improvements exibited in young and elderly healthy volunteers when they were treated with a chronic dose of paroxetine (see Experiments Two and Three) were not replicated in this study. Unfortunately, as both the patient groups were performing at the lowest possible level on the task, drug-related impairments on the task, may not have been detected. The methodological problems associated with devising an appropriately difficult and sensitive task to measure both recall and recognition are discussed with reference to Experiment Four.

The performance of the two patient groups on the three measures of the Fuld OME was characterised by a decline at T2 which implied that treatment with both lofepramine and paroxetine had an initially detrimental effect on object recall. At T3 the paroxetine-treated subjects showed a greater trend toward recovery relative to the lofepramine-treated subjects on the total and repeated retrieval measures, although

there was no evidence of an overall improvement from baseline. The only exception to this pattern was observed on the delayed recall of the Fuld OME where treatment with paroxetine led to a trend toward improvement at T2, although this was not sustained at T3. It appears from these results that paroxetine had a less impairing effect than lofepramine on the measures of the Fuld OME.

Trends towards improvement in the paroxetine group relative to the lofepramine group were also observed on the delayed Verbal Memory test, the Stroop colour naming task, the digit span test and the short story recall test (at T2 only). However comparable improvements on these measures were found in the control group which suggests that the tasks are susceptible to the effects of practice. The ameliorated scores in the paroxetine group must therefore be attributed to the effect of practice rather than the effect of the drug.

The baseline difference between the patient groups and the control group bear out the depression-related deficits found in Experiment Four on the immediate recall and false alarm measures of the VMT, delayed Fuld OME recall and the Speed of Comprehension test. Additionally, significant baseline differences between the two patient groups and the control group were identified on the colour naming Stroop control measure which suggests that the task may also be affected by depression.

Given that the subjects in both the drug groups experienced a dramatic clinical recovery over the eight weeks of the clinical trial (see figure 9.1.), it is perhaps surprising that they do not show a considerable cognitive recovery by the end of the clinical trial. There was clearly sufficent scope for cognitive recovery in the patient groups, but despite the observed differences between patients and controls, the changes in the two drug groups scores between baseline and T3 are minimal.

The lack of a cognitive recovery in line with clinical recovery may be attributable to the effects of the drugs. Theoretically, the subjects in the two drug groups should be performing at the same level as the control subjects throughout the trial on the measures that are unaffected by depression, while on measures that are impaired, cognitive recovery should mirror clinical recovery. However the only tests where there were no differences between the three groups of subjects were the story recall and the digit span test. On all other measures the control group performed at a higher level throughout the trial, although this difference was generally non-significant. It is possible therefore that both lofepramine and paroxetine were actually impairing cognitive performance. Whether or not this was the case could only be established by including an additional control group of untreated depressed patients thus allowing the effects of depression and drug treatment to be partialled out. Inclusion of such a group would however be ethically unacceptable. One alternative possibility is that the confounding effect of recovery from depression can be controlled for to some degree by comparing cognitive recovery in subjects who recover clinically with subjects who remain depressed throughout the clinical trial. This proposed comparison was carried out and is discussed in Chapter 10.

The paroxetine and lofepramine groups were equally depressed at each of the six testing occasions. However, it can be seen from figure 9.1 that subjects were more depressed when they completed set B tests than set A tests. When subjects completed set A tests for the second time they had been on medication for three weeks and their mean score on the MADRS suggest that they were only just reaching criteria for depression i.e. a score of more than 20. Performance on set B tests that are susceptible to the effects of depression e.g. immediate verbal memory recall, are

theoretically more likely to be confounded by the effects of depression than performance on set A tests.

Conclusions

Prior research indicated that measures of word list recall are sensitive to the enhancing effects of the SSRIs and the impairing effects of the tricyclic antidepressants. It was also anticipated that depressed elderly subjects would be a suitable group to investigate possible cognitive enhancement as they have pre-existing deficits associated with depression and old age. There was no indication from the results of this study that treatment with paroxetine or lofepramine produced differential cognitive changes on any of the measures used. Trends in performance on the three measures of the Fuld OME suggest that paroxetine has a less impairing effect relative to the tricyclic lofepramine on this task. Improvement trends on some other measures were attributed to the effects of practice. The lack of cognitive improvement in relation to clinical recovery raises the possibility that both drugs are actually impairing performance. It can therefore be concluded that paroxetine does not enhance, and may in fact impair, performance on some of the cognitive measures. Treatment with lofepramine was not found to lead to any impairments relative to paroxetine which suggests that it is no more detrimental to cognitive function in the elderly than paroxetine.

CHAPTER 10

Study 1: A comparison of the cognitive performance of elderly patients with depression resistant to treatment by paroxetine with patients who responded to treatment.

Introduction

The results of Experiment Five indicated that the clinical recovery of the depressed elderly patients in both treatment groups was not accompanied by full recovery of cognitive function. This applied particularly to measures that were susceptible to the effects of depression, which might have been expected to return to control levels. The aim of the present study was to examine the relationship between clinical state and cognitive function during the clinical trial by comparing the cognitive performance in the two patient groups; subjects who made a complete clinical recovery and subjects who were resistant to treatment and remained depressed at the end of the clinical trial. The subjects in both groups were treated with paroxetine. It was predicted that the group of recovered patients would show a greater cognitive improvement than the patients who did not recover, particularly on measures that are affected by depression.

Method

Two groups of subjects were selected from the sample of 53 clinical trial subjects who had been treated with paroxetine. One group comprised eight patients who did not respond to treatment and had scores of 20 and over on the MADRS at the end of the trial. The other group was made up of seven patients who had responded to antidepressant treatment and had scores of less than 5 on the MADRS on day 56 of the trial.

Results

The cognitive data from the two groups were analysed using the non-parametric Mann-Whitney U test, as the measures were not normally distributed and the data was unmatched. Statistical comparisons were made between baseline and Test session 3 (T3) minus baseline scores. T3 was on day 35 in the case of set B tests and day 56 in the case of set A tests. The critical value of significance was taken as $p<0.01$ to reduce the chance of making a type 1 error as many measures were analysed. Results at the $p<0.05$ level were regarded as marginally significant.

No significant differences were found between the groups of recovered and treatment resistant subjects on the NART or on their scores on the MADRS on days -7, 0, and 7, although it can be seen from the graph (figure 10.1.) that at baseline the treatment resistant group were slightly more depressed than the recovered group. However the treatment resistant patients were significantly more depressed on day 21 ($z=-3.1$, $p<0.01$), day 35 ($z=-3.2$, $p<0.01$) and day 56 ($z=-3.3$, $p<0.01$).

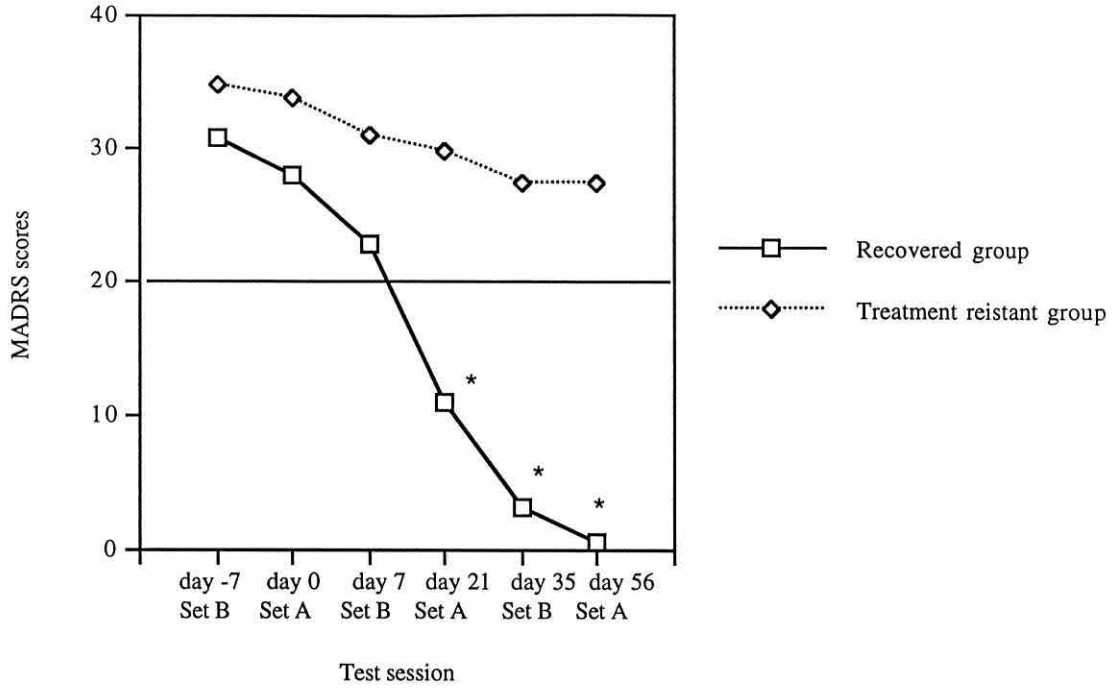


Figure 10.1.Mean MADRS scores of the recovered and treatment resistant patients.
* $p<0.01$

The patients in the two groups differed in their previous history of depression. 70% of the treatment-resistant patients had previously been diagnosed as being depressed, while only 25% of the subjects that were treated effectively had been depressed before.

Verbal Memory test

Figures 10.2. and 10.3. show a trend towards improvement between baseline and T3 in the performance of the patients with treatment-resistant depression, while the recovered patients show a declining trend in their scores. The mean false alarm scores on the recognition test (see table 10.1.) declined in both groups of subjects. There were no significant differences between the two groups on the immediate or delayed recall or recognition measures of the Verbal Memory test. A within-subjects analysis of the treatment-resistant groups' scores using Wilcoxon's signed ranks test indicated that the improvement between baseline and T3 was not significant in the immediate recall condition ($z=-1.1$ $p=0.27$) or the delayed recall condition ($z=-1.6$, $p=0.12$).

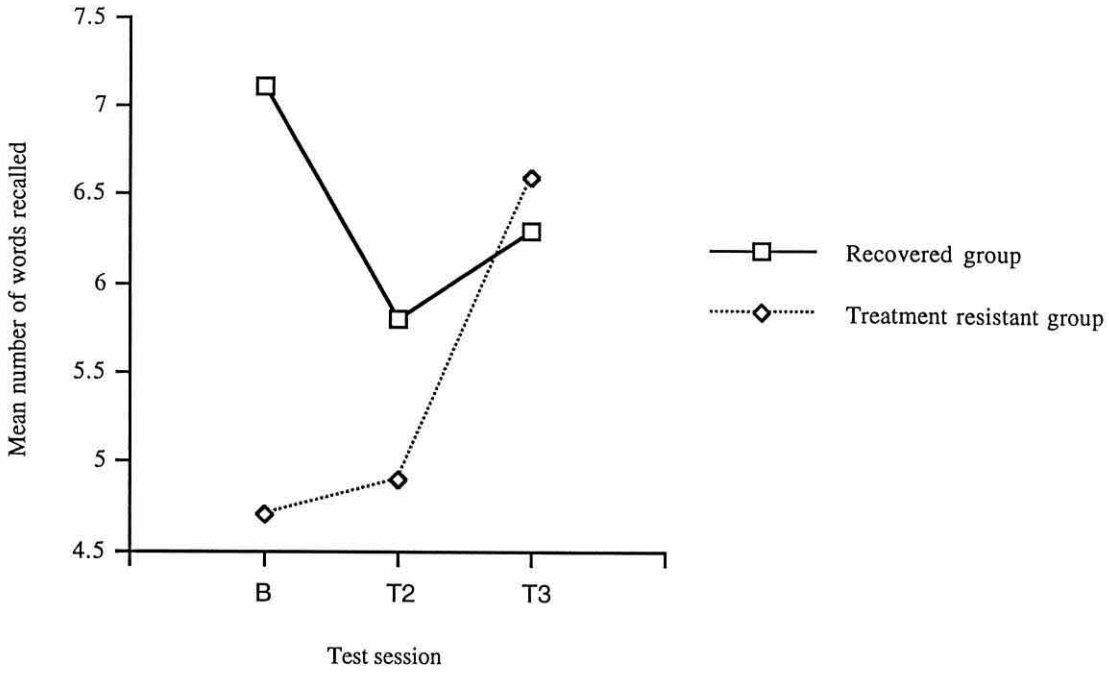


Figure 10.2. Mean immediate recall scores of the recovered and the treatment resistant patients

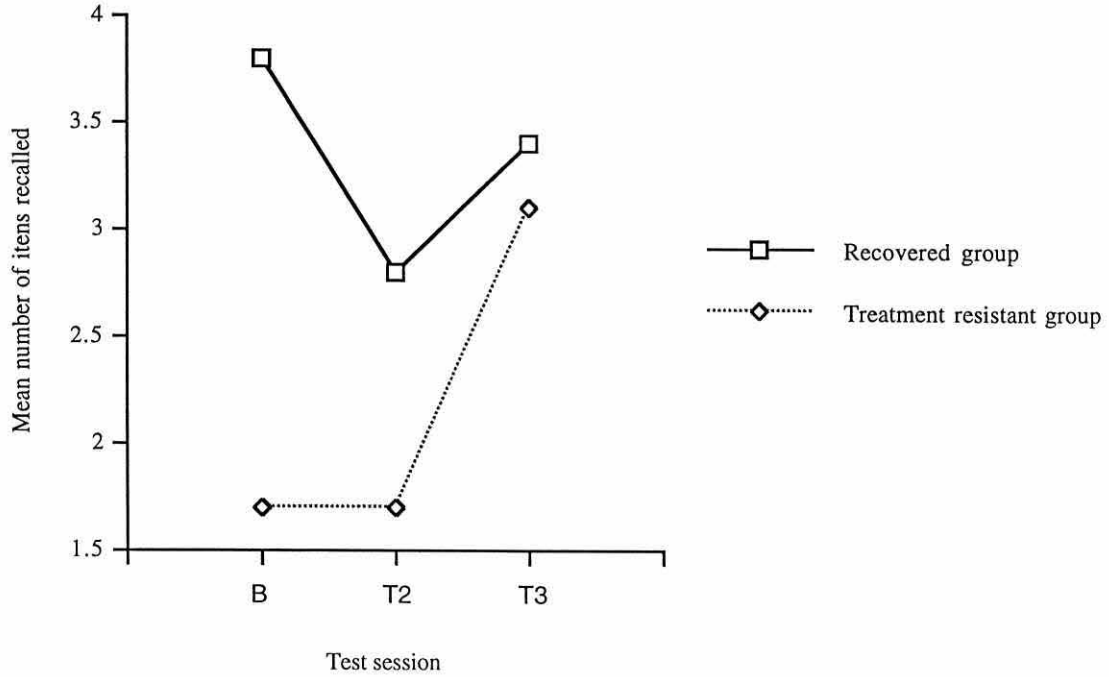


Figure 10.3. Mean delayed recall scores in te recovered and treatment resistant patients

Table 10.1. Mean scores on the recognition condition of the VMT.

		Treatment-resistant grp			Recovered Group		
		B	T2	T3	B	T2	T3
Recognition hits	Mean	**12.4**	**10.9**	**10**	**11.8**	**8.5**	**11.4**
	SD	2.6	5.8	4.6	2.3	3.4	3.2
Recognition false alarms	Mean	**5.0**	**3.7**	**2.9**	**3.5**	**2.4**	**2.1**
	SD	4.7	3.0	2.7	3.3	3.2	2.9

The Fuld OME.

Figures 10.4., 10.5., and 10.6., show that the treatment resistant group performed at a lower level than the recovered group on all the testing occasions. The recovered group showed a trend toward improvement at T3 relative to baseline, while the treatment resistant groups' performance remained at the same level at T3 as at baseline.

The Fuld total retrieval scores were significantly lower in the treatment resistant group compared with the recovered group at both baseline ($z=-2.05$, $p<0.05$) and at T3 ($z=-2.65$, $p<0.01$). The difference between the two groups on the Fuld repeated retrieval measure approached significance at baseline ($z=-1.9$, $p=0.06$) while at T3 it was highly significant ($z=-2.6$, $p<0.01$). On the Fuld delayed measure there were no differences between the two groups at baseline while at T3 the treatment resistant group was significantly impaired compared to the recovered group ($z=-2.0$, $p<0.05$).

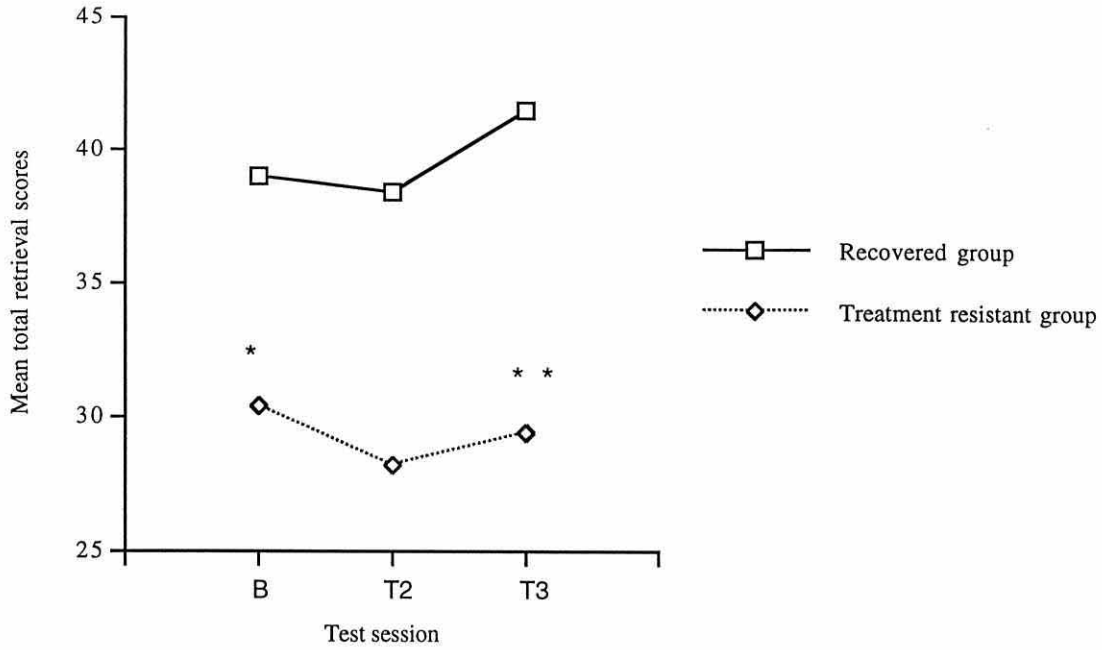


Figure 10.4. Mean Fuld total retrieval scores.
*p<0.05, **p<0.01

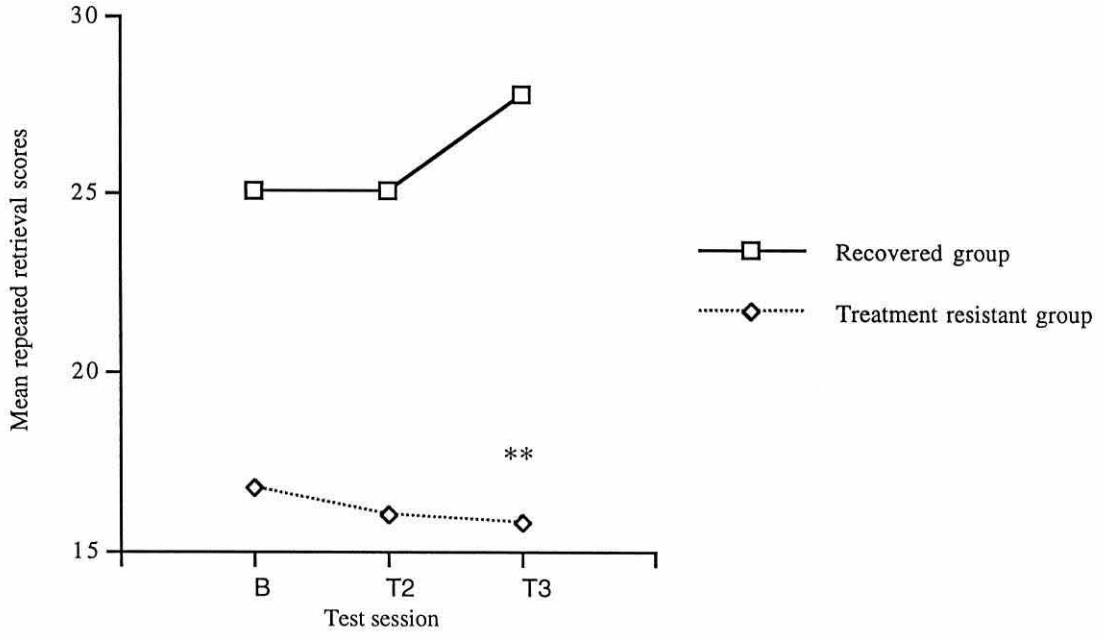


Figure 10.5. Mean Fuld repeated retrieval scores
**p<0.01

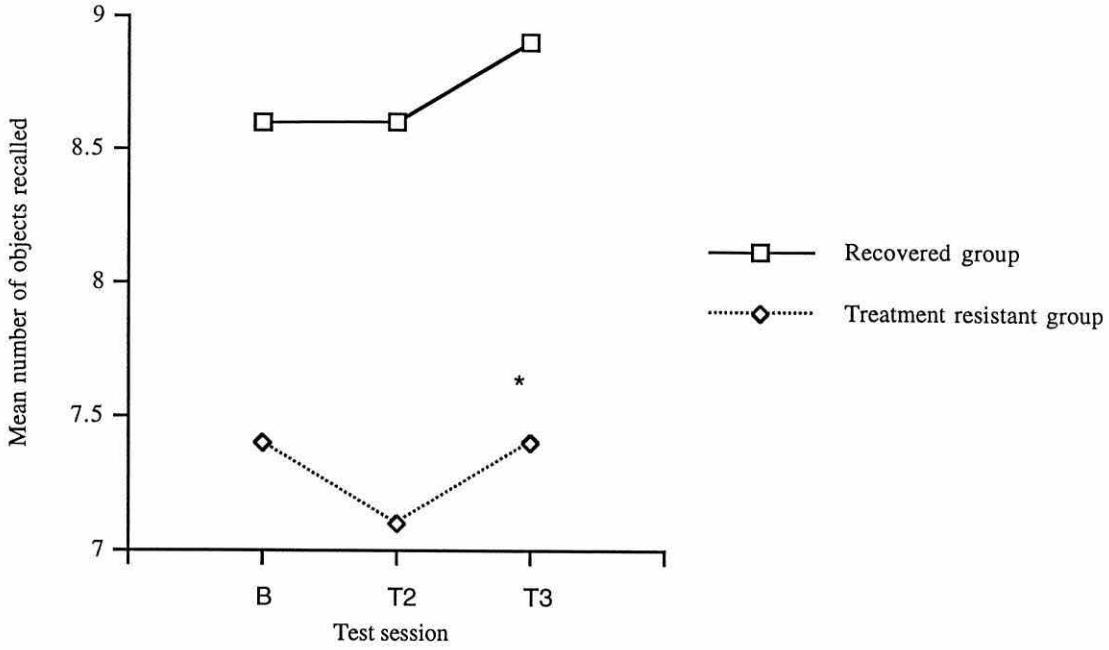


Figure 10.6. Mean delayed Fuld scores
*p<0.05

Speed of Comprehension and Stroop measures.

No significant group differences were found at baseline or T3 on the Stroop measures or the Speed of Comprehension task. Both the recovered group and the treatment resistant group showed trends toward improvement between baseline and T3 on the Speed of Comprehension test and the Stroop Interference test.

Table 10.2. Mean scores on the Speed of Comprehension and Stroop test.

		Treatment-resistant grp			Recovered Group		
		B	T2	T3	B	T2	T3
Speed of Comprehension	Mean	**29.7**	**31.4**	**37.4**	**35.1**	**37.6**	**41.1**
	SD	22.2	14.0	18.4	13.5	15.0	10.9
Colour naming Stroop	Mean	**124.2**	**117.8**	**138.3**	**85.1**	**72.7**	**84.1**
	SD	85.8	75.9	90.8	24.4	16.8	52.6
Stroop Interference	Mean	**185.7**	**103.5**	**80.0**	**122.5**	**99.6**	**64.8**
	SD	179.3	111.9	65.8	33.3	48.1	36.0

The Benton VRT

There were no differences between the scores of the two groups on the Benton VRT and the two groups were scoring at the same level.

Delayed shory story recall and the digit span test

No differences were found between the two groups on the delayed short story recall test and the digit span test, although it can be seen from the mean scores (table 10.4.) on these two tasks the treatment resistant group of patients' scores were higher than the recovered group at both baseline and T3.

Table 10.3. Mean scores on the Benton VRT, Short story recall and Digit span test.

		Treatment-resistant grp.			Recovered Group		
		B	T2	T3	B	T2	T3
Benton VRT	Mean	**2.4**	**2.4**	**3.0**	**3.0**	**2.1**	**3.5**
	SD	1.3	2.4	2.2	2.0	1.2	0.9
Short story	Mean	**6.4**	**7.6**	**7.0**	**5.0**	**4.8**	**6.4**
	SD	3.3	4.3	4.2	2.1	3.8	4.6
Digit span	Mean	**14.4**	**13.9**	**15.1**	**11.4**	**11.9**	**12.1**
	SD	5.9	4.8	4.0	5.6	2.8	4.5

Discussion

It was predicted that the recovered patients would show greater cognitive improvement than the treatment resistant patients, particularly on the measures that had been shown to be sensitive to the effects of depression. Contrary to this prediction, the treatment-resistant group showed a statistically non-significant trend toward improved performance between baseline and T3 on the immediate and delayed recall and false alarm scores of the VMT, the Speed of Comprehension task and the Stroop Interference test. This upward trend occured particularly in the

immediate recall condition of VMT where the treatment resistant patients baseline scores were markedly lower than the recovered groups'. In contrast, the scores of the recovered group did not increase, indicating that clinical recovery from depression was not necessarily accompanied by cognitive recovery.

A similar, but less well defined pattern of performance was found in the delayed recall condition, although floor effects made the results difficult to interpret. False alarms scores were not differentially affected in the two groups of patients. The upward trend in the performance of the treatment-resistant group on the Speed of Comprehension task and Stroop interference task may have been due to the effects of practice as the performance of the control group in Experiment Five indicated that the tasks were susceptible to practice related improvements.

It could be argued that the upward trend in the immediate and delayed verbal memory recall performance of the treatment resistant group was due to practice and the the initial low level of their performance at baseline. However, although treatment-resistant patients also showed a significant baseline deficit on the Fuld OME measures, they showed no upward trend in performance over the eight weeks. Therefore, it cannot be concluded that treatment resistant patients tend to improve in all areas of relative impairment; it is also difficult to see why performance on the Verbal Memory test measures but not the Fuld OME should improve. Neither group of subjects showed any significant change in performance on the Fuld OME during the clinical trial period which parallels the results of Experiment Four and Five, in which the OME did not appear to be as senstive to the effects of depression and paroxetine.

Comparisons of the pattern of performance of the two subjects groups indicate that the treatment resistant group performed at a lower baseline level than the recovered group on all measures of verbal memory,

with the exception of the short story recall test. Thus, subjects with treatment resistant depression were more impaired on the verbal memory tests at baseline (and T3 on the Fuld OME) than the patients that recovered. This may be because the treatment-resistant group contained a large proportion of patients (70%) who had experienced previous depressive episodes and were therefore chronically rather than acutely depressed. Conversely the group of treatment responders comprised a large proportion (75%) of subjects with no previous history of depression. The factor underlying the differences in cognitive recovery between the two groups may therefore be whether or not they were recurrent or first episode depressed patients. This issue is explored in Study 2.

On the measures of digit span and delayed short story recall the treatment-resistant subjects performed at a higher level (non-significant) than the recovered subjects at baseline. This superior level of performance was maintained over the three testing sessions on the digit span, but on the short story recall the recovered subjects improved at T3. Thus, subjects with depression who did not respond to treatment with paroxetine were less impaired on measures of digit span and short story recall. The results of Experiment Four showed that the digit span and short story recall tasks were the measures that were least sensitive to the effects of depression, while the Verbal Memory test measures were the most sensitive to depression. In this study the Verbal Memory test measures were the most sensitive to cognitive improvement in the treatment resistant group of subjects which suggests that Verbal Memory test measures may be more predictive of treatment response and recurrent depression than other measures. This issue will be explored further in Study 2.

The fact that treatment with paroxetine lead to a trend toward improved word list recall in the treatment-resistant patients, but failed to induce clinical recovery suggests that these improvements were mediated

by the cognitive rather than the clinical effect of paroxetine. Conversely, paroxetine produced a clinical recovery in the recovered group but had no effect on cognitive performance. This double dissociation between clinical and cognitive state raises the possibility that clinical recovery and cognitive improvement are mediated by independent systems. In order to clarify whether this effect is unique to paroxetine it would be desirable to compare a group subjects resistant to treatment with lofepramine with a group who recover. Unfortunately the numbers of subjects in each of these groups were too small for that comparison to be made. It must therefore be concluded that the results of this study are tentative as they are based on trends in the data of small groups of patients.

Study 2: A comparison of the cognitive performance of patients with recurrent depression with first episode depressed patients.

Introduction

The results of Study One raised two issues. Firstly, trends in the immediate and delayed recall data indicated that patients with treatment-resistant depression had lower scores at baseline and showed a greater drug related cognitive improvement than subjects who recovered as a result of treatment with paroxetine. The majority (70%) of the subjects in the treatment-resistant group had been depressed previously, while the majority of subjects in the recovered group had not been depressed before. Whether patients had been depressed previously or not was therefore identified as a possible underlying cause of the difference in cognitive recovery in the two groups. In order to test this hypothesis, it was necessary to compare the cognitive performance of a group of previously depressed subjects with a group of first episode depressed subjects. It

was predicted that the recurrent depressed group would show a similar pattern of cognitive performance as the treatment resistant subjects i.e. more impaired at baseline relative to the first episode patients. As these patients may have experienced long periods of depression in their lives they are more likely to have established cognitive impairments than the first time depressed patients. They may consequently show greater cognitive improvement over the course of the trial .

Secondly, the treatment resistant and recovered patients' data showed that the two groups had different performance profiles across the cognitive tests. The treatment-resistant depressed group peformed at a lower level than the recovered patients on the VMT (baseline only) and the Fuld OME (on all testing occasions), but at a higher level on the digit span tests and the short story recall test. These non-significant trends could be associated with the differential sensitivity of the various tasks to the effects of depression (see Experiment Four). The second goal of the study was to asssess whether a similar differential pattern of results was found when previously depressed patients were compared with first episode depressed.

Method

Subjects in the clinical trial were classified as either being first episode depressed or as having had at least one previous depressive episode. Analyses were carried out on all the subjects who participated in the clinical trial of which 58 had a previous history of depression and 43 were first episode depressed. Other analyses were carried out on the paroxetine subjects only, (31 of whom had experienced previous episodes of depression and 24 of whom had not) and on the lofepramine group only (27 of whom had experienced previous episodes of depression and 19 of whom had not).

Results

Differences between the groups were analysed using unpaired t-tests. The critical level of significance was taken as $p<0.01$ and differences at the $p<0.05$ level were regarded as marginally significant. Initial analyses were carried out on all the subjects in the clinical trial regardless of which drug treatment group they were assigned to. Where significant differences were found, further analyses were carried out within the two drug groups separately in order to establish where the differences occured.

NART and MADRS scores

The group of recurrently depressed subjects had significantly higher mean NART scores than the groups of first episode depressed subjects ($t=2.6$, $p<0.01$). Analysis of the MADRS scores of the two groups of subjects showed that the previously depressed subjects were marginally significantly more depressed than the first episode depressed at the two baseline testing sessions ($t=2.0$, $p<0.05$; $t=2.3$, $p<0.05$) (see figure 10.4.). These difference were also found between the two groups of lofepramine-treated subjects ($t=2.2$, $p<0.05$; $t=2.5$, $p<0.05$)(see figure 10.5), but not when the MADRS scores of the paroxetine-treated subjects were analysed alone.

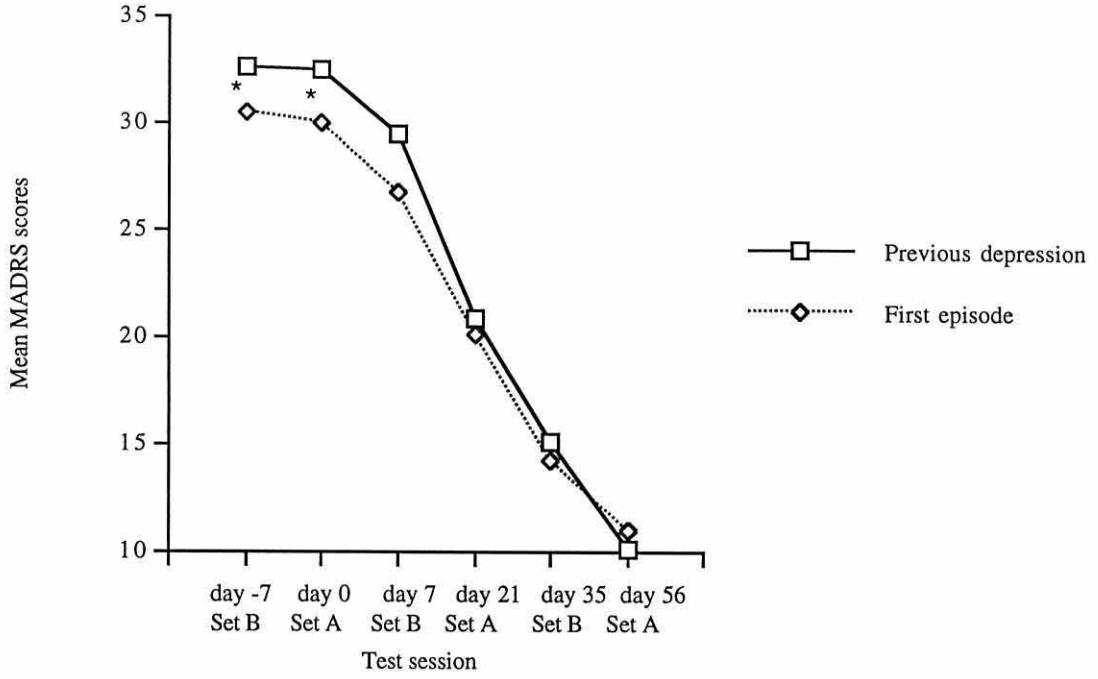


Figure 10.4. Mean scores on the MADRS of all previous and first episode depressed subjects * $p<0.05$

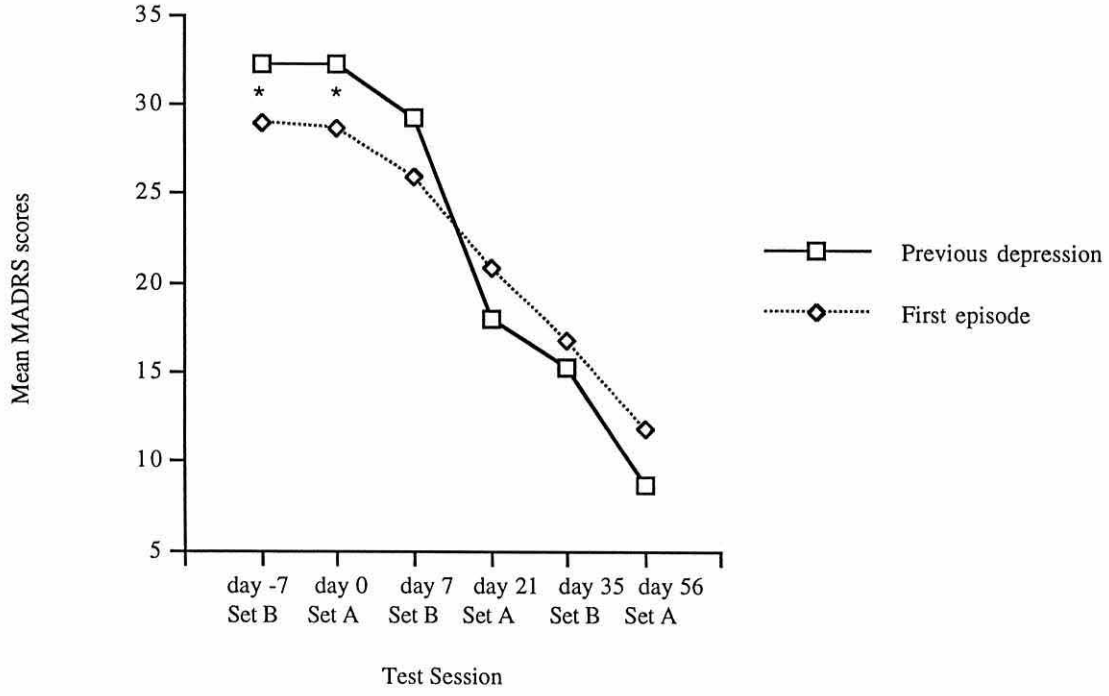


Figure 10.5. Mean MADRS scores of the lofepramine treated subjects only * $p<0.05$

Verbal Memory test

Immediate recall

There was no significant difference between the previous and first episode depressed groups of subjects on the immediate recall measure at baseline (t= 0.43, p=0.66) or T2 (t=0.55, p=0.58) or T3 (t= 1.3, p=0.2), although figure 10.6. shows that the previous depression group showed a greater upward trend in cognitive performance between baseline and T3 than the first episode depression group.

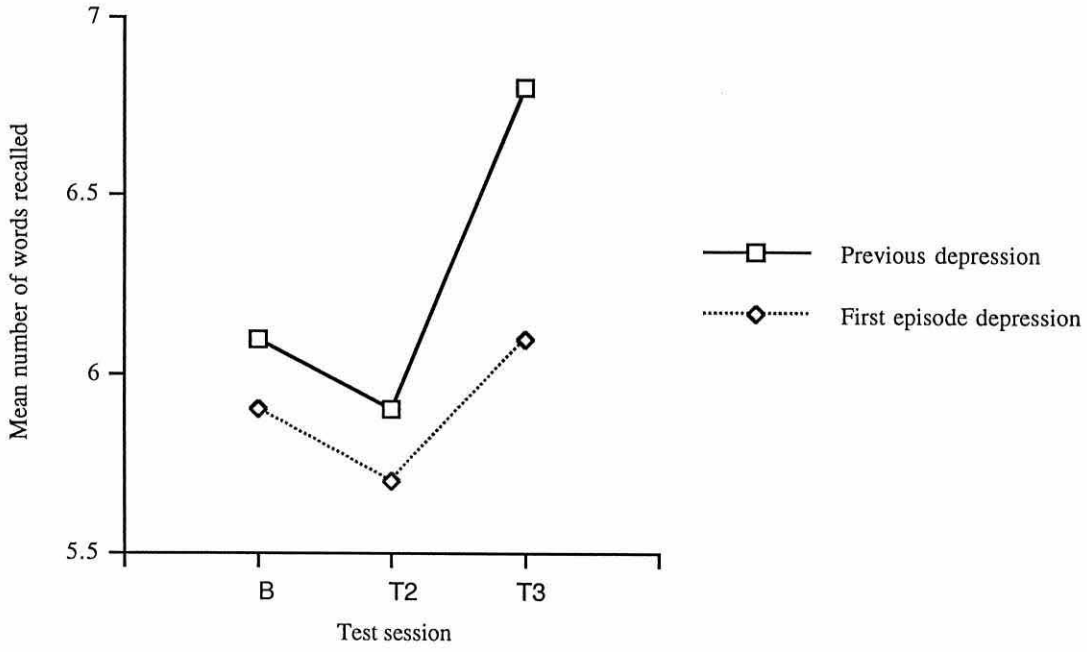


Figure 10.6. Mean immediate recall scores of previous and first episode depressed patients

Delayed recall

A marginally significant difference was found between the previous and first episode depression subjects at T3 (t=2.5, p<0.05) but not at baseline (t=0.67, p=0.51) or T2 (t=1.13, p=0.26). Figure 10.7. illustrates that the previous depression group show a greater improvement from baseline than the first episode depression group. Analysis of the previous and first episode patients that were treated with paroxetine showed that there were

no significant differences at baseline, or T2, or T3. No group differences were found between the lofepramine-treated subjects at baseline, but the previous depression group had marginally significantly higher scores than the first episode depression group at T2 ($t=2.1$, $p<0.05$) and significantly higher scores at T3 ($t= 3.0$, $p<0.01$).

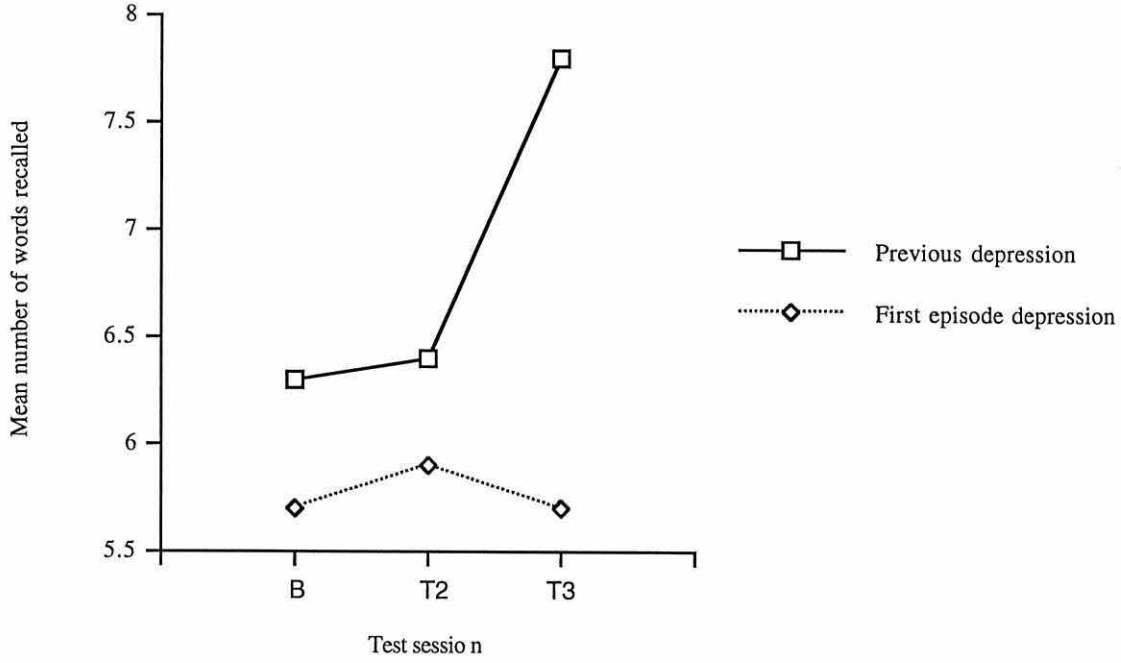


Figure 10.7. Mean delayed recall scores of the previous and first episode depression patient

Short story recall

The previous depression group show a sharp upward trend over the three testing sessions while the scores of the first episode depressed remain stable (see table 10.5.). However there were no significant differences between the previous and first episode depressed patients on the short story recall task on any of the testing occasions .

Table 10.5. Mean short story scores

	Baseline		T2		T3	
	Mean	SD	Mean	SD	Mean	SD
Previous	**5.6**	3.7	**6.8**	4.6	**7.2**	4.4
First episode	**5.1**	3.2	**5.9**	4.5	**5.9**	3.5

Digit Span Test

The mean scores of the previous depression group were higher and show more of an improvement than the first episode depression scores (see table 10.6). However, no significant differences were found between the previous and first episode depression groups on the digit span test on the three testing occasions.

Table 10.6. Mean digit span scores

	Baseline		T2		T3	
	Mean	SD	Mean	SD	Mean	SD
Previous	**13.9**	4.4	**14.6**	4.3	**14.8**	3.4
First episode	**13.0**	4.4	**13.3**	3.9	**12.9**	4.5

Speed of Comprehension

Figure 10.8. illustrates that the previous depression subjects processed significantly more sentences in two minutes than the first episode depressed did on all three testing occasions. They also showed a greater trend toward improvement between baseline and T3. Marginally significant differences were found between the previous and first episode depressed groups at baseline ($t=2.1$, $p<0.05$), T2 ($t=2.2$, $p<0.05$) and T3 ($t=2.6$, $p<0.05$). These differences were also found in the lofepramine treated group but not in the paroxetine treated group.

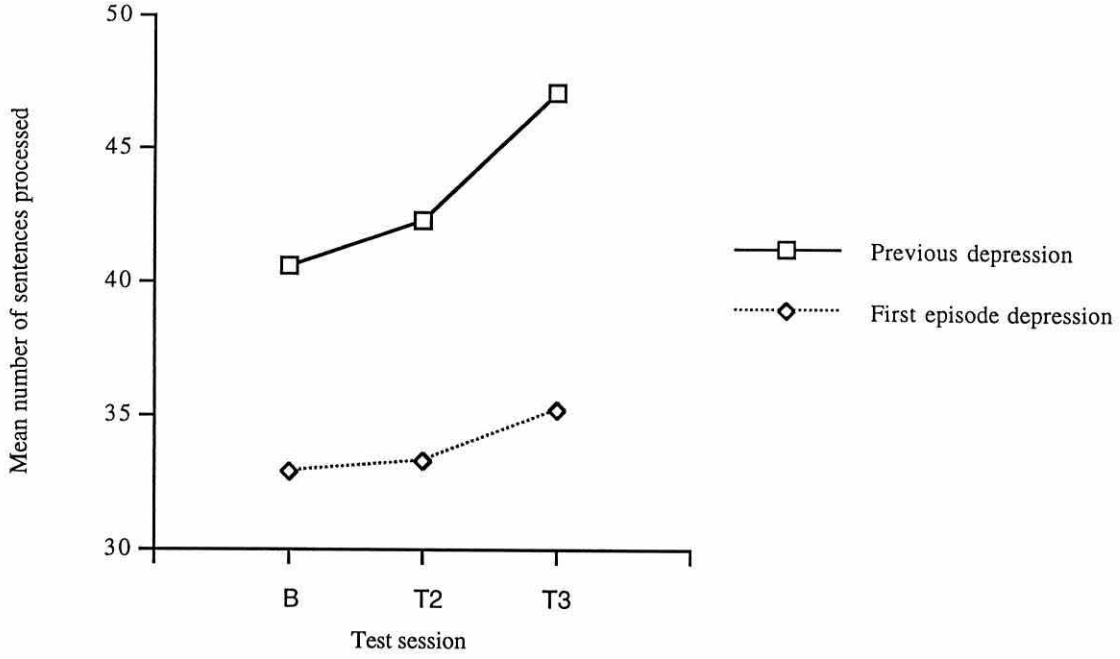


Figure 10.8. Mean scores on the Speed of Comprehension test

Other measures

There were no significant differences between the previously depressed and first episode depressed groups on any of the measures of the Fuld OME, the verbal recognition scores, the Stroop, or the Benton VRT .

Discussion

It was predicted that the previously depressed subjects would show a similar pattern of immediate and delayed recall performance as the treatment resistant group i.e. impairments at baseline and an upward trend in performance over the three testing sessions. Although the previously depressed group were significantly more depressed at baseline than the first episode depressed group, their baseline scores were not inferior to the first episode group on the immediate and delayed recall condition of the VMT or on any of the other measures.

Although the baseline predictions were not upheld, the previously depressed group did show greater improvement in immediate recall performance over the three testing sessions relative to the first episode depressed group. They also showed a significantly greater improvement than the first episode patients at T3 on the delayed recall test. These improvements are similar to those found in the treatment resistant group and suggest that previously depressed subjects show greater cognitive recovery when treated for depression. However, these improvements were only identified in the lofepramine treated group and not the paroxetine treated group. The previously depressed lofepramine-treated subjects showed a greater clinical improvement than the first episode depressed subjects (see Figure 10.5.). As word list recall tests have been shown to be particularly sensitive to the deleterious effect of depression (see Experiment Four), the recurrent depressed patients' improved cognitive scores may therefore be due to their clinical recovery.

The previously depressed subjects were more depressed at baseline than the first episode patients were, but they did not exibit greater cognitive impairment. This indicates that recurrent depression does not result in greater overall cognitive impairments. On the contrary, the previously depressed subjects performed significantly better than the first episode depressed on all three testing occasions on the Speed of Comprehension task. As seen in Study 1, short story recall and the digit span test performance did not differ from that on the other measures in first episode and recurrent depressed patients. This indicates that persistant recurrent depression was not the factor causing these differential trends.

Thus, contrary to expectation, recurrent depression patients were not more cognitively impaired than first episode depressives. There was a trend for the recurrent depression group to show a greater cognitive

recovery during the clinical trial on the immediate and delayed recall measures relative to the first episode depressives. However, these improvements were evident in the lofepramine treated subjects only and may therefore be a result of them undergoing a greater clinical recovery relative to the first episode depressives.

Conclusions

The results of Studies One and Two suggest that the recurrent depressed patients and the treatment resistant patients both showed a greater trend in cognitive recovery on the Verbal Memory test than patients who recovered or were first episode depressed. This was contrary to the prediction that the clinical improvements in the recovered patients would be accompanied by a greater cognitive recovery than the treatment resistant patients. Equally it was expected that the recurrent depressed patients would be more impaired at baseline than the first episode depressed patients due to the chronic nature of their depression, and thus make a greater cognitive recovery. Contrary to these expectations, the recurrent depressed patients were no less impaired at basline and show more of a trend towards improved verbal memory scores than the first episode depressed group. Significant differences and trends towards differences between the sub-populations of depressed subjects used in these studies were found most reliably on the immediate and delayed Verbal Memory test measures and the Speed of Comprehension test. The finding that a differentiation can be made between the performance of different sub-populations of depressed patients on these tasks suggests that the tasks are not only senstitive to the effects of depression, but also sensitive to differential patterns of performance in sub-populations of depressed patients.

CHAPTER 11

General Discussion

Introduction

The primary objective of this thesis was to assess the effects of the SSRI, paroxetine on cognitive function. The underlying theoretical motivation for this came from the results animal and human studies which suggested that the SSRIs have the potential to enhance cognitive performance. Three separate experiments assessed the effects of paroxetine in young healthy volunteers, in elderly healthy volunteers and in depressed elderly patients who participated in a clinical trial comparing the cognitive effects of paroxetine with those of the tricyclic, lofepramine. Subjects were assessed on a range of measures and it was predicted that paroxetine would be most likely to affect verbal memory in subjects with pre-existing memory deficits.

A secondary aim of the thesis was to assess the effects of depression on cognitive function in unmedicated elderly depressed patients during the baseline phase of the clinical trial. This phase of the study provided an unusual opportunity to assess unmedicated patients and contributed towards the resolution of the debate surrounding the nature and extent of cognitive deficit in depression. It was hypothesised that the lack of consistent results in previous studies was because the depressed subjects in many of these studies were either taking psychotropic medication, or their medication status was not specified. As tricyclic antidepressants have been shown to cause cognitive impairments which may confound or compound the effects of depression on the cognitive tasks, it was considered important to measure cognitive function in drug-free, placebo-treated depressed patients and compare the results with those of medicated patients. The assessment of patients at the baseline phase of the

study also allowed depression-related cognitive deficits to be taken into account when considering the effects of paroxetine and lofepramine on cognitive function.

A third aim of the thesis was to develop and evaluate the effects of repeated administration of a set of cognitive tests with multiple versions for use in healthy volunteer studies. This was necessitated by the lack of available published tests with multiple versions. As the subjects in healthy volunteer studies were tested repeatedly, and their drug performance compared with their baseline and placebo performance, the effects of practice on the tasks needed to be accounted for.

The effects of paroxetine on cognitive function

The rationale for the proposed studies came from four sources. Firstly, evidence from animal studies described earlier have demonstrated SSRI-enhanced retrieval and memory consolidation in rats and mice. Secondly, the results of a healthy volunteer study showed that alcohol induced memory impairments were attenuated by treatment with an SSRI. Thirdly studies showed that the SSRI, fluvoxamine, enhanced memory recall in patients with pre-existing deficits resulting from Korsakoff's psychosis. The fourth source of evidence comes from the finding that the memory enhancing effects of SSRIs and 5HT antagonists are similar in animals. Theoretically the pharmacological actions of the 5HT antagonists and the SSRIs should oppose one another. However they appear to produce similar cognitive improvements in animals. The 5HT3 antagonist improved performance on a name-face associate learning task in healthy elderly subjects (Crook and Lakin, 1991), thus providing a theoretical basis for the assumption that the SSRIs would also improve memory in healthy volunteers, particularly the elderly. However, a recent study exploring the effects of ondansetron on cognitive and psychomotor performance in

cancer patients prescribed the drug as an anti-emetic, found no evidence of any cognitive enhancement (Shattock and Wetherell, 1995).

A range of studies evaluating the effects of the SSRIs on memory performance in young healthy volunteers also indicated that they neither impaired nor enhanced human cognitive function (see review by Thompson, 1991). However some SSRIs, including paroxetine, raised CFFT in young healthy volunteers (Kerr et al., 1991). It was predicted that this central activating effect of the SSRIs would lead to improvements in some aspects of low level cognitive processing, in particular attentional measures. The aim of Experiment Two was to explore the effects of paroxetine on measures of selective attention, vigilance and arousal in young healthy volunteers. The primary negative priming measure was obtained using a spatial localisation task. It was predicted that the general alerting effect of the drug would increase both speed and negative priming effects and enhance performance on other measures of attention and verbal memory. Ten healthy volunteers were given placebo for a week followed by 20 mg paroxetine for a week. Their performance on a range of cognitive tests was compared with a comparison group of ten subjects matched for sex, age and educational background.

Overall, paroxetine had a neutral effect on all measures assessed. This was contrary to the results reported by Kerr et al. (1991; 1992) who found CFFT raised by paroxetine (20 mg and 30 mg) in both young and elderly healthy volunteers. Furthermore, in a recent study, an acute dose of the SSRI fluvoxamine raised CFFT relative to a placebo group and a dothiepin-treated group (Fairweather and Hindmarch, 1995).

A within subject comparison of the delayed recall scores in Experiment Two showed the scores were higher on days 2 and 3 of the drug week (test sessions 6 and 7) than in the placebo week. This result was interpreted as drug related rather than the result of practice as the results

of Experiment One indicated that asymptote on this task was reached by day 5. The finding that paroxetine did not significantly raise CFFT questions the assumption that paroxetine improves cognitive information processing by increasing cortical arousal (Kerr et al., 1992). The present evidence indicated that some enhancement of verbal recall scores may have occurred, but that it was independent of a general alerting effect of paroxetine.

Given the very modest improvement seen in young healthy volunteers (Experiment Two), and that SSRI-related improvements had only previously been reported in subjects with pre-existing deficits caused by alcohol or Korsakoff's psychosis, it was predicted that paroxetine would be more likely to improve memory performance in elderly subjects than young subjects. This prediction was based on the premise that a reversible neurochemical deficiency would be more likely in an ageing brain than a young brain (e.g. Marcusson, Oreland, and Winbald, 1984). Deficits in episodic memory have also been documented as a feature of normal ageing (White and Cunningham, 1982), making elderly subjects' initial performance baseline lower and thus any drug effects more detectable. Crook and Lakins' (1991) finding that the 5HT3 antagonist, ondansetron enhanced the episodic memory performance of healthy subjects with age associated memory impairment further supported the rationale for attempting to identifying enhancement in the elderly.

Experiment Three therefore re-examined paroxetine-related effects on delayed recall and other cognitive measures in healthy elderly volunteers. A single-subject ABACA design was employed in which baseline phases (A) were alternated with week long active drug and placebo phases (B and C). Subjects were tested daily on a battery of tests that focused on episodic memory, but included an extended version of the Benton Visual Retention Test, the digit span test, the Speed of

Comprehension test and a spatial location memory test. It was predicted from previous research that paroxetine was most likely to enhance verbal episodic memory, most particularly delayed recall, as it is a more pure measure of episodic memory than immediate recall, which also involves working memory. The results indicated that paroxetine improved performance in one subject on the delayed recall condition of the verbal memory test only. This effect was not found in the two other subjects making it difficult to conclude that paroxetine had an enhancing effect, although this tentative result was supported by the results of Experiment Two. Paroxetine had no impairing or enhancing effects on any of the other measures.

Cognitive assessments made during a clinical trial comparing the efficacy of paroxetine with the tricyclic, lofepramine in depressed elderly patients, provided the opportunity to further examine and clarify the predicted enhancing effects of paroxetine. It was hypothesised that any cognitive enhancing effects would be more detectable in subjects with pre-existing deficits resulting from the combined effects of depression and old age. As depression apparently involves a depletion of serotonin (Montgomery, 1990), treatment with an SSRI was considered more likely to cause enhancement than in the healthy elderly studies. Thus, cognitive enhancement in this group might be mediated by a change in clinical state resulting from raised serotonin levels, or by raised serotonin levels per se.

In the last of the three experiments exploring the effects of paroxetine on cognitive function, fifteen paroxetine-treated subjects were selected from the clinical trial data and matched (on age, sex and IQ) with fifteen subjects treated with lofepramine and fifteen healthy control subjects. Measures of verbal episodic memory, visual episodic memory, short term memory, semantic processing and attention were made at baseline and on four other occasions during the eight week clinical trial. It

was predicted that paroxetine would enhance cognitive performance relative to lofepramine which was anticipated to cause impairments as a result of its anticholinergic properties. Paroxetine-related improvements were particularly predicted on measures of verbal episodic memory.

There was no evidence of a difference between paroxetine and lofepramine treatment on cognitive performance. Neither drug caused any significant impairments or improvements relative to each other on any of the measures. The failure to find verbal memory improvements in the paroxetine-treated group could be due to a number of factors. Firstly, paroxetine may not have the same memory enhancing potential as other SSRIs that have been found to reverse pre-existing cognitive deficits. This explanation is not supported by the results of a clinical trial comparing the effects of paroxetine and fluoxetine in depressed elderly patients, in which paroxetine-treated subjects showed a greater improvement in cognitive function compared to fluoxetine-treated subjects at week three of the six week trial (Schone and Ludwig, 1993). Cognitive function was measured rather crudely by the Sandoz Clinical Assessment Geriatric Scale (an 18 item scale designed to evaluate mental function in the elderly) and the Mini-Mental State Examination. Thus, it seems unlikely that paroxetine has less potential as a memory enhancing drug than other SSRIs.

A second possible explanation for the failure to find improved cognitive performance in the paroxetine-treated subjects relative to the lofepramine treated subjects relates to the nature of the comparator drug used in the trial. It was predicted that lofepramine would have impairing effects as there is considerable evidence to suggest that other tricyclic antidepressants, such as amitriptyline and imipramine, impair cognitive performance as a result of their anti-cholinergic action. However lofepramine was not predicted to be as impairing as other tricyclics. For example, a recent study comparing the cognitive effects of lofepramine

with the tricyclic dothiepin in healthy volunteers indicated that lofepramine is less impairing than dothiepin on measures of episodic memory, visual working memory and a range of attention tasks (with the exception of CFFT) (Allen, Curran and Lader, 1993). Hopes and Wandmacher (1992) also found lofepramine did not impair speed and accuracy on attentional tasks compared to maprotiline. Reports of the comparative enhancing effects of SSRIs relative to an impairing tricyclic, rather than one with a more neutral cognitive profile, (e.g. Lamping et al., 1984, Richardson et al., 1994), are likely to reflect the impairing effect of the tricyclic rather than the enhancing effect of the SSRI.

In Experiment Five decreasing MADRS scores over the eight weeks of the trial in both the paroxetine and lofepramine treated patients indicated a considerable recovery from depression. However, clinical recovery was not accompanied by a complete cognitive recovery in either group as indicated by mean scores on any of the measures. Cognitive recovery was particularly anticipated on the measures that were sensitive to the effects of depression at baseline on the grounds that these should improve as patients became less depressed, regardless of the effects of the drugs. Theoretically, as the patients in both groups were no longer depressed at the end of the trial, they might have been expected to perform at the same level as the control subjects. However, only performance on the short story recall and digit span tests were at the same level as the controls.

One possibility is that both paroxetine and lofepramine were exerting comparable impairing effects on performance. The impairing effect of lofepramine could be attributed to its anticholinergic effects. However, prior research into the SSRIs in healthy volunteers have found them to be either neutral or beneficial in their effect on memory performance (e.g. Moskowitz and Burns, 1988). This raises the possibility

that paroxetine may have an impairing effect on cognitive performance in depressed patients, but a neutral or beneficial effect in healthy volunteers. Another possible explanation of the lack of cognitive improvement relative to clinical improvement, is that cognitive impairment associated with depression may last longer than the clinical symptoms, in which case poor cognitive recovery would be unrelated to drug effects.

In order to clarify the influence of depression on subjects' performance independent of the influence of paroxetine, Study One compared of a group of 8 depressed subjects who did not respond to paroxetine treatment with a group of 7 subjects who recovered over the eight week trial. The treatment resistant group of patients were significantly more impaired at baseline and T3 on the total and repeated retrieval measures of the Fuld OME. They also showed trends toward baseline impairment on the immediate and delayed Verbal Memory test measures. Trends in the immediate and delayed recall data indicated that, while the treatment resistant group demonstrated improved cognitive performance independent of clinical recovery, the recovered group showed a clinical recovery independent of cognitive improvements. This indicates a possible double dissociation between the clinical and cognitive effects of paroxetine on verbal recall. However in order for this to be established a larger subject group would be necessary.

It was noted that the majority of the subjects who did not respond to antidepressant treatment had been depressed before, while the majority of the responders were first episode patients. The patient characteristic that produced the pattern of results in the group of treatment non-responders may therefore have been whether or not they had been depressed previously. To explore this possibility a group of recurrently depressed patients were selected from the clinical trial data and compared with a group of first episode depressed patients. While both groups

demonstrated clinical recovery, only the recurrent patients showed trends towards improved immediate and delayed recall scores. This dissociation between clinical and cognitive recovery was similar to the trends displayed by the treatment resistant group, and suggest that the two groups were similar in some way. However, the fact that this dissociation was only found in the patients treated with lofepramine but not in the paroxetine-treated patients suggests that it may due to the greater clinical recovery made by the lofepramine group than the paroxetine group. These results merit further investigation to establish further the existence and underlying cause of the dissociation found between clinical and cognitive recovery in different sub-populations of depressed patients.

A similar pattern of baseline impairment on verbal memory measures to that found in the treatment resistant patients was anticipated in the recurrently depressed patients, as the recurrent nature of their depression may have resulted in more established cognitive impairments than in the first episode depressed patients. However, contrary to expectations, the recurrent depressed patients were no more cognitively impaired overall on the verbal memory measures. It may therefore be a unique feature of the treatment resistant depressed patients that produced the verbal memory impairments. This characteristic of treatment resistant patients may be more closely related to the type and severity of their depression rather than the number of previous episodes of depression they have experienced.

Of all the measures used, verbal episodic memory measures were the most sensitive to the effects of paroxetine in all the studies described above. Performance on verbal memory measures were also sensitive to the differential clinical outcome of groups of depressed patients i.e. treatment resistant and recurrent depressed patients. Selective verbal memory sensitivity has also been identified in studies assessing the impairing

effects of scopolamine and tricyclic antidepressants, and the enhancing effects of the SSRIs.

The size of the subject groups in the experiments described above is relatively small. However, the differences that exist between small groups of subjects can be considered as clinically significant even if the sample size is small. An analysis of the complete set of clinical trial data has independently supported the finding that paroxetine and lofepramine do not have differential effects on cognitive function.

The effects of depression on cognitive function

A separate section of the thesis addressed the issue of cognitive deficits in unmedicated depressed elderly subjects. In Experiment Four, data from the clinical trial were used to match eighteen unmedicated depressed elderly subjects on age, sex and IQ with eighteen controls. All the subjects had been assessed on the Verbal Memory test, the Fuld Object Memory test, the short story recall test, the Benton VRT, the Speed of Comprehension test, the digit span test and the Stroop Test during the initial placebo week of the clinical trial. As predicted by previous studies (Weingartner et al., 1981; Cohen et al., 1982), deficits were found on the recall of materials that required effort and spontaneous use of organisational strategies, but not those that were less effortful. Immediate recall decrements were identified on the Verbal Memory test but not on the supported immediate recall measures of the Fuld OME, while delayed recall was impaired on the delayed Fuld measure, but unimpaired on the VMT. However floor effects on the delayed recall scores of the Verbal Memory test and ceiling effects on the Fuld OME meant only tentative conclusions could be drawn as to the implication of these results on retention and retrieval in depressed patients.

A recent meta-analysis of the existing studies assessing the association between verbal and visual recall, recognition memory and depression found that they were significantly linked (Burt, Zembar and Niederehe, 1994). The analysis illustrated that impairments were greater overall for immediate recall than delayed recall. The Verbal Memory test findings therefore supported the theory that deficits in depression are the result of impairments at acquisition without corresponding consolidation and retrieval deficits. The converse pattern of deficits in the Fuld i.e. impaired delayed recall but unimpaired immediate recall, suggest a differential pattern of impairments on less effortful tasks. However, immediate Verbal Memory recall and delayed Fuld OME recall could be considered to be comparably effortful, as neither task is supported by selective reminding.

The pattern of recognition memory scores obtained from unmedicated depressed subjects in Experiment Four differed from medicated patients examined in previous studies. Signal detection measures indicated that the unmedicated depressed patients exhibited a reduction in memory sensitivity (d') compared to controls. However, there was no significant difference in response bias (ß) between the depressed and control groups in this study, although the significantly higher false alarm scores of the depressed group indicated that they were responding less cautiously than controls. Previous studies found that medicated depressed subjects responded more cautiously than controls (i.e. had reduced hit and false alarms rates), but differed from controls on the response bias measure, ß, rather than on the discriminability measure, d' (Miller and Lewis, 1977; Neiderehe and Camp 1985). The inconsistencies between the performance pattern of medicated and unmedicated subjects may be due to the medication affecting response bias. However the results of a recent study of recognition memory in

elderly unmedicated depressed subjects supports the findings that depressed patients have a conservative response bias (Backman and Forsell, 1994).

The response bias found in depressed subjects has lead to the formulation of the theory that memory impairment in depression is due to depressed people lacking confidence when responding (Johnson and Marago, 1987). The results of the meta-analysis described above (Burt, et al., 1994) indicated that, while depressed patients respond more conservatively than controls, they also have impaired ability to discriminate between target and distractor words in a recognition test. Impaired discrimination, as measured by d', was also identified in the Experiment Four and by Backman and Forsell (1994), which suggests that response bias does not account for all the differences between depressed and control subjects. These discrepant response bias and d' findings of the present and prior studies indicate the need for further research in this area.

Depression-related deficits in Experiment Four were not found when verbal material was presented as structured prose. All the previous studies assessing the effects of short story recall were carried out on medicated subjects. Two found that subjects were impaired (Kopelman et al., 1986; Watts et al., 1987) and two studies found no impairment (Coughlan and Hollows, 1984; Williams et al., 1987). The results of the present study fail to resolve the inconsistency of the results of previous studies, which may be due to differing levels of difficulty in the prose passages. One of the assumptions of the Processing Resource Theory (Ellis and Ashbrook, 1987) is that depression impairs recall of unstructured rather than structured material. This assumption is supported by the finding that unmedicated depressed subjects' recall of a structured passage of prose is unimpaired, while their recall an unstructured list of words is impaired.

Decrements in performance on the Speed of Comprehension task were found in the depressed group at baseline. These impairments can be attributed to the demanding nature of semantic retrieval element of the task rather than the processing element per se, as depressed patients were not impaired on the colour naming condition of the Stroop. Few studies have explored the effects of depression on semantic memory, and those that have, used questionnaire methods to assess how well subjects retrieved information from semantic memory. These studies concluded that depression did not affect semantic retrieval (Niederehe, 1986). Baddeley (1992) designed the Speed of Comprehension task to provide a measure of semantic processing that is sensitive to individual differences in performance. The present results suggest that the task is sensitive to the effects of depression.

Performance on the Benton visual retention task was found to be unimpaired. This is contrary to the findings of Shipley et al. (1981) who found that unmedicated depressed subjects were impaired on the Benton VRT. Further clarification of the existence and nature of visual memory deficits is therefore desirable. The finding that unmedicated depressed subjects show no impairments on the digit span test conforms with the results of previous studies.

The pattern of deficits found in unmedicated depressed subjects was similar to those in previous studies of medicated patients on some, but not all, measures. The immediate list recall deficits that were found are concordant with the results of a wealth of studies using both medicated and unmedicated subjects. The recognition memory results do not however conform to established findings of reduced hits and conservative response bias. Performance on the Stroop was not impaired in unmedicated subjects, although previous studies found impairments in depressed subjects whose medication status was not specified (Raskin et

al., 1984). The deficits found on the Speed of Comprehension in depressed patients was a novel finding that indicates that depression impairs semantic information processing.

The results of the meta-analysis of patient characteristic that moderate the extent to which depression and memory are associated showed that greater depression effects were associated with unmedicated patients than those on medication (Burt et al., 1994). Other important moderator variables were also identified; age and patient status. A greater association of depression with impairment was found in younger depressed that older depressed patients and in inpatients than outpatients. All these factors must therefore be taken into account when comparing the results of different studies.

Cognitive test evaluation

There were no published memory test with multiple, repeatable versions that had been assessed for equivalence and the effects of practice available for use in the healthy volunteer studies. Four memory tests were therefore devised to measure both visual and verbal episodic memory performance; the 20 Word Memory test, the Name-face-occupation associate learning test, the Extended visual retention test and the Spatial location memory test. The study involved the evaluation of these four tests, each of which comprised nine parallel forms. The aim was to assess the equivalence of the nine parallel forms and to determine a learning curve for 27 young healthy adults who completed the nine parallel forms of each test on successive occasions.

Seven of the nine tests were found to be equivalent to each other. The patterns of performance on the four tests in the study differed across the tests. Repeated administration affected verbal and non-verbal tests differently. Performance on the verbal tests were characterised by an initial decline in scores, while scores on the non-verbal tests improved

progressively over the study period. The spatial location memory task showed a further large improvement over the last three days. These results demonstrate the desirability of assessing and taking into account the effects of practice particularly on episodic verbal memory tasks, otherwise improvements in performance cannot be attributed to the drug intervention. The unpredictability of the pattern of practice effects means that assumptions regarding the extent of the effects of practice should not be made.

Conclusions

The aim of this thesis was to assess the effects of paroxetine on cognitive function in healthy volunteers and depressed elderly patients. Although the results of the three studies carried out with this aim in mind did not yield any conclusive findings, they raised several important issues. The healthy volunteer study results suggest that paroxetine enhanced delayed recall and had a neutral effect on other measures of attention and memory. Contrary to this, the results of Experiment Five indicated that depressed elderly subjects treated with paroxetine did not show cognitive improvement relative to lofepramine-treated subjects. The lack of cognitive recovery relative to the clinical recovery made by the patients, coupled with the fact that the patients scores were well below the control subjects on most measures throughout the trial, raises the possibility that both paroxetine and lofepramine may impair cognitive performance in elderly depressed patients.

The clinical implication of this finding for the treatment of depression in the elderly is that, contrary to expectations, treatment with paroxetine does not confer additional cognitive advantages over treatment with lofepramine. However, the possibility that paroxetine impairs performance in clinical subjects needs to be substantiated as the healthy

volunteers treated with paroxetine showed trends toward improvement, rather than impairment. Conversely, the delayed recall improvements found in healthy volunteers (Experiments Two and Three) were not replicated in the group of subjects with established deficits resulting from depression. These differential effects of paroxetine in clinical patients and healthy volunteers may be related to specific neurotransmitter-related deficits which result in the differing actions of paroxetine in the two types of subject group.

A comparison of a group of treatment-resistant and recovered patients selected from the clinical trial showed trends in the Verbal Memory test data that suggest a double dissociation between clinical recovery and cognitive improvement. Paroxetine may thus have a differential cognitive effect in patients with depression that is resistant to treatment with paroxetine, to that in patients who recover clinically. These trends also indicate that, contrary to speculation, cognitive recovery is not mediated by clinical recovery and the two processes may occur entirely independently of each other. Further research is needed to clarify this result which, once established, could provide important information as to the differential psychopharmacological actions of the SSRIs on the clinical and cognitive deficits caused by depression.

Previously depressed patients also demonstrated a similar trend in improvements on verbal memory measures compared to first episode depressed patients. However these trends were not found specifically in the paroxetine group, but rather in the lofepramine treated subjects. As the recurrent depression group treated with lofepramine made more of a clinical recovery than the first episode lofepramine-treated subjects, their relatively greater cognitive recovery could have been a result of clinical recovery and could not therefore be reliably attributed to the fact that they had been depressed before.

Analysis of the baseline data of the clinical trial confirmed the results of previous studies in finding that depression caused deficits on effortful verbal tasks that require subjects to spontaneously impose structure on information, while recall of structured verbal information was unimpaired. The fact that the subjects were unmedicated meant that some of the inconsistent results of studies assessing the effects of depression on recognition memory, the Stroop task and the Benton could be resolved. Depression was found to cause deficits on the Speed of Comprehension test which suggests that the test is sensitive to the effects of depression and may therefore be a useful tool for applied research into depression.

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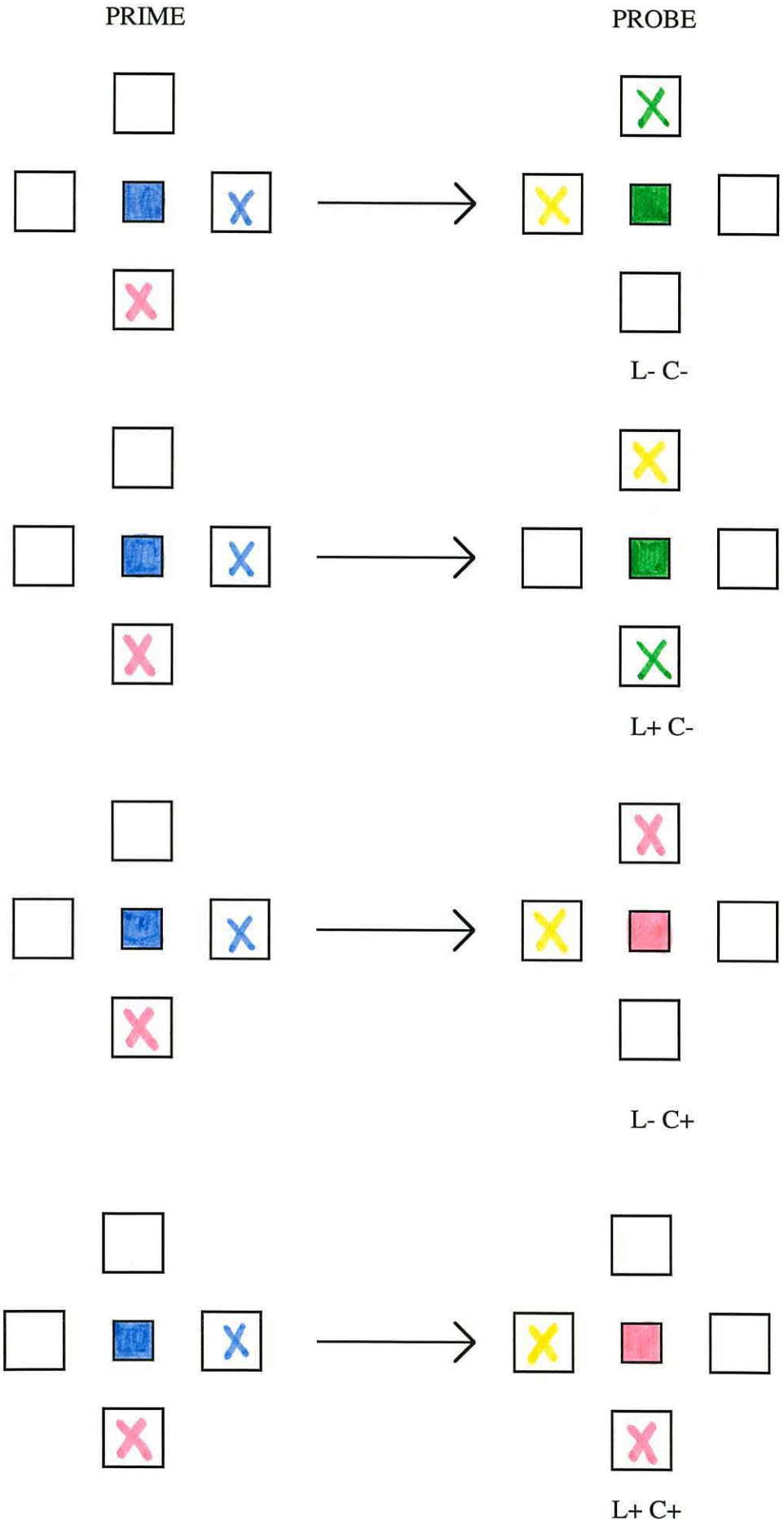
APPENDIX A

Cognitive test materials

Figure 3.1. Examples of the conditions used in the spatial localisation experiment. APPENDIX A



APPENDIX A

Nine parrellel versions of theTwenty word memory test

SET 1		SET 2		SET 3	
TARGETS	DIS	TARGETS	DIS	TARGET	DIS
CHAIN	*TASTE*	CHOOSE	*SPEND*	FILL	*LAKE*
CAMP	*DESK*	QUICK	*CELL*	BEAT	*DRY*
SPREAD	*WORTH*	BANK	*POST*	KEY	*FIT*
WALK	*SHARE*	MOUTH	*HIT*	DRIVE	*OIL*
WRONG	*BRING*	FRIEND	*TRUTH*	HOUR	*SIZE*
COLD	*SPACE*	HEART	*WIFE*	DEAD	*CLEAR*
JOB	*BEST*	REAL	*WORD*	HEARD	*WEEK*
WORLD	*HAND*	LIFE	*OWN*	YEAR	*LONG*
ENGINE	*NOTICE*	ADVICE	*DISEASE*	COUSIN	*SYMBOL*
FASHION	*IDEAL*	CAREER	*WEATHER*	RELIEF	*EMPTY*
BESIDE	*MISSION*	SECRET	*COLUMN*	TITLE	*DAUGHTER*
TEACHER	*CIVIL*	EVENT	*AWARE*	PREVENT	*BEGIN*
SEASON	*CATTLE*	VISIT	*DESIGN*	STATION	*HEAVY*
PATTERN	*VOLUME*	JUSTICE	*RESPECT*	FORWARD	*FREEDOM*
MODERN	*CENTRAL*	NATURE	*ALONE*	PERSON	*PRIVATE*
MORNING	*AGAINST*	PARTY	*VALUE*	CENTRE	*FIGURE*
WONDERFUL	*SOLUTION*	UNIFORM	*EVIDENT*	AVENUE	*APPROVAL*
NEGATIVE	*PRIMARY*	POSITIVE	*UNITY*	POLITICS	*REGULAR*
PRESIDENT	*IMPORTANCE*	IMPORTANT	*INTEREST*	HISTORY	*COMPANY*
EDUCATION	*AVAILABLE*	SOCIETY	*VARIETY*	TELEVISION	*CAPACITY*

SET 4		SET 5		SET 6	
TARGETS	DIS	TARGETS	DIS	TARGETS	DIS
TAUGHT	*CROSS*	PAIR	*WORRY*	STRIKE	*DRAW*
BIRTH	*DROVE*	WARM	*DRESS*	THICK	*SHOP*
WAIT	*STAFF*	SIGHT	*PLANE*	PARK	*TOUCH*
WRITE	*HALL*	TEETH	*SQUARE*	REACH	*CLUB*
STEP	*SHAPE*	GAME	*BUILD*	MONTH	*HEAT*
BOOK	*CHILD*	LIVE	*HARD*	VIEW	*LEAVE*
PAST	*ACT*	FIELD	*LAW*	BODY	*ROOM*
SMALL	*WORK*	PLACE	*KNOW*	HOME	*TAKE*
MINUTE	*PLENTY*	LISTEN	*MOTOR*	BITTER	*UNCLE*
BELIEF	*TRAFFIC*	FOREST	*RIFLE*	MESSAGE	*NARROW*
DETAIL	*VALLEY*	PERMIT	*PLATFORM*	SHELTER	*LEADER*
PRODUCT	*CAPTAIN*	ALLOWED	*REQUIRE*	PATIENT	*ACTIVE*
TALKING	*INCLUDE*	MACHINE	*ATTACK*	DEMAND	*CORNER*
HUSBAND	*DIRECT*	HOTEL	*STUDENT*	WINDOW	*ARMY*
ISLAND	*SUPPORT*	PICTURE	*SECTION*	STUDY	*RETURN*
HUMAN	*FUTURE*	SIMPLE	*MOMENT*	MONEY	*OFFICE*
TYPICAL	*ARTICLE*	BRILLIANT	*ELECTRIC*	ANIMAL	*MINIMUM*
OPPOSITE	*MUSICAL*	MEMORY	*PREVIOUS*	SEPARATE	*MANAGER*
NATURAL	*FINALLY*	POSITION	*PERSONAL*	EVIDENCE	*DIFFERENCE*
COMPETITION	*IDENTITY*	ACADEMIC	*ORDINARY*	FAMILIAR	*IMMEDIATE*

SET 7		SET 8		SET 9	
TARGET	DIS	TARGET	DIS	TARGET	DIS
DEPTH	*WILD*	WORSE	*SAFE*	SEAT	*PALE*
SEARCH	*FLAT*	SLEEP	*PAGE*	WON	*SITE*
BRIGHT	*DANCE*	THIN	*BREAK*	CLOTHES	*CHECK*
PRICE	*CHIEF*	SERVE	*WISH*	CHOICE	*DEEP*
PLANT	*TALK*	FEAR	*WALL*	FLOOR	*REST*
MEAN	*ROAD*	TYPE	*FIRE*	STRONG	*STAGE*
NAME	*YOUNG*	HELP	*FEET*	KIND	*FREE*
SCHOOL	*GREAT*	THINK	*HIGH*	HAND	*TOLD*
FORGET	*CULTURE*	MARINE	*BUSY*	AFRAID	*EXIST*
RIPPLE	*FELLOW*	REDUCE	*STRUGGLE*	TRAVEL	*PLEASURE*
MASTER	*BOTTLE*	VILLAGE	*QUIET*	CHAPTER	*SOLID*
COVER	*FAMOUS*	CRISIS	*REGARD*	BATTLE	*BALANCE*
KITCHEN	*UNLESS*	PROPER	*CONCERN*	MARRIAGE	*SUPPOSE*
RECORD	*NORMAL*	COLOUR	*METHOD*	NATION	*EFFORT*
RIVER	*REPORT*	FOREIGN	*SINGLE*	CENTRAL	*FINAL*
POWER	*COLLEGE*	PRESENT	*LOCAL*	CITY	*PUBLIC*
NEWSPAPER	*TOMORROW*	DOMINANT	*ARGUMENT*	DRAMATIC	*CHEMICAL*
CAPITAL	*DEVELOP*	ENEMY	*OBVIOUS*	POETRY	*TRADITION*
DIFFICULT	*PHYSICAL*	ANYONE	*AVERAGE*	EVENING	*BEAUTIFUL*
MACHINERY	*GRADUALLY*	IMPOSSIBLE	*COMPETITION*	ABILITY	*DICTIONARY*

APPENDIX A

Materials for the Name-face-occupation associate learning test

SET A

CLAIRE JONES	DOCTOR
MAX HANCOCK	BUS-DRIVER
JUDITH BRUMBY	RECEPTIONIST
ANDREW ROBINSON	SOCIALWORKER

SET B

JANE HUGHES	COOK
HUGH BOURNER	DUSTMAN
GLENDA PILSTOW	LAWYER
STEVEN MACDONALD	TEACHER

SET C

ANNE BROWN	LOLLIPOP LADY
GLYN HARTSHORNE	BUTCHER
EDNA RUMBELL	COURIER
TERRY HARRISON	PILOT

SET D

LIZ SMITH	JOURNALIST
EARL WHIFFIN	FARMER
ELSIE SEEMEY	SINGER
THOMAS MEREDITH	BARMAN

SET E

GILL LLOYD	CLEANER
WYN RICKFORD	MECHANIC
CLARA TOMKIN	SECRETARY
DANNY STEVENSON	VICAR

SET F

KATE WHITE	DISC JOCKEY
MEL EBBRELL	OPTICIAN
BRENDA WHELANDS	HAIRDRESSER
MARTIN ATKINSON	BRICK LAYER

SET G

SUE MOORE	LIFE GUARD
SHAUN PILCHER	ENGINEER
TRUDY COPPARD	AIR-HOSTESS
MICHAEL RICHARDSON	GARDENER

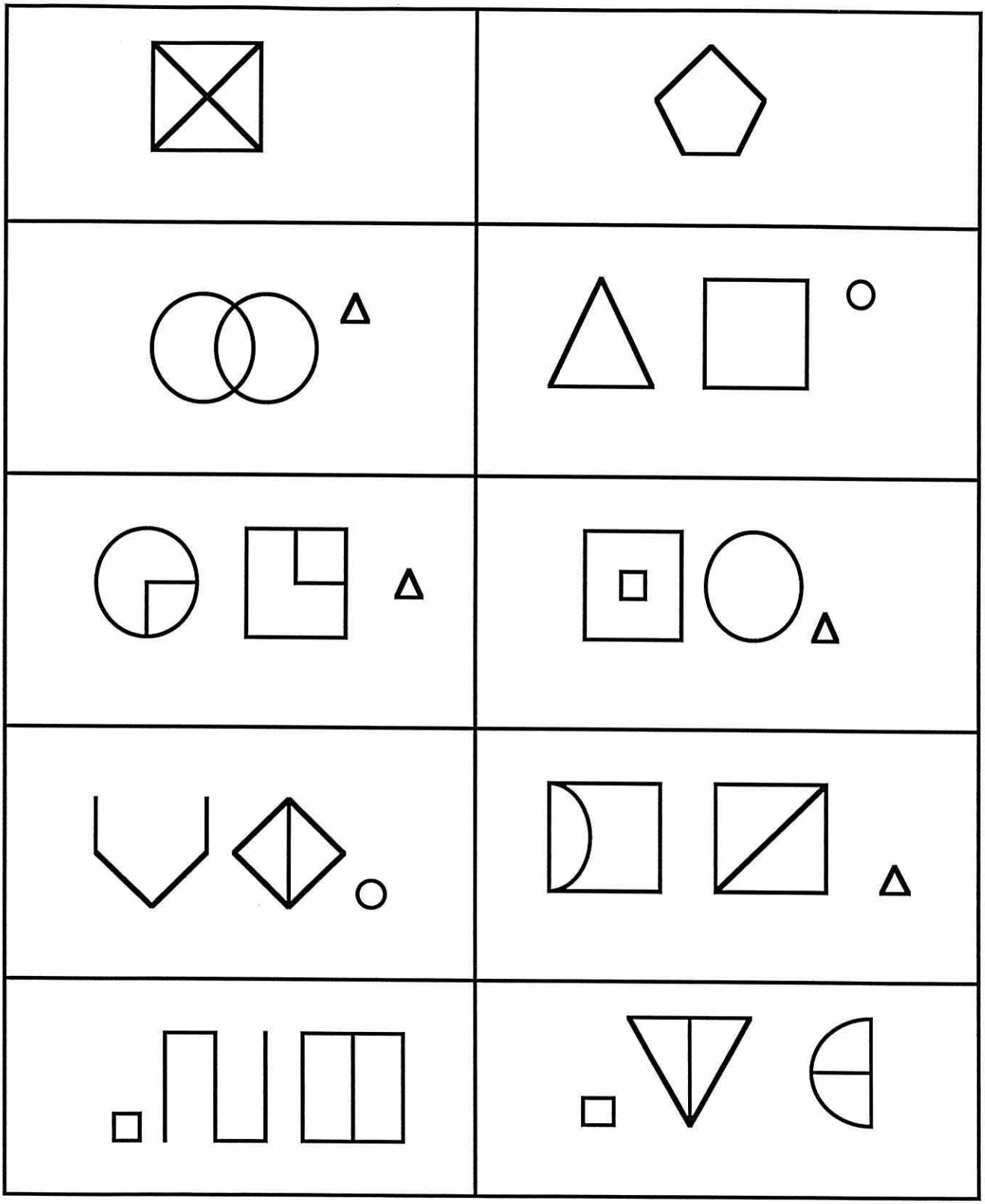
SET H

PAT HUNT	FACTORY WORKER
BEN ABNETT	ACTOR
MABEL HOLLETT	VET
DAVID WILLIAMS	NURSE

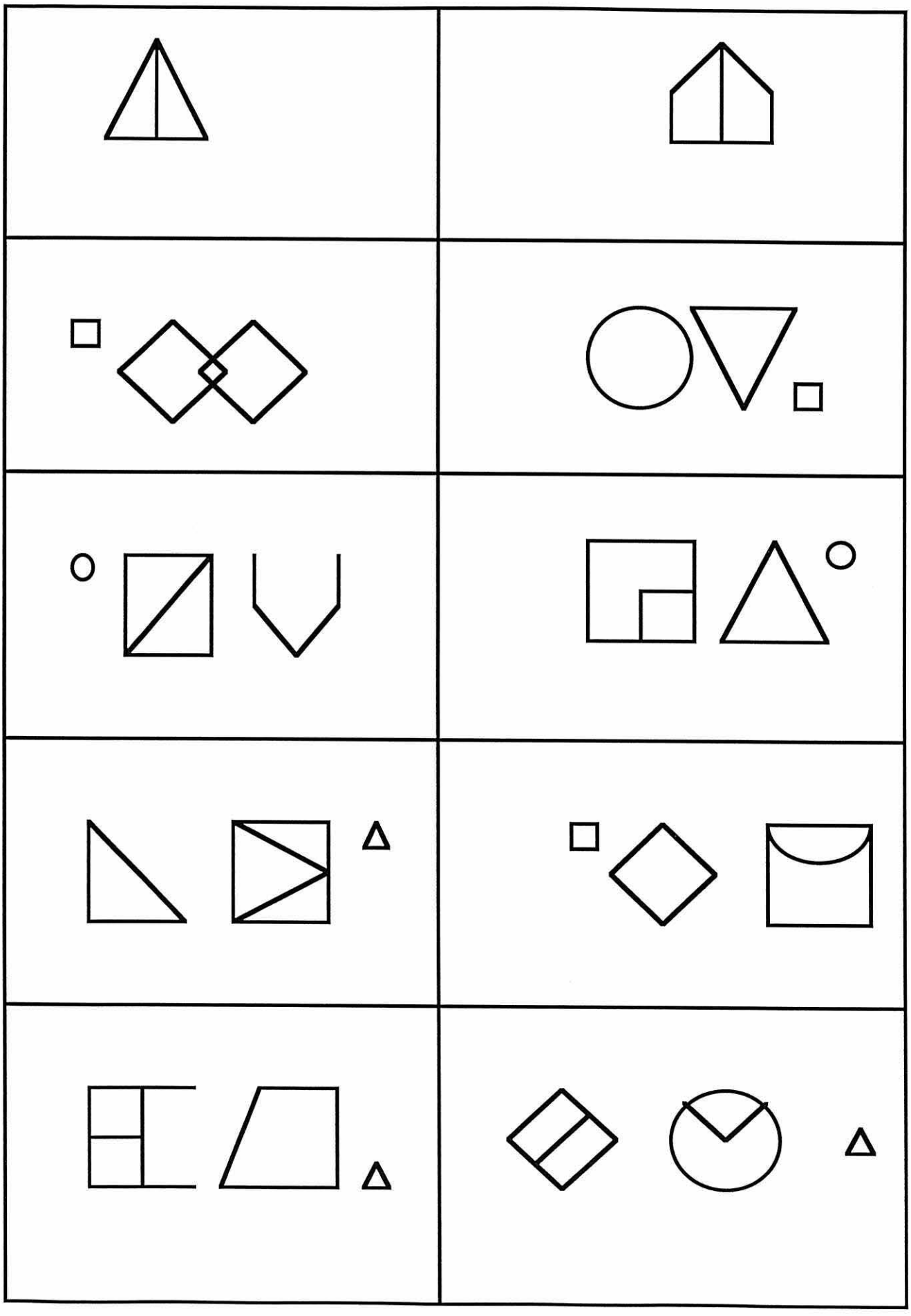
SET I

LYNNE BATES	LECTURER
CARL STINTON	STUDENT
PHYLLIS CROCKETT	SALES-ASSISTANT
RICHARD SULLIVAN	BANK CLERK

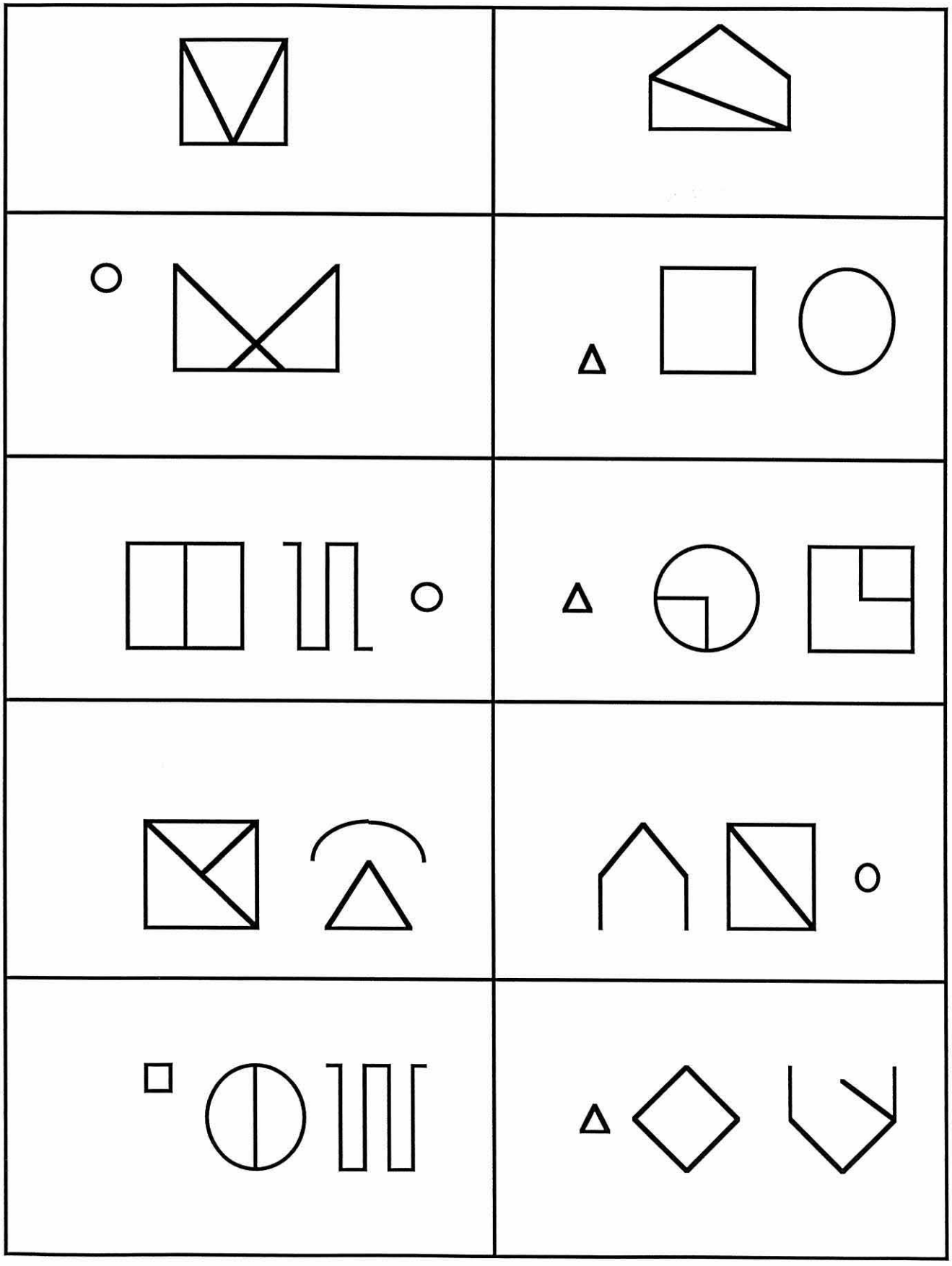
Additional forms of the Benton VRT- SET D **APPENDIX A**



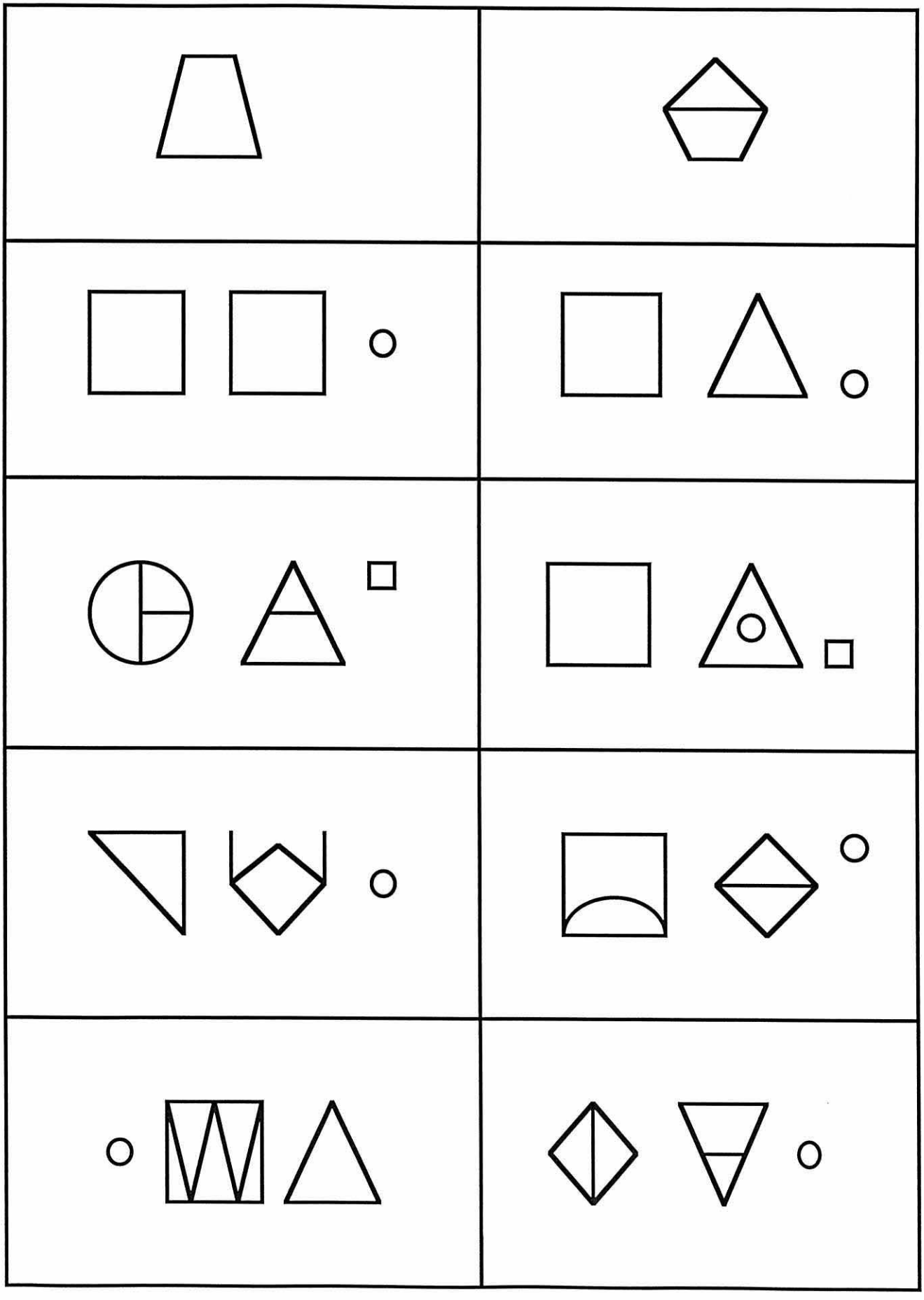
Additional forms of the Benton VRT- SET E **APPENDIX A**

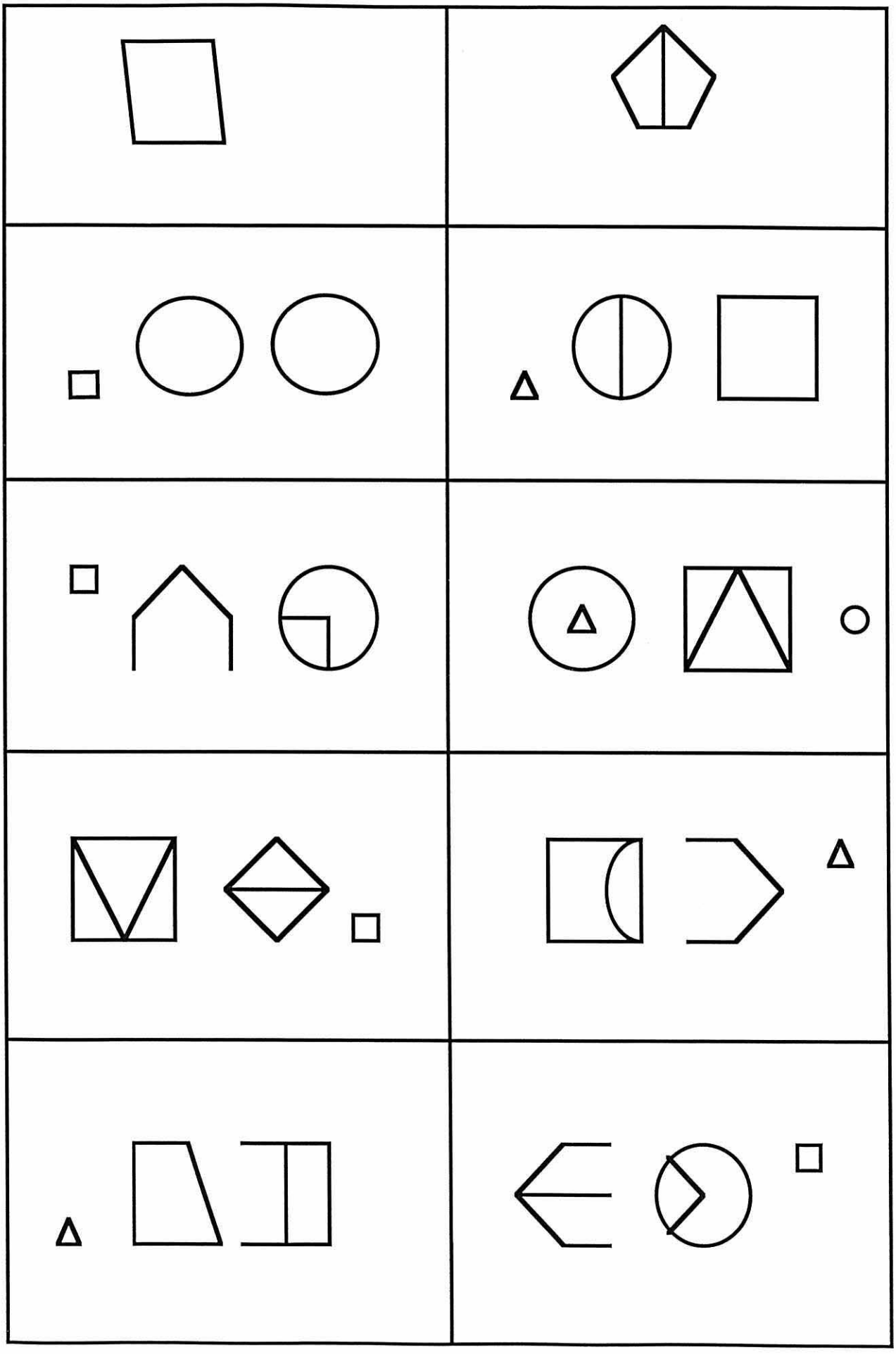


Additional forms of the Benton VRT- SET F **APPENDIX A**

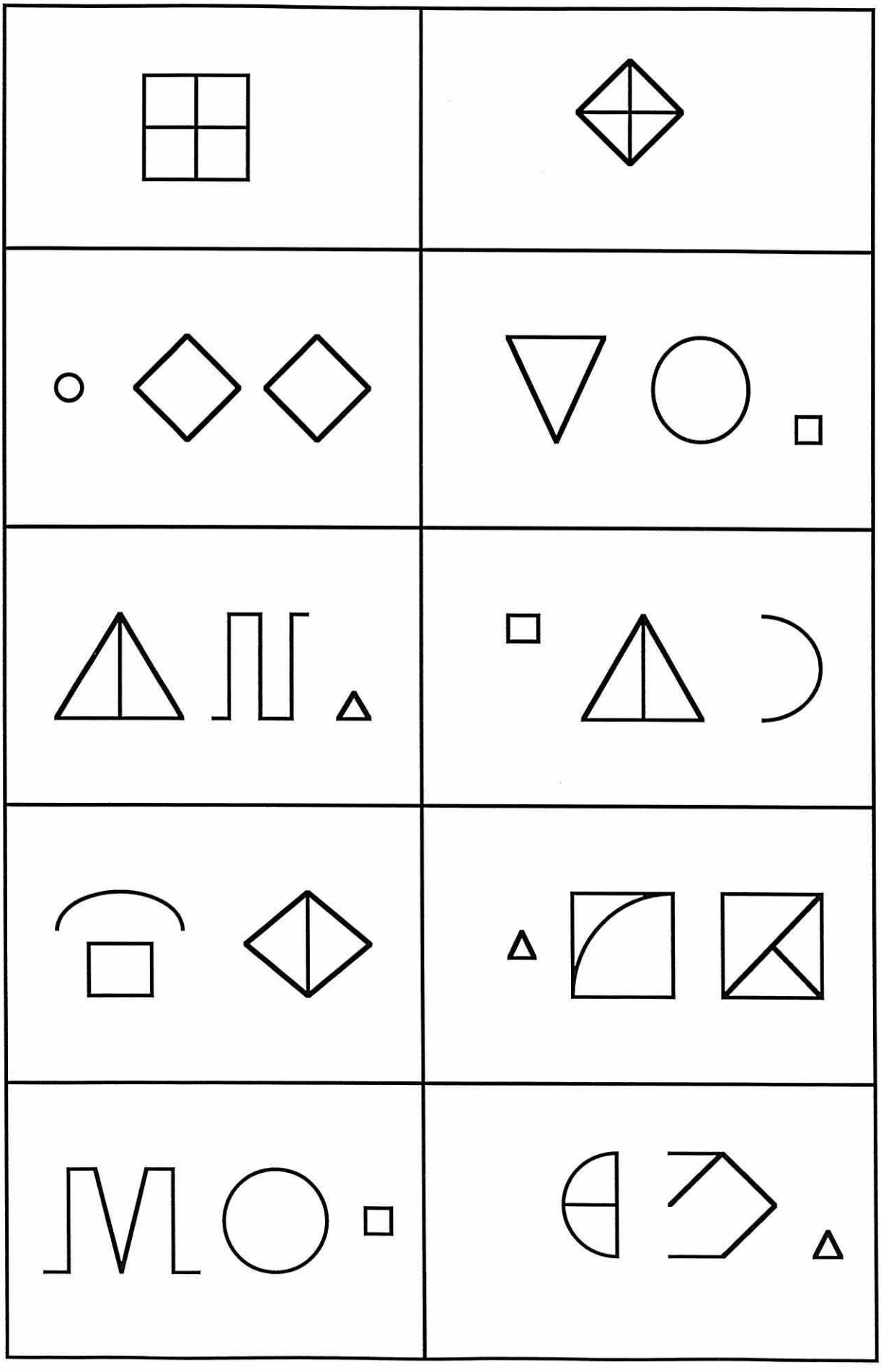


Additional forms of the Benton VRT- SET G **APPENDIX A**





Additional forms of the Benton VRT- SET I **APPENDIX A**



APPENDIX A

Materials used for the Verbal Memory test

SET A

TARGETS	DISTRACTERS
Chair	*Husband*
Gun	*Music*
Hall	*River*
Train	*Hair*
Bread	*Room*
Army	*Radio*
School	*Van*
Doctor	*Summer*
Mouth	*Family*
Boy	*Floor*
Trousers	*Car*
Hotel	*Game*
Candle	*Pear*
Woman	*Barn*
City	*Bookcase*
Butter	*Forest*

SET B

TARGETS	DISTRACTERS
Machine	*Son*
Ball	*Book*
Picture	*Wife*
Ship	*Heart*
Cup	*Door*
Letter	*Friend*
Face	*Bus*
Record	*Dark*
Foot	*Home*
County	*Bed*
Sock	*Town*
Office	*Television*
Lamp	*Banana*
Money	*Bicycle*
Water	*Vase*
Plate	*Grass*

SET C

TARGETS	DISTRACTERS
Tractor	*Child*
Paper	*Farm*
Table	*Horse*
Tree	*Arm*
Glass	*Fire*
Market	*Meat*
Cold	*Painting*
Plant	*Field*
Eye	*College*
Father	*Head*
Cushion	*Road*
House	*Police*
Apple	*Statue*
Light	*Flower*
Window	*Elephant*
Shoe	*Plane*

APPENDIX B

ANOVA summary tables and Tables of Means

Table 3.1. Mean memory test scores for each of nine test days (N = 27 subjects).

Test Day	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
20 word test:									
Immediate recall									
Mean	**9.8**	**8.2**	**9.3**	**9.4**	**10.3**	**10.3**	**10.4**	**10.5**	**10.3**
SD	3.3	2.6	2.9	3.3	3.4	2.9	2.9	3.7	2.7
Delayed recall									
Mean	**7.0**	**5.0**	**6.0**	**6.2**	**6.8**	**6.6**	**6.4**	**7.0**	**6.9**
SD	3.7	2.7	3.8	4.3	4.0	4.0	4.0	4.8	3.8
Recognition									
Correct positives									
Mean	**15.2**	**15.3**	**14.3**	**15.0**	**14.7**	**14.2**	**14.6**	**14.6**	**14.1**
SD	3.2	2.4	3.0	2.9	3.2	3.5	3.3	3.4	3.6
Recognition									
Correct negatives									
Mean	**17.7**	**16.2**	**16.6**	**17.2**	**17.1**	**17.3**	**17.8**	**17.8**	**17.4**
SD	2.4	2.6	2.2	2.7	2.4	2.9	2.3	2.6	2.5
Visual retention									
Mean	**7.2**	**8.3**	**8.0**	**8.6**	**8.6**	**8.5**	**8.7**	**8.9**	**8.4**
SD	1.8	1.8	1.7	1.6	1.7	1.5	1.3	1.4	1.4
Face-name-occupation									
Mean	**43.0**	**41.5**	**40.1**	**41.0**	**42.0**	**42.0**	**42.3**	**42.3**	**42.3**
SD	3.5	4.4	4.3	3.2	3.8	4.5	4.7	4.0	4.0
Spatial location									
Mean	**18.0**	**20.9**	**22.5**	**23.1**	**23.6**	**23.3**	**23.0**	**24.9**	**26.2**
SD	5.5	6.0	5.9	5.3	5.0	5.8	5.5	4.8	4.6

Table 3.2. Mean memory test scores for each of nine parallel test forms (N = 27 subjects).

Test Form	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
20 word test:									
Immediate recall									
Mean	**10.7**	**10.2**	**10.4**	**8.8**	**9.6**	**9.7**	**9.6**	**9.4**	**9.9**
SD	3.5	2.8	3.4	3.1	3.1	2.8	3.8	2.6	3.6
Delayed recall									
Mean	**7.0**	**6.3**	**6.3**	**5.6**	**7.1**	**6.3**	**6.8**	**6.0**	**6.3**
SD	4.6	3.5	4.1	3.2	4.1	3.7	4.9	3.5	3.7
Recognition									
Correct positives									
Mean	**15.1**	**13.7**	**14.9**	**14.2**	**14.7**	**14.5**	**14.8**	**14.1**	**15.4**
SD	2.8	2.6	3.4	3.7	3.2	3.5	3.4	3.2	2.8
Recognition									
Correct negatives									
Mean	**17.3**	**17.4**	**17.7**	**17.1**	**17.1**	**17.7**	**17.8**	**17.0**	**16.3**
SD	2.4	2.4	2.2	1.9	2.7	2.2	2.4	3.0	3.0
Visual retention									
Mean	**8.6**	**8.5**	**8.3**	**8.6**	**8.2**	**8.3**	**8.2**	**8.1**	**8.1**
SD	1.4	1.5	1.6	1.5	1.5	1.9	1.9	1.5	1.8
Face-name-occupation									
Mean	**17.4**	**18**	**18.8**	**16.5**	**17.9**	**19.6**	**19.8**	**18.0**	**17.7**
SD	3.5	4.4	4.3	3.2	3.8	4.5	4.7	4.0	4.0

Figure 3.3. Anova of study day effects on immediate verbal recall

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	1453.630	55.909		
Study days	8	120.889	15.111	3.918	.0002
Study days * Subject	208	802.222	3.857		

Dependent: Study days

Figure 3.4. Anova of study day effects on delayed verbal recall

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	2447.407	94.131		
Study days	8	89.111	11.139	1.989	.0492
Study days * Subject	208	1164.667	5.599		

Dependent: Study days

Figure 3.5. Anova of study day effects on correct positive (hits) scores

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	1431.490	55.057		
Study days	8	38.082	4.760	1.034	.4116
Study days * Subject	208	957.695	4.604		

Dependent: Study days

Figure 3.6. Anova of study day effects on correct negative scores.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	851.342	32.744		
Study days	8	62.601	7.825	2.605	.0098
Study days * Subject	208	624.733	3.004		

Dependent: Study days

Figure 3.7. Anova of study day effects on the extended Benton visual retention test

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	302.897	11.650		
Study days	8	52.008	6.501	4.652	.0001
Study days * Subject	208	290.658	1.397		

Dependent: Study Days Study days

Figure 3.8. Anova of study day effects on Name -face-occupation associate learning test.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	2169.333	83.436		
Study days	8	154.519	19.315	2.276	.0235
Study days * Subject	208	1764.815	8.485		

Dependent: Study days

Figure 3.9. Anova of study day effects on spatial location memory test.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	3760.947	144.652		
Study days	8	1167.761	145.970	9.959	.0001
Study days * Subject	208	3048.683	14.657		

Dependent: Study days

Figure 3.10. Anova of test form equivalence on immediate recall condition of the 20 word memory test.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	1470.255	56.548		
Test version	8	74.848	9.356	2.122	.0351
Test version * Subject	208	916.930	4.408		

Dependent: Test scores

Figure 3.11. Anova of test form equivalence on delayed recall condition of the 20 word memory test.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	2438.576	93.791		
Test versions	8	52.280	6.535	1.116	.3538
Test versions * Subject	208	1218.165	5.857		

Dependent: Test versions Test scores

Figure 3.12. Anova of test form equivalence on correct positive scores on the verbal memory test.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	1482.296	57.011		
Test version	8	60.593	7.574	1.729	.0933
Test version * Subject	208	911.185	4.381		

Dependent: Test scores

Figure 3.13. Anova of test form equivalence on correct negative scores on the verbal memory test.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	825.416	31.747		
Test version	8	47.045	5.881	1.929	.0572
Test version * Subject	208	634.066	3.048		

Dependent: Test scores

Figure 3.14. Anova of test form equivalence of the Extended Benton VRT

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	320.741	12.336		
Test version	8	7.630	.954	.615	.7648
Test version * Subject	208	322.593	1.551		

Dependent: Test scores

Figure 3.15. Anova of test form equivalence of the Name-face-occupation associate learning test

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	26	2169.333	83.436		
Test version	8	241.111	30.139	3.735	.0004
Test version * Subject	208	1678.222	8.068		

Dependent: Test scores

Table 3.16. Mean scores on the immediate and delayed recall scores of the elderly subjects over the nine days.

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Immed recall	5.5	4.7	6.0	7.3	6.3	6.0	5.5	7.8	6.5
Delay recall	2.8	1.3	2.0	4.5	2.5	1.5	2.3	1.8	1.5

Over page Table 4.1. ANOVA table of spatial localisation task reaction time data.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Group	1	13714.362	13714.362	.159	.6955
Subject(Group)	16	1381699.812	86356.238		
week	1	192991.812	192991.812	43.716	.0001
week * Group	1	1452.245	1452.245	.329	.5742
week * Subject(Group)	16	70634.345	4414.647		
day	3	133933.576	44644.525	26.808	.0001
day * Group	3	3313.406	1104.469	.663	.5788
day * Subject(Group)	48	79937.589	1665.366		
Col	1	309.760	309.760	.618	.4433
Col * Group	1	559.323	559.323	1.116	.3065
Col * Subject(Group)	16	8020.857	501.304		
Loc	1	52109.476	52109.476	75.896	.0001
Loc * Group	1	23.603	23.603	.034	.8552
Loc * Subject(Group)	16	10985.448	686.590		
week * day	3	52864.545	17621.515	9.265	.0001
week * day * Group	3	415.601	138.534	.073	.9743
week * day * Subject(Group)	48	91294.550	1901.970		
week * Col	1	264.604	264.604	1.192	.2911
week * Col * Group	1	.034	.034	1.514E-4	.9903
week * Col * Subject(Group)	16	3552.576	222.036		
day * Col	3	1397.096	465.699	1.744	.1705
day * Col * Group	3	306.594	102.198	.383	.7659
day * Col * Subject(Group)	48	12815.543	266.990		
week * Loc	1	2922.303	2922.303	11.263	.0040
week * Loc * Group	1	143.401	143.401	.553	.4680
week * Loc * Subject(Group)	16	4151.298	259.456		
day * Loc	3	3956.882	1318.961	4.396	.0082
day * Loc * Group	3	1501.944	500.648	1.669	.1862
day * Loc * Subject(Group)	48	14401.355	300.028		
Col * Loc	1	146.410	146.410	.615	.4444
Col * Loc * Group	1	3.300	3.300	.014	.9077
Col * Loc * Subject(Group)	16	3809.927	238.120		
week * day * Col	3	105.196	35.065	.149	.9299
week * day * Col * Group	3	705.161	235.054	.998	.4017
week * day * Col * Subject(Gro...	48	11301.152	235.441		
week * day * Loc	3	2425.577	808.526	3.399	.0251
week * day * Loc * Group	3	631.469	210.490	.885	.4556
week * day * Loc * Subject(Gro...	48	11416.910	237.852		
week * Col * Loc	1	358.471	358.471	1.618	.2215
week * Col * Loc * Group	1	23.200	23.200	.105	.7504
week * Col * Loc * Subject(Gro...	16	3544.740	221.546		
day * Col * Loc	3	429.019	143.006	.584	.6286
day * Col * Loc * Group	3	194.379	64.793	.264	.8507
day * Col * Loc * Subject(Group)	48	11761.138	245.024		
week * day * Col * Loc	3	969.413	323.138	1.151	.3383
week * day * Col * Loc * Group	3	115.712	38.571	.137	.9372
week * day * Col * Loc * Subje...	48	13478.385	280.800		

Dependent: clxxss RTs

Table 4.2. ANOVA summary table of location effect data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	57.507	57.507	.096	.7610
Subject(Group)	16	9614.306	600.894		
Week	1	5196.007	5196.007	13.290	.0022
Week * group	1	65.340	65.340	.167	.6881
Week * Subject(Group)	16	6255.528	390.970		
Day	3	4975.910	1658.637	5.450	.0026
Day * group	3	1228.965	409.655	1.346	.2706
Day * Subject(Group)	48	14608.250	304.339		
Week * Day	3	1373.465	457.822	1.541	.2160
Week * Day * group	3	329.021	109.674	.369	.7756
Week * Day * Subject(G...	48	14262.139	297.128		

Dependent: Location effect

Table 4.3. ANOVA summary table of colour effect data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	506.250	506.250	.850	.3702
Subject(Group)	16	9526.472	595.405		
week	1	1.778	1.778	.010	.9209
week * group	1	13.444	13.444	.077	.7850
week * Subject(Group)	16	2796.028	174.752		
day	3	597.194	199.065	.819	.4899
day * group	3	986.306	328.769	1.352	.2686
day * Subject(Group)	48	11669.750	243.120		
week * day	3	1023.444	341.148	1.495	.2278
week * day * group	3	464.222	154.741	.678	.5697
week * day * Subject(G...	48	10953.083	228.189		

Dependent: colour effect

Table 4.4. ANOVA summary table of LC effect data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value	G-G
group	1	112.007	112.007	.080	.7804	
Subject(Group)	16	22288.694	1393.043			
week	1	966.174	966.174	1.679	.2134	.2134
week * group	1	410.062	410.062	.713	.4110	.4110
week * Subject(Group)	16	9205.639	575.352			
day	3	4825.687	1608.562	2.341	.0850	.1001
day * group	3	815.354	271.785	.395	.7568	.7145
day * Subject(Group)	48	32987.083	687.231			
week * day	3	1850.076	616.692	.999	.4016	.3921
week * day * group	3	1180.076	393.359	.637	.5949	.5678
week * day * Subject(G...	48	29643.472	617.572			

Dependent: lc effect

Over page Table 4.5. ANOVA summary table of error scores on the spatial localisationtask

Source	df	Sum of Squares	Mean Square	F-Value	P-Valu
GROUP	1	.825	.825	.034	.8557
Subject(Group)	14	336.493	24.035		
week	1	2.043	2.043	.383	.5459
week * GROUP	1	6.927	6.927	1.299	.2735
week * Subject(Group)	14	74.647	5.332		
day	3	17.493	5.831	.689	.5637
day * GROUP	3	13.781	4.594	.543	.6556
day * Subject(Group)	42	355.356	8.461		
Col.	1	.091	.091	.024	.8800
Col. * GROUP	1	8.335	8.335	2.171	.1627
Col. * Subject(Group)	14	53.737	3.838		
Loc.	1	.342	.342	.083	.7770
Loc. * GROUP	1	.997	.997	.243	.6300
Loc. * Subject(Group)	14	57.516	4.108		
week * day	3	11.261	3.754	.969	.4161
week * day * GROUP	3	35.011	11.670	3.014	.0405
week * day * Subject(Group)	42	162.616	3.872		
week * Col.	1	.387	.387	.128	.7259
week * Col. * GROUP	1	9.781	9.781	3.237	.0936
week * Col. * Subject(Group)	14	42.310	3.022		
day * Col.	3	12.364	4.121	2.037	.1233
day * Col. * GROUP	3	3.158	1.053	.520	.6707
day * Col. * Subject(Group)	42	84.977	2.023		
week * Loc.	1	.759	.759	.416	.5294
week * Loc. * GROUP	1	2.803	2.803	1.535	.2357
week * Loc. * Subject(Group)	14	25.564	1.826		
day * Loc.	3	2.256	.752	.340	.7967
day * Loc. * GROUP	3	8.556	2.852	1.289	.2908
day * Loc. * Subject(Group)	42	92.958	2.213		
Col. * Loc.	1	6.735	6.735	4.777	.0463
Col. * Loc. * GROUP	1	4.560	4.560	3.234	.0937
Col. * Loc. * Subject(Group)	14	19.738	1.410		
week * day * Col.	3	9.150	3.050	1.287	.2913
week * day * Col. * GROUP	3	2.568	.856	.361	.7812
week * day * Col. * Subject(Group)	42	99.526	2.370		
week * day * Loc.	3	1.924	.641	.295	.8289
week * day * Loc. * GROUP	3	5.059	1.686	.775	.5144
week * day * Loc. * Subject(Group)	42	91.360	2.175		
week * Col. * Loc.	1	2.736	2.736	1.358	.2633
week * Col. * Loc. * GROUP	1	4.470	4.470	2.218	.1586
week * Col. * Loc. * Subject(Grou...	14	28.209	2.015		
day * Col. * Loc.	3	3.305	1.102	.424	.7365
day * Col. * Loc. * GROUP	3	3.682	1.227	.473	.7029
day * Col. * Loc. * Subject(Group)	42	109.024	2.596		
week * day * Col. * Loc.	3	3.025	1.008	.378	.7693
week * day * Col. * Loc. * GROUP	3	2.778	.926	.347	.7913
week * day * Col. * Loc. * Subjec...	42	112.013	2.667		

Dependent: error data

Table 4.6. ANOVA summary table of immediate recall data with comparison group 1

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	24.001	24.001	.443	.5148
Subject(Group)	17	922.013	54.236		
week	1	64.453	64.453	5.856	.0270
week * group	1	8.401	8.401	.763	.3945
week * Subject(Group)	17	187.112	11.007		
day	3	91.390	30.463	8.359	.0001
day * group	3	7.969	2.656	.729	.5395
day * Subject(Group)	51	185.860	3.644		
week * day	3	9.008	3.003	.920	.4378
week * day * group	3	2.429	.810	.248	.8623
week * day * Subject(G...	51	166.426	3.263		

Dependent: immed. recall

Table 4.7. ANOVA summary table of immediate recall data with comparison group 2.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	.756	.756	.015	.9026
Subject(Group)	18	883.713	49.095		
week	1	100.806	100.806	12.697	.0022
week * group	1	1.406	1.406	.177	.6788
week * Subject(Group)	18	142.912	7.940		
day	3	63.369	21.123	4.529	.0066
day * group	3	41.169	13.723	2.943	.0411
day * Subject(Group)	54	251.838	4.664		
week * day	3	9.819	3.273	1.058	.3746
week * day * group	3	14.519	4.840	1.565	.2086
week * day * Subject(G...	54	167.037	3.093		

Dependent: immed. recall

Table 4.8. ANOVA summary table of delayed recall data with comparison group 1

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	190.660	190.660	2.367	.1424
Subject(Group)	17	1369.590	80.564		
week	1	43.905	43.905	4.219	.0557
week * group	1	3.379	3.379	.325	.5763
week * Subject(Group)	17	176.924	10.407		
day	3	58.664	19.555	5.126	.0036
day * group	3	13.138	4.379	1.148	.3387
day * Subject(Group)	51	194.560	3.815		
week * day	3	89.558	29.853	7.613	.0003
week * day * group	3	35.768	11.923	3.041	.0372
week * day * Subject(G...	51	199.982	3.921		

Dependent: delayed recall

Table 4.9. ANOVA summary table of immediate recall data with comparison group 2.

Source	df	Sum of Squares	Mean Square	F-Value	P-Value	G-G
group	1	24.025	24.025	.265	.6129	
Subject(Group)	18	1631.075	90.615			
week	1	44.100	44.100	5.468	.0311	.0311
week * group	1	4.225	4.225	.524	.4785	.4785
week * Subject(Group)	18	145.175	8.065			
day	3	60.000	20.000	3.913	.0134	.0244
day * group	3	46.475	15.492	3.031	.0371	.0544
day * Subject(Group)	54	276.025	5.112			
week * day	3	88.100	29.367	4.635	.0059	.0073
week * day * group	3	38.275	12.758	2.014	.1229	.1279
week * day * Subject(G...	54	342.125	6.336			

Dependent: delayed recall

Table 4.10. ANOVA summary table of correct positive (hits) data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	8.904	8.904	.221	.6441
Subject(Group)	17	684.057	40.239		
week	1	4.176	4.176	1.467	.2424
week * group	1	7.439	7.439	2.613	.1244
week * Subject(Group)	17	48.390	2.846		
day	3	12.873	4.291	1.443	.2412
day * group	3	25.978	8.659	2.911	.0432
day * Subject(Group)	51	151.693	2.974		
week * day	3	32.301	10.767	2.673	.0571
week * day * group	3	5.670	1.890	.469	.7051
week * day * Subject(G...	51	205.449	4.028		

Dependent: hits

Table 4.11. ANOVA summary table of correct negative data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Group	1	74.421	74.421	6.358	.0220
Subject(Group)	17	198.974	11.704		
week	1	3.193	3.193	1.000	.3314
week * Group	1	2.667	2.667	.835	.3737
week * Subject(Group)	17	54.307	3.195		
Day	3	28.062	9.354	3.740	.0166
Day * Group	3	24.325	8.108	3.242	.0295
Day * Subject(Group)	51	127.543	2.501		
week * Day	3	31.532	10.511	4.067	.0115
week * Day * Group	3	6.690	2.230	.863	.4664
week * Day * Subject(G...	51	131.810	2.585		

Dependent: correct negatives

Table 4.12. ANOVA summary table of CFFT means data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	16.846	16.846	.349	.5625
Subject(Group)	17	820.685	48.276		
week	1	9.603	9.603	2.768	.1145
week * group	1	1.302	1.302	.375	.5483
week * Subject(Group)	17	58.973	3.469		
day	3	2.960	.987	.456	.7141
day * group	3	.405	.135	.062	.9794
day * Subject(Group)	51	110.286	2.162		
week * day	3	6.490	2.163	1.156	.3357
week * day * group	3	3.663	1.221	.652	.5851
week * day * Subject(G...	51	95.454	1.872		

Dependent: cfft-mean.

Table 4.13. ANOVA summary table of CAT data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	152.111	152.111	1.881	.1892
Subject(Group)	16	1294.139	80.884		
week	1	2.778	2.778	.126	.7268
week * group	1	.444	.444	.020	.8887
week * Subject(Group)	16	351.528	21.970		
day	3	38.167	12.722	2.285	.0907
day * group	3	6.389	2.130	.383	.7660
day * Subject(Group)	48	267.194	5.567		
week * day	3	9.722	3.241	.686	.5653
week * day * group	3	12.611	4.204	.889	.4535
week * day * Subject(G...	48	226.917	4.727		

Dependent: CAT

Table 4.14. ANOVA summary table of the Stroop colour-naming data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	14.216	14.216	.064	.8040
Subject(Group)	17	3803.112	223.712		
week	1	563.723	563.723	22.747	.0002
week * group	1	35.512	35.512	1.433	.2477
week * Subject(Group)	17	421.290	24.782		
day	3	631.836	210.612	13.683	.0001
day * group	3	146.783	48.928	3.179	.0317
day * Subject(Group)	51	784.993	15.392		
week * day	3	199.162	66.387	2.687	.0562
week * day * group	3	36.846	12.282	.497	.6860
week * day * Subject(G...	51	1260.193	24.710		

Dependent: stroop-colour naming

Table 4.15. ANOVA summary table of the Stroop interference data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
group	1	148.021	148.021	.144	.7088
Subject(Group)	17	17450.124	1026.478		
week	1	4409.816	4409.816	67.024	.0001
week * group	1	62.816	62.816	.955	.3422
week * Subject(Group)	17	1118.512	65.795		
day	3	2422.139	807.380	30.278	.0001
day * group	3	36.666	12.222	.458	.7126
day * Subject(Group)	51	1359.926	26.665		
week * day	3	1143.234	381.078	15.927	.0001
week * day * group	3	34.655	11.552	.483	.6957
week * day * Subject(G...	51	1220.226	23.926		

Dependent: Stroop-interference

Table 9.1 Anova summary table of immediate recall data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	12	178.991	14.916		
Group	2	162.513	81.256	5.459	.0111
Group * Subject	24	357.265	14.886		
Test day	2	10.205	5.103	1.085	.3540
Test day * Subject	24	112.906	4.704		
Group * Test day	4	29.590	7.397	1.959	.1160
Group * Test day * Subj...	48	181.299	3.777		

Dependent: VMT-Immed. recall

Table 9.2 Anova summary table of delayed recall data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	11	315.657	28.696		
Group	2	105.685	52.843	3.156	.0624
Group * Subject	22	368.315	16.742		
Test day	2	46.685	23.343	17.128	.0001
Test day * Subject	22	29.981	1.363		
Group * Test day	4	25.704	6.426	2.251	.0789
Group * Test day * Subj...	44	125.630	2.855		

Dependent: VMT-delayed recall

Table 9.3 Anova summary table of correct positive data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	11	300.630	27.330		
Group	2	36.352	18.176	.913	.4159
Group * Subject	22	437.870	19.903		
Test day	2	.519	.259	.046	.9550
Test day * Subject	22	123.704	5.623		
Group * Test day	4	13.481	3.370	.607	.6597
Group * Test day * Subj...	44	244.296	5.552		

Dependent: VMT-hits

Table 9.4. Anova summary table of false positive data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	10	135.071	13.507		
Group	2	82.990	41.495	2.930	.0766
Group * Subject	20	283.232	14.162		
Test day	2	6.081	3.040	1.083	.3576
Test day * Subject	20	56.141	2.807		
Group * Test day	4	14.343	3.586	.779	.5454
Group * Test day * Subj...	40	184.101	4.603		

Dependent: VMT-false alarms

Table 9.5. Anova summary table of FULD total data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	10	3149.556	314.956		
Group	2	1612.687	806.343	4.724	.0209
Group * Subject	20	3413.535	170.677		
Test day	2	93.960	46.980	3.252	.0599
Test day * Subject	20	288.929	14.446		
Group * Test day	4	68.889	17.222	1.745	.1593
Group * Test day * Subj...	40	394.889	9.872		

Dependent: FULD total

Table 9.6. Anova summary table of FULD repeated data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value	G-G
Subject	10	2456.404	245.640			
Group	2	1600.141	800.071	6.245	.0078	.0132
Group * Subject	20	2562.081	128.104			
Test day	2	125.717	62.859	4.328	.0274	.0316
Test day * Subject	20	290.505	14.525			
Group * Test day	4	63.131	15.783	1.159	.3432	.3413
Group * Test day * Subj...	40	544.646	13.616			

Dependent: Fuld-repeated retrieval

Table 9.7. Anova summary table of FULD delayed recall data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	12	728.855	60.738		
Group	2	56.838	28.419	.275	.7620
Group * Subject	24	2480.940	103.373		
Test day	2	130.889	65.444	.897	.4210
Test day * Subject	24	1750.889	72.954		
Group * Test day	4	235.932	58.983	.831	.5122
Group * Test day * Subj...	48	3407.624	70.992		

Dependent: Fuld-delayed recall

Table 9.8. Anova summary table of delayed story recall data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	12	27.455	2.288		
Group	2	.809	.404	.232	.7947
Group * Subject	24	41.839	1.743		
Test day	2	.566	.283	1.771	.1918
Test day * Subject	24	3.836	.160		
Group * Test day	4	.212	.053	.165	.9549
Group * Test day * Subj...	48	15.363	.320		

Dependent: Story delay

Table 9.9. Anova summary table of Speed of Comprehension data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	14	20133.584	1438.113		
Group	2	10573.497	5286.748	5.961	.0070
Group * Subject	28	24834.562	886.949		
Test day	2	1217.077	608.539	9.379	.0008
Test day * Subject	28	1816.682	64.881		
Group * Test day	4	50.922	12.731	.247	.9106
Group * Test day * Subj...	56	2891.425	51.633		

Dependent: Speed of Comprehension

Table 9.10. Anova summary table of Benton data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	12	117.658	9.805		
Group	2	81.590	40.795	4.316	.0251
Group * Subject	24	226.855	9.452		
Test day	2	3.231	1.615	.941	.4043
Test day * Subject	24	41.214	1.717		
Group * Test day	4	5.641	1.410	.884	.4807
Group * Test day * Subj...	48	76.581	1.595		

Dependent: Benton

Table 9.11. Anova summary table of Digit span data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	13	1217.024	93.617		
Group	2	.905	.452	.005	.9954
Group * Subject	26	2525.762	97.145		
Test day	2	209.333	104.667	1.941	.1638
Test day * Subject	26	1402.000	53.923		
Group * Test day	4	269.905	67.476	1.166	.3366
Group * Test day * Subj...	52	3009.429	57.874		

Dependent: Digit span

Table 9.12. Anova summary table of Stroop colour naming data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	8	27385.934	3423.242		
Group	2	15352.978	7676.489	5.167	.0186
Group * Subject	16	23771.491	1485.718		
Test day	2	936.541	468.270	1.192	.3292
Test day * Subject	16	6285.128	392.820		
Group * Test day	4	1434.704	358.676	.785	.5432
Group * Test day * Subj...	32	14615.700	456.741		

Dependent: Stroop-control

Table 9.13. Anova summary table of Stroop interference data

Source	df	Sum of Squares	Mean Square	F-Value	P-Value
Subject	8	46955.882	5869.485		
Group	2	17390.852	8695.426	1.075	.3646
Group * Subject	16	129366.461	8085.404		
Test day	2	2060.415	1030.208	.905	.4242
Test day * Subject	16	18211.632	1138.227		
Group * Test day	4	4105.638	1026.409	1.022	.4108
Group * Test day * Subj...	32	32138.056	1004.314		

Dependent: Fuld-total

Mean scores on the measures of the clinical trial

Table 9.14. Mean immediate recall scores.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**5.9**	**5.7**	**9.4** *
	SD	3.5	3.0	2.8
T2	Mean	**6.0**	**6.4**	**7.5** *
	SD	2.1	2.3	2.3
T3	Mean	**6.9**	**6.4**	**8.4**
	SD	3.0	3.0	2.7

*$p<0.05$

Table 9.15. Mean delayed recall scores.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**3.5**	**3.1**	**4.9**
	SD	3.0	2.8	3.4
T2	Mean	**2.4**	**3.6**	**4.1**
	SD	2.5	2.8	2.1
T3	Mean	**4.1**	**3.6**	**6.3**
	SD	2.4	3.2	3.2

Table 9.16. Mean number of hits in the recognition phase.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**11.6**	**10.6**	**12.5**
	SD	3.0	3.1	3.4
T2	Mean	**11.8**	**11.0**	**11**
	SD	2.9	3.5	3.1
T3	Mean	**11.5**	**11.1**	**11.8**
	SD	2.9	4.5	2.8

Table 9.17. Mean number of false alarms scored.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**3.7**	**2.5**	**1.3**
	SD	3.1	2.4	1.6
T2	Mean	**3.5**	**3.5**	**1.5**
	SD	2.5	3.5	1.8
T3	Mean	**3.4**	**3.1**	**1.5**
	SD	3.2	3.3	1.8

Table 9.18. Mean Fuld OME total retrieval scores.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**38.2**	**36.7**	**42.5**
	SD	8.0	11.9	4.6
T2	Mean	**34.7**	**32.6**	**42.1**
	SD	11.3	12.9	6.6
T3	Mean	**37.5**	**34.3**	**44.4**
	SD	10.4	12.4	3.9

Table 9.19. Mean Fuld OME repeated retrievals scores.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**25.4**	**25.0**	**29.9**
	SD	8.5	10.2	6.3
T2	Mean	**21.7**	**20.3**	**29.7**
	SD	10.6	10.1	7.5
T3	Mean	**30.3**	**23.0**	**32.4**
	SD	22.0	9.9	4.7

Table 9.20 Mean Fuld delayed recall scores.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**8.2**	**7.9**	**9.4** *
	SD	2.4	2.6	1.2
T2	Mean	**8.5**	**7.2**	**9.2**
	SD	2.1	3.0	1.1
T3	Mean	**8.3**	**7.6**	**9.3**
	SD	2.3	3.2	0.8

*$p<0.05$

Table 9.21. Mean scores on the delayed short story recall

		Paroxetine	Lofepramine	Control
Baseline	Mean	**5.7**	**6.2**	**6.7**
	SD	3.2	3.4	3.4
T2	Mean	**7.4**	**6.9**	**6.9**
	SD	5.0	4.1	4.0
T3	Mean	**6.0**	**7.0**	**7.5**
	SD	2.9	4.0	3.6

Table 9.22. Mean scores on the Benton VRT

		Paroxetine	Lofepramine	Control
Baseline	Mean	**4.1**	**3.5**	**5.0**
	SD	2.7	2.3	1.7
T2	Mean	**3.6**	**2.2**	**5.0**
	SD	2.1	1.7	2.1
T3	Mean	**3.9**	**3.3**	**5.2**
	SD	2.4	1.9	2.2

Table 9.23. Mean number of sentences processed in two minutes.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**42.3**	**38.1**	**57.9** **
	SD	19.6	11.2	18.4
T2	Mean	**44.4**	**42.1**	**61.5**
	SD	23.7	17.2	21.2
T3	Mean	**48.0**	**45.9**	**66.7**
	SD	24.6	20.6	20.7

**p<0.01

Table 9.24. Mean colour naming scores on the Stroop.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**106.5**	**112.2**	**61.8**
	SD	62.4	46.1	11.1
T2	Mean	**101.1**	**96.4**	**60.1**
	SD	58.8	44.4	13.6
T3	Mean	**91.9**	**108.6**	**55.7**
	SD	54.0	70.3	9.8

Table 9.25. Mean difference between the time taken on the colour naming task and the interference task of the Stroop

		Paroxetine	Lofepramine	Control
Baseline	Mean	**84.7**	**84.2**	**74.8**
	SD	51.0	48.5	35.0
T2	Mean	**75.8**	**78.7**	**62.8**
	SD	57.9	35.8	34.8
T3	Mean	**88.5**	**74.2**	**56.5**
	SD	111.8	69.7	21.0

Table 9.26. Mean scores on the digit span task.

		Paroxetine	Lofepramine	Control
Baseline	Mean	**12.8**	**14.3**	**14.0**
	SD	4.7	3.7	1.9
T2	Mean	**13.6**	**14.3**	**14.2**
	SD	4.1	4.2	2.8
T3	Mean	**14.1**	**14.8**	**14.6**
	SD	4.1	4.6	3.7

APPENDIX C

Extracts from the clinical trial protocol.

2. OBJECTIVE OF STUDY

Primary

To assess the efficacy and tolerability of paroxetine (20-30mg daily) in the treatment of major depression in the elderly by double-blind comparison with lofepramine (70-210mg daily).

Secondary

To compare the effects of paroxetine and lofepramine on cognitive function in elderly patients with major depression.

3. STUDY DESIGN

3.1 EXPERIMENTAL DESIGN

A randomised, multicentre, double-blind, between patient comparative study in hospital in - or out-patients.

An eight week period of "active" treatment will be preceded by a one week placebo run-in period. At Day 56, patients who have responded or partially responded to study medication will enter a 12 month continuation study (see Long-term protocol).

3.2 PATIENT SELECTION

3.2.1 Definition of Disease State

Major depression defined according to DSM-III-R 296.2x (a single major depressive episode - no manic or unequivocal hypomanic episode), and 296.3x (major depression recurrent, two or more major depressive episodes each separated by at least two months of return to more or less usual functioning - no manic or unequivocal hypomanic episode). Definitions as follows:

A. At least five of the following symptoms have been present during the preceding two-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood, or (2) loss of interest or pleasure. (Do not include symptoms that are clearly due to a physical condition, mood-incongruent delusions or hallucination, incoherence or marked loosening of associations.)

1) Depressed mood most of the day, nearly every day, as indicated either by subjective account or observation by others.

2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated either by subjective account or observation by others of apathy most of the time).

3) Significant weight loss or weight gain when not dieting (e.g. more than 5% of body weight in month), or decrease or increase in appetite nearly every day

4) Insomnia or hypersomnia nearly every day.

5) Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

6) Fatigue or loss of energy nearly every day.

7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. 1) It cannot be established that an organic factor initiated and maintained the disturbance.

2) The disturbance is not a normal reaction to the death of a loved one (Uncomplicated Bereavement).

Note: Morbid preoccupation with worthlessness, suicidal ideation, marked functional impairment or psychomotor retardation, or prolonged duration suggest bereavement complicated by Major Depression.

C. At no time during the disturbance have there been delusions or hallucinations for as long as two weeks in the absence of prominent mood symptoms (i.e. before the mood symptoms developed or after they have remitted).

D. Not superimposed on Schizophrenia, Schizopreniform Disorder, Delusional Disorder, or Psychotic Disorder NOS.

3.2.2. Source and Number

170 patients (85 per treatment group) will be required to complete the study. All will be patients seen as hospital in or out-patients. In order to achieve this, it is anticipated that about 220 patients will need to be recruited to account for drop-outs. It is estimated that a maximum of 10 hospital centres will participate.

3.2.3 Entrance Criteria

Inclusion Criteria

1) Male or female hospital in - or out-patients aged 65-85 years capable of giving written informed consent.

2) Major Depression defined according to DSM-III-R 296.2x and 296.3x.

3) Score of at least 20 on the Montgomery Asberg Depression Rating Scale and a total score of 23 or more on the Folstein Mini Mental State Examination.

Exclusion Criteria

1) Clinically Significant co-existing disease including:

- Renal, hepatic or cardiovascular disorders
- Ischaemic heart disease, recent myocardial infarction (within the past 6 months) or angina requiring treatment.
- Glaucoma, prostatism, urinary retention.
- Neurological disorders including epilepsy, Parkinsonism (other than early untreated).
- Uncontrolled hypertension and/or that requiring treatment with guanethidine (ISMELIN or CLONIDINE), bethanidine (ESBATAL)
- Non stabilised diabetes or insulin dependent diabetes, or other significant endocrine disease.

2) Dementia (clinical diagnosis).

3) Mania or bipolar disorder.

4) Patients exhibiting psychotic symptomatology who require neuroleptic medication or ECT.

5) Schizophrenia

6) ECT within 3 months prior to entering the study or patients requiring ECT.

7) History of allergy or poor tolerance to tricyclic-like drugs or paroxetine.

8) Treatment with anticoagulants.

9) Patients with significant suicidal tendencies.

10) Treatment with psychotropic medication (see section 4.8 below); including monoamine oxidase inhibitors within 2 weeks of entering the study, and depot/oral neuroleptics in the past 2 months.

11) Clinically significant abnormalities in clinical chemistry or haematology prior to entering the study.

12) Treatment with an investigational compound in the 3 month period prior to entering the study.

13) Patients unable to co-operate with study procedures, including those with significant visual/physical handicap.

3.3 STUDY MEDICATION

3.3.1 Dosage form

Paroxetine will be presented as white film-coated capsule shaped tablets each containing 20mg paroxetine hydrochloride, and blue film-coated tablets each containing 30mg paroxetine hydrochloride.

Lofepramine (GAMANIL) will be presented as brownish/violet coated tablets each containing 70mg lofepramine hydrochloride.

Placebos to match the above will be visually and cosmetically identical to their active counterparts.

3.3.2 **Dosing Schedule**

It is intended that paroxetine will be administered once daily in the morning and lofepramine in a divided daily dose (morning and evening). Dosing will begin on Day 0, commencing with the evening dose.

During the first week of active medication patients will receive paroxetine 20mg or lofepramine 70mg. On Day 7, patients allocated to receive paroxetine will continue on 20mg daily, whilst those allocated to lofepramine will have the dose increased to 140mg daily.

N.B. If at the Day 21 assessment, the investigator considers that the clinical response to study medication is inadequate, the dosage may be increased such that patients receive either 30mg paroxetine or 210mg lofepramine, unless this is contra-indicated by poor tolerance. Information relating to dose changes will be recorded in the Case Record Form.

Patients should continue to the end of the study on the dose given at the end of Week 3 assessment. The decision to increase the dose should only be taken at the end of Week 3.

Patients will be asked to return unused medication at each subsequent visit.

Summary - Dosing Schedule

- Pre-treatment Week (Placebo run-in Day -7 to Day 0

1 white tablet (placebo) and 1 violet tablet (placebo) in the morning, and 1 violet tablet (placebo) at night.

- Day 0 to Day 7

Paroxetine

1 white tablet (paroxetine 20mg) and 1 violet tablet (placebo) in the morning

and

1 violet tablet (placebo) in the evening.

Lofepramine

1 white tablet (placebo) and 1 violet tablet (placebo) in the morning.

and

1 violet tablet (lofepramine 70mg) in the evening.

- Day 7 to Day 56 (standard dose)

Paroxetine

1 white tablet (paroxetine 20mg) and 1 violet tablet (placebo) in the morning.

and

1 violet tablet (placebo) in the evening.

Lofepramine

1 white tablet (placebo) and 1 violet tablet (lofepramine 70mg) in the morning.

and

1 violet tablet (lofepramine 70mg) in the evening.

- Day 21 to Day 56 (optional increased dose)

Paroxetine

1 blue tablet (paroxetine 30mg) and 1 violet tablet (placebo) in the morning.

and

2 violet tablets (placebo) in the evening.

Lofepramine

1 blue tablet (placebo) and 1 violet tablet (lofepramine 70mg) in the morning.

and

2 violet tablets (lofepramine 2 x 70mg) in the evening.

3.4 EXPERIMENTAL FLOW

3.4.1 General Description of Study Flow

After pre-study screening (Day -7) patients will enter a placebo run-in period at the end of which they will (if not barred by exclusion criteria) enter the eight week active phase of the study during which efficacy and safety evaluations will be performed on Days 0, 7, 21, 35 and 56. At Day 56, patients who have responded or partially responded to study medication will enter a 12 month continuation study (see Long-term protocol).

Screening Assessments (Day -7)

The following assessments will be performed at the screening examination:

- Inclusion/exclusion criteria
- DSM-III-R major depression
- Montgomery Asberg Depression Rating Scale (score of at least 20)
- Medical and psychiatric history
- Physical examination and Vital Signs including - blood pressure and pulse (lying and standing), temperature and weight.
- Concurrent conditions/therapies
- Demographic data
- Folstein Mini-Mental Examination (score 23 or more)
- Blood sample for clinical chemistry and haematology

After completion of the above, the placebo run-in period will begin.

3.4.2 Drug Sequence

At the start of the placebo run-in phase of the study (day -7), patients will be allocated a randomisation number in sequential order of their entry to the study. This randomisation number will determine whether they receive paroxetine or lofepramine (see section 3.3.2 for doses), when they enter the active phase of the study.

3.4.3 **Clinical Observations**

Efficacy evaluation

Assessment Day -7 and Days 0, 7, 21, 35 and 56

- Montgomery Asberg Depression Rating Scale
- Geriatric Depression Rating Scale (Days 0, 21, 35 and 56 only)
- Clinical Global Impression
- Cognitive Test Battery

Safety

Assessment Day -7 and Days 0, 7, 21, 35 and 56

- Adverse experiences (not Day -7)
- Blood pressure and Pulse (lying and standing)
- Clinical chemistry and haematology (Day -7 and 56 only)
- Weight (Days -7 and 56 only)

3.4.4 Laboratory Observations

The following laboratory investigations will be performed on Days -7 and 56 or on discontinuation of therapy:

- Haematology, to include: RBC, haemoglobin, haematocrit, MCH, MCHC, MCV, WBC (and differential) and platelets.
- Clinical Chemistry to include (when available): sodium, potassium, bicarbonate, chloride, glucose, blood urea, alkaline phosphatase, creatinine, calcium, phosphate, uric acid, total protein, albumin, globulin, ALT, AST and gamma GT.

Normal values used for these tests must be provided by the laboratory concerned to the Sponsor. Any result which falls outside the laboratory normal range will be considered abnormal. If this occurs after the start of the study therapy, the Investigator will indicate in the appropriate section of the Case Report Form whether this is of clinical significance. All laboratory tests which are considered to be abnormal and clinically significant will be repeated until the values return to normal. If this does not occur within a reasonable period of time, then (as far as possible) the aetiology will be identified and the Sponsor informed.

N.B Patients, who in the opinion of the Investigator, have clinically significant abnormalities in Day -7 haematological and/or clinical chemistry results should be withdrawn from the study and should not proceed to the active phase of the study.

3.4.5 ASSESSMENT SCHEDULE

	VISITS					
ASSESSMENT	DAY -7	DAY 0	DAY 7	DAY 21	DAY 35	DAY 56
Informed Consent	X					
Medical History	X					
Physical Examination	X					
Psychiatric History	X					
History of Depression	X					
Mini-Mental State	X					
Vital signs	X	X	X	X	X	X
Montgomery Asberg Scale	X	X	X	X	X	X
Geriatric Depression (Rating Scale GDS)		X		X	X	X
Clinical Global Impression	X	X	X	X	X	X
Cognitive Function Battery	X	X	X	X	X	X
Haematology and Biochemistry	X					X
Compliance Check		X	X	X	X	X
Adverse Experience Check		X	X	X	X	X
Dispense Medication	X	X	X	X	X	
Optional Dose Increase				X		

4. EXPERIMENTAL CONTROL

4.1 RANDOMISATION

On entry to the placebo run-in phase of the study, patients will be randomly allocated to either one of the two treatment groups.

A master randomisation list will be held with the Sponsor. Individual sealed code envelopes indicating the treatment received by each study patient will be lodged with the hospital pharmacy department.

Code breaking will take place at the end of the Long-term study unless the following circumstances arise:

i. A patient experiences an alarming or serious adverse event as defined in SmithKline Beecham Standard Operating Procedures or Regulatory Authority guidelines. The randomisation code will be broken by SmithKline Beecham for the purpose of reporting to the appropriate Regulatory Authorities.