

# IMMUNOLOGICAL INVESTIGATION IN MULTIPLE SCLEROSIS

Bernard Souberbielle

A Thesis Submitted for the Degree of PhD  
at the  
University of St Andrews



1993

Full metadata for this item is available in  
St Andrews Research Repository  
at:  
<http://research-repository.st-andrews.ac.uk/>

Please use this identifier to cite or link to this item:  
<http://hdl.handle.net/10023/13440>

This item is protected by original copyright

INVESTIGATIONS INTO THE COGNITIVE FUNCTIONING  
OF SUBJECTS WITH EPILEPSY  
IN RELATION TO ANTICONVULSANT MEDICATION.

AUTHOR : KAY GARVEY

SUPERVISOR : DR. RHONA JOHNSTON

Thesis submitted for the degree of PhD, University of  
St. Andrews, December, 1994



ProQuest Number: 10167419

All rights reserved

INFORMATION TO ALL USERS

The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript and there are missing pages, these will be noted. Also, if material had to be removed, a note will indicate the deletion.



ProQuest 10167419

Published by ProQuest LLC (2017). Copyright of the Dissertation is held by the Author.

All rights reserved.

This work is protected against unauthorized copying under Title 17, United States Code  
Microform Edition © ProQuest LLC.

ProQuest LLC.  
789 East Eisenhower Parkway  
P.O. Box 1346  
Ann Arbor, MI 48106 – 1346

TL

13678

Disclaimer

(a) I, Kathleen Ann Garvey, hereby certify that this thesis has been composed by myself, that it is a record of my own work, and that it has not been accepted in partial or complete fulfilment of any other degree or professional qualification

Signed

Date 13th December, 1995

(b) I was admitted to the Faculty of Science of the University of St. Andrews under the Ordinance General No. 12 on 1st October, 1985 and as a candidate for the degree of Ph.D. on 1st October, 1985.

Signed

Date 13th December, 1995

(c) In submitting this thesis to the University of St. Andrews, I understand that I am giving permission for it to be made available for the use in accordance with the regulations of the University Library for the time being in force, subject to any copyright vested in the work not being affected thereby. I also understand that the title and abstract will be published, and that a copy of the work may be made and supplied to any bona fide library or research worker.

### ACKNOWLEDGEMENTS

This research has been funded by Medical Research Council research studentship and I am grateful for that support.

The psychology department has provided me with facilities and expertise to carry out the research. In particular, Dr. Alan Milne (Medical Research Council scientific officer) and Mr. Jim Daley (computer technician) have given time and knowledge to help me develop computerised batteries of tests and Dr. Milne has been also been of invaluable assistance in guiding me in the use various statistical analyses of the data.

I would like to thank Dr. Richard Morris, my supervisor at the beginning of the research and a provider of much positive support through to thesis submission. I have also gained from discussions with Dr. Michael Rugg and guidance from Dr. Rhona Johnston, who stepped into the position of supervisor at the stage of writing-up and has, from my point of view, done a splendid job.

The clinical work conducted in the thesis could not have been completed without the on-going cooperation of Dr. Duncan Davidson and Dr. Richard Roberts at the Dundee Royal Infirmary and Dr. Martin Brodie at the Glasgow Western Infirmary and I am grateful for their support. I would also like to thank the those individuals who suffer from

epilepsy and the control subjects who agreed to give their time freely to participate in the studies. They made the most important contribution.

I obtained much personal as well as practical support from Dr Ian Davison and from members of my family. Their encouragement maintained my commitment, in moments of weakness, to submit the thesis.

## CONTENTS

<u>Chapter</u>		<u>Page</u>
	Abstract	1
One	Introduction	4
Two	Epilepsy, the disorder and its effects on cognitive functioning	11
Three	Anticonvulsant drugs : Actions, Side-effects and cognitive functioning	39
Four	Study one : Investigation of cognitive functioning of subjects with epilepsy on anticonvulsant medication	68
Five	Study one : Dundee study one : Results	95
Six	Cognitive Functioning : Theory and application	137
Seven	Study two : Measuring cognitive functioning using a new test battery	166
Eight	Study two : Glasgow study two : Results	195
Nine	A new drug : Lamotrogine	292
Ten	Exploratory studies using response-timed tasks	319
Eleven	Summary and discussion	331
	References	360
	Appendices	372

## ABSTRACT

The literature on epilepsy is vast. The first review in this thesis presented a short introduction to the nature of the disease and its relationship to cognitive functioning. The pharmacological treatment of epilepsy by three major anticonvulsant drugs (carbamazepine, sodium valproate and phenytoin) and the possibility of effects of this treatment on cognitive functioning is presented in the second review. This review identified certain areas of cognitive functioning, for example memory, that warrant further investigation. A third review discussed those relevant areas of cognitive functioning, including both theory and suitable methodologies for investigating working memory (Baddeley and Hitch 1974) and attentional resources (Normon and Bobrow 1975). The three review chapters provided theoretical and practical frameworks to carry out investigations of the effects of anticonvulsant medication on cognitive functioning.

Four experimental studies are presented. The design of the first study was a between-groups comparison, in which four groups of subjects with epilepsy (three on monotherapy and a polytherapy group) and a control group were compared on a battery of memory tests. The only significant group difference was the impaired performance of the polytherapy group compared to the control group.

The second study was a between-groups comparison of the performance of four groups with epilepsy (three on monotherapy and one untreated group) and one control

group, on a new battery of tests measuring working memory and attentional resources. The sodium valproate group was significantly impaired on two of the working memory tasks compared to the control group. No other group differences were found and increasing task complexity did not significantly affect the drug groups compared to the control group.

Of interest in both study one and two was the consistent pattern of results across the test batteries, which did not produce significant differences between the groups. Both studies revealed large variance in the clinical subject groups, such that a number of the subjects with epilepsy, particularly on sodium valproate and phenytoin were performing very poorly compared to control group performance. No obvious reasons were identified for the poor performance.

Study three investigated the effects on cognitive functioning of a new anticonvulsant drug (Lamotrogine). The clinical subject group was very impaired compared to a control group, and a small amount of further impairment was present after the subjects began taking Lamotrogine.

The fourth study piloted tests designed to measure aspects of perceptual and motor functioning. The only significant result obtained was that the polytherapy group performed significantly worse compared to the control and the monotherapy groups on simple reaction time tasks.

The focus of the discussion chapter was a summary of the important aspects of the studies in the thesis with

comparisons made to other studies in the published literature.

## CHAPTER ONE

### INTRODUCTION

#### 1.1 Aims of thesis

The primary aim of the thesis was to investigate the possibility of effects on cognition of anticonvulsant drugs (ACDs) as taken by individuals suffering from epilepsy (the clinical population under investigation). The drugs investigated included carbamazepine (CBZ), sodium valproate (VPA), phenytoin (DPH) and Lamotrogine. The subjects in the studies were individuals diagnosed with epilepsy and control subjects i.e. individuals not suffering from epilepsy. A second aim was to compare the performance of subjects with epilepsy to control subjects.

A further aim of the thesis was to develop a suitable battery of tests to measure cognitive functioning, based on robust theories of cognition.

#### 1.2 Aim of chapter

This chapter will endeavour to describe the format of the thesis in order that the reader can follow the lay-out and knows where different types of relevant information can be found. The chapter will not include literature reviews, but instead will describe the functions and content of each of the chapters contained in the thesis.

### 1.3 Contents of thesis

#### 1.31 Chapter two : Epilepsy, the disorder and its effects on cognitive functioning

Chapter two is one of three literature review chapters. Relevant information concerning the clinical manifestations of epilepsy and the classification of seizures is described in this chapter. The relationship between epilepsy and cognitive functioning is explored. Also included, is a summary of factors, relating to epilepsy, that may effect cognitive functioning.

#### 1.32 Chapter three : Anticonvulsant Drugs (ACDs) : actions, side-effects and cognitive functioning.

The main treatment of epilepsy, i.e. pharmacological treatment by the three main-line anticonvulsant drugs is described in this second review chapter. The literature exploring the possible effects of anticonvulsant medications on cognitive functioning is presented. From this literature, variables are identified that need to be monitored in this area of experimental work.

The literature in this chapter is divided into two parts. Firstly, the literature published before 1987 is described as this literature is used to inform both the hypotheses and methodology of the experimental work described in the body of the thesis. Literature published after the completion of the experimental work is then

presented, as this is used in the interpretation of results and discussion of findings.

1.33 Chapter four : Study One : Investigation of  
cognitive functioning of subjects with epilepsy on  
anticonvulsant medication

This chapter is one of two chapters presenting a study carried out at the Dundee Royal Infirmary. This study was designed on the basis of the information presented in chapters two and three, taking into account the practical constraints, for example, the limited number of subjects available.

The study was a between-groups design, comparing the four clinical groups on different anticonvulsant medication (CBZ, VPA, DPH or polytherapy) and one control group, on a battery of tests measuring, for the most part, memory function.

The study is presented in the thesis in two separate chapters. The introduction, the subjects included in the study and the methods employed, including the rationale for the test battery, are presented in this chapter.

1.34 : Chapter five : Study One : Results

The results from the analysis of the data from study one are presented in this chapter. The results include descriptive clinical data about subjects as well as the quantitative analysis of the performance data from the

battery of tests. The results are summarised at the end of the chapter, but discussion is left to chapter eleven.

(Note, the summaries of the tests are described on Card One to remind the reader of the test battery when reading this chapter.)

### 1.35 Chapter six : Cognitive functioning : theory and application

The theories of cognition and the experimental paradigms, that provide a useful framework for the design of tests for investigating the relationship between anticonvulsant drugs (ACDs) and cognitive functioning, are described in this third review chapter.

The concepts of memory and attention and the merits of the working memory model (Baddeley and Hitch, 1974) are discussed. The model is proposed as a suitable model for investigating the relationship between ACDs and cognitive functioning. The use of dual-tasks is also suggested, as these tasks allow the investigation of the effects of changes in task complexity on performance.

### 1.36 : Chapter seven : Study Two : Measuring cognitive functioning using a new battery of tests

A study carried out at the Glasgow Western Infirmary is described in this chapter. The the study was designed using the information presented in chapters two and three, and using the theoretical ideas presented in chapter six.

The study was primarily a between-groups design, in which four clinical subject groups (all clinical subjects had a diagnosis of epilepsy and were taking either CBZ, VPA, DPH or no ACD medication) and one control group completed a newly devised test battery. The repeated testing of some subjects allowed for two small within-group sets of comparisons of firstly, subjects, for whom medication had been changed and secondly, subjects who had recently suffered a seizure. The performance of subjects across test sessions was analysed to identify any practice effects on repeated testing.

The introduction, details of subject selection, rationale behind the test battery and the methods employed in administering the study are described in this chapter.

### 1.37 : Chapter eight : Study Two : Results

The results of the analysis of the data from study two are described in this chapter. The qualitative data pertaining to clinical characteristics are presented, as well as the quantitative analysis. The main findings of the study are summarised at the end of the chapter, but no in depth discussion is included (see chapter eleven).

(Note, the summaries of the tests are described on Card Two to remind the reader of the test battery when reading this chapter).

### 1.38 : Chapter nine: A new drug ; Lamotrogine

A study is presented comparing the performance of subjects suffering from epilepsy, before and after they commence on Lamotrogine, a new anticonvulsant drug. The study is a within-subject design with Lamotrogine being taken as an adjunct ACD. The complete study from introduction through to the summary of the main findings is described in the chapter, with further discussion in chapter eleven.

### 1.39 : Chapter ten : Further investigations using response time tasks

This study developed from the information contained in chapter three and the findings in study one, i.e as few differences were found between the subjects with epilepsy and control groups on the memory tasks, it may be possible that perceptual and motor aspects of tasks are sensitive to ACD medication. A between-groups design is used. Clinical and control subjects completed a battery of perceptual and motor tasks. The methodology and data analysis are described in this chapter.

1.39a : Chapter eleven : Discussion and Conclusions

The main findings of the four studies are presented in this chapter. Various aspects of the studies are discussed in greater detail. These aspects include those relating to the design of the studies, the role of clinical factors, the test batteries and analysis of the data.

CHAPTER TWO  
EPILEPSY, THE DISORDER AND ITS EFFECTS ON COGNITIVE  
FUNCTIONING.

2.1 Characteristics and classification  
of epileptic seizures

A good definition of epilepsy requires that the salient features of the disease should be identified and that the complexities of the disorder should not be disguised. After careful consideration of the scientific knowledge, Rodin (1987) defined epilepsy as :

"a disturbance of brain function characterized by excessive fluctuations in its electrochemical balance that express themselves at their height in spontaneously recurring seizures. The clinical manifestations of the seizure depend upon point of origin, extent, and speed of spread of the electrical discharges. The aetiology is unknown, but its appearance is facilitated by brain damage and/or hereditary factors."P.269

A great deal of information is conveyed in this definition. Firstly, epilepsy is a disease that has its origins in excessive or abnormal electrical activity in the brain. The physiological mechanisms active in the epileptogenic brain involve changes in membrane conductances and neurotransmitter function (Meldrum, 1988). These changes can result in neurons discharging too easily and/or failure in inhibition of neurotransmission.

The abnormal electrical activity can be measured by an electroencephalogram (EEG). Specific patterns of electrical activity, different to those of normal brain functioning, are characteristic of the brain of individuals suffering from epilepsy. Not all abnormal or excessive activity results in the occurrence of a seizure. The activity must reach a threshold and/or be of a certain type before clinical manifestations can be observed. Hence, there is the distinction of ictal and interictal activity, describing abnormal electrical activity occurring during seizures and between them.

Variations in the amount of electrical activity and the extent and parts of the brain affected produce a range of clinical manifestations. These may include obvious physical symptoms, for example shaking, and/or more psychological changes, for example loss of consciousness or changes in emotional state. The classification of seizures considers such aspects of the disorder. "The International classification of epileptic seizures" was adopted by the "International League Against Epilepsy" in 1981 and is a classification system in widespread use. The classification divides seizures into three major types :

1. Partial seizures or seizures beginning locally :

Sub-groups of this group are simple partial and complex partial (with complex partial seizures involving impairment of consciousness), and also partial seizures secondarily generalised.

2. Generalised seizures : bilateral symmetrical seizures or seizures without local onset.

Sub-groups include absences and tonic-clonic seizures.

3. Unclassified seizures : seizures for which insufficient information is available.

The clinical presentation of seizures is very varied. For instance, complex partial seizures are characterised by loss of awareness only or loss of awareness and automatisms. Automatisms are "more or less coordinated adapted involuntary motor activity" (Feldman, 1983) and can themselves be divided into five categories. The most common are alimentary automatisms, with swallowing, salivating, chewing and sucking being the most common (Escueta and Walsh, 1983). However, in addition there are mimetic automatisms which include facial expressions consistent with fear, bewilderment, discomfort, or even laughing. There are also gestural automatisms including the repetitive movements of hands and more rarely ambulatory automatisms which include running or walking. The seizure may last from 20 seconds to more than 60 seconds.

Gastaut and Broughton (1972) gave a detailed description of the tonic-clonic seizure, and their account is used as the basis for the following description. The tonic phase consists of contraction of muscles of the trunk, face and neck, forcing the body forward, the eyelids to draw open and the eyes to roll upwards. The jaw muscles also contract and the mouth becomes rigid and half open. Next there is involvement of the shoulder muscles, the shoulders rise, the arms become semi-elevated and outwardly rotated. The legs may show similar changes to a lesser extent.

The clonic phase then becomes one of extension rather than flexion; the neck and back arch and the mouth opens wide and then snaps shut. There may be a cry lasting between two and twelve seconds. The arms then cross in front of the chest but later become extended, wrists and fingers may also extend or the wrists extend and the fists clench. The legs may also show extension as do the feet and big toes. The tonic phase characteristically lasts from 25 to 30 seconds and the clonic phase from 45 to 50 seconds.

One of the difficulties in classifying seizures is the measurement of alterations in consciousness. In order to measure consciousness, the clinician often employs the concept of "responsiveness". However, "reponsiveness," is on many occasions, very variable. During an absence seizure individuals may vary from moment to moment in their ability

to respond to stimuli (Brown, Penry, Porter. and Dreifuss, 1974).

Another difficulty in classifying seizures is that of seizure progression. It is possible that there may be gradual increases in the severity of the manifest seizures, for example a simple partial seizure may lead on to a complex partial seizure, which may culminate in a secondarily generalised tonic-clonic seizure.

A further possible complication arises because the identification of seizure type is dependant on the history obtained from the patient and their family. Patients and their families may not know the terminology or descriptive words to describe the seizures and frequently resort to vague terms such as "mild", "large", "small", "funny turn" and "dizzy spell", both to describe the type of seizure and the severity of seizures.

In addition to the information provided by the patient and their family the Electroencephalogram (EEG) is also used to identify seizure type.

Epilepsy is a chronic disorder and attempts have been made to classify the epilepsies, including the 1989 Classification of Epileptic Syndromes. As well as information on seizure type, information on aetiology is extremely important in the diagnosis of the epileptic syndromes.

The aetiology of seizures is wide and in many cases unknown. In a case where there is no discernible cause, but

there may be a familial history of epilepsy, the epilepsy is commonly referred to as idiopathic epilepsy. When the cause is known the epilepsy is often referred to as symptomatic epilepsy. The range of causes of symptomatic epilepsy include infections, head injury, birth traumas, tumours, poisoning and metabolic disorders.

Other factors that are relevant in classifying the epilepsies include, anatomical substrate of the epilepsy, further aetiological information such as hereditary factors and cerebral injury/damage, the age of the individual at onset of seizures (from birth onwards) and information obtained from the EEG. Examples of epilepsy syndromes related to anatomical localizations are temporal lobe epilepsy, parietal lobe epilepsy and occipital lobe epilepsy.

Hence, the EEG is an important tool to aid in the identification of seizure type and the diagnosis of the epilepsies. Usually a combination of EEG techniques, including a waking and sleeping study and the use of hyperventilation and photic stimulation, are carried out on a routine EEG investigation. Other more specialised recordings are sometimes required, for example ambulatory recordings.

Adjunctive medical and biochemical investigations may be carried out, particularly if the probable aetiology is the result of infections, immune disorders etc.

Brain-imaging techniques are becoming increasingly available and are appropriate to establish the focal pathology when focal discharges are suspected. The most common tool available is computerised tomography (CT) which reveals variations in brain tissue density and areas of brain atrophy. Other techniques include magnetic imaging techniques (Magnetic Resonance Imaging, MRI) which provide a more accurate image of the brain structure being investigated, based on electrochemical characteristics of the brain. In addition, positron emission tomography (PET) can be used and works by revealing local metabolic activity, such that alterations of this activity can identify the epileptogenic focus.

The prevalence of epilepsy is usually found by determining the number of people who have suffered from recurrent seizures, and is normally quoted as being around one in two hundred in Western countries.

The frequency of various types of seizures has been studied epidemiologically in large in-patient and out-patient studies. A large study involving 4590 patients was carried out by Gastaut (1975) and revealed 38% of the sample suffered generalised seizures, 62% suffered partial seizures. It is worth noting that 40% of this sample suffered partial seizures originating from the temporal lobes i.e. more individuals suffered seizures originating from the temporal lobe than from generalised seizures.

Epilepsy is a chronic disorder and can have a great many medical and psychosocial implications. For some individuals (approximately 3% according to Pond and Burden, 1963) the implications are so severe that long-term care in hospitals or other institutions is required. The main reasons for this are severe mental and/or neurological handicap.

The description to this point has concentrated on the clinical manifestations and the clinical diagnostic criteria used to identify important seizure variables. The following sections explore the effects of epilepsy on the functioning of the brain.

## 2.2 The relationship between epilepsy, anatomical brain areas and cognitive functioning

To understand the nature of the possible relationships between epilepsy, the brain and cognitive functioning, it is necessary to have an understanding of the functional anatomy of the brain, particularly in relation to cognitive functioning. The following information on brain anatomy and functioning is from Walsh (1987).

The brain has three main divisions; the cerebral hemispheres, the brain stem and the cerebellum. The two cerebral hemispheres are the primary areas involved in cognitive functioning. The hemispheres are made up of the cerebral cortex, the internal white matter (connecting cell fibres) and a number of neuronal masses, including the

basal ganglia. The hemispheres are connected chiefly by the corpus callosum, and also by the anterior and hippocampal commissures.

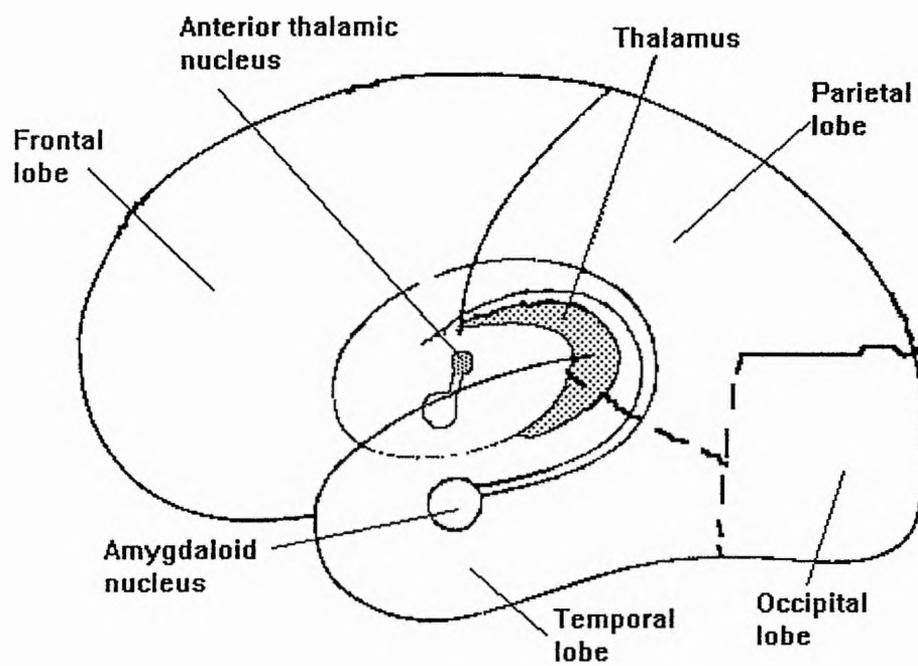
There is considerable evidence on the asymmetries of functioning of the two hemispheres, with the two hemispheres now thought to act in a complimentary way (Levy, 1974). For instance, the left hemisphere can encode information linguistically, whereas the right hemisphere can encode information in terms of images.

The cortex of each hemisphere is divided into four lobes; frontal, temporal, parietal and occipital lobes.

#### 2.21 Frontal Lobes

The frontal lobes are sub-divided into four major divisions; (i) the motor area, (ii) the premotor area, (iii) the prefrontal area and (iv) the basomedial portion. The frontal lobe has well-developed efferent nerve cells leading to such areas as the dorsomedial nuclei of the thalamus as well as to the other three lobes.

The role of the frontal lobes in cognitive functioning is complex. Furster (1980) suggested that the frontal lobes act to unify information in order that the individual can have a purpose or goal. Hence, the frontal lobes enable the individual to deal with complexity of information, novelty of information, information gathered over time, and executes plans based on this information. The frontal lobes are sometimes described as having "executive functions".



**Figure 2a : Medial view of the right hemisphere**

### 2.22 Parietal lobes

The parietal lobes are to be found between the other three lobes (see fig 2.2a) and are closely connected in function to them. One of the primary functions of the parietal lobes is to receive somatic information, including touch, pain and body position.

### 2.23 Occipital lobes

The occipital lobes make up the most posterior portions of the cerebral hemispheres. They receive visual information and with connections to the temporal lobes, the occipital lobes are involved in visual memory.

### 2.24 Temporal lobes

The temporal lobes lie behind the frontal lobes, below the parietal lobes and in front of the occipital lobes. Their functioning is very complex and is related to the senses, in uniting information from sensory input to form a coherent perception of the world. In addition the temporal lobes play important roles in memory and providing a record of conscious experience.

The temporal lobes have close connections with the limbic system, through which they interact to form the emotional and motivational experience of the organism.

The limbic system refers to a complex system of structures including the limbic lobe, and a number of

subcortical nuclei including the thalamic, hypothalamic, septal and amygdaloid nuclei, in close association to the mid-brain reticular formation.

The reticular formation is a core of nerve cell found in the pons, a part of the brain-stem. The reticular formation is concerned with the alertness of the organism.

-----  
Table 2a : The association and projection fibres of the  
brain

Fibres	Areas connected by fibres
<u>Association Fibres :</u>	
Superior longitudinal fasciculus	Frontal to occipital lobes
Inferior longitudinal fasciculus	Middle frontal gyri to temporal lobes
Urcinate fasciculus	Anterior and inferior parts of the frontal lobes with parts of the temporal lobes
Cingulum	Frontal and parietal lobes to parahippocampal and adjacent temporal lobe
<u>Projection Fibres :</u>	
Efferent Corona radiata	Cortex to brain-stem
Afferent fibres	Thalamus to cortex

-----

### 2.25 Connections in the brain

The white matter of the two hemispheres is made up of millions of axons of nerve cells. These nerve cells connect the various regions of the brain, including the four lobes and the two hemispheres. These connections play a major role in the spread of seizures, as will be described in the next section (section 2.3).

The major connections between the two hemispheres are the corpus callosum and the commissural fibres. The association fibres connect the various parts within each hemisphere and the projection fibres connect the cortex to the deeper structures of the brain. Table 2a identifies several of the important neural pathways and shows the areas connected by these pathways.

The thalamus is a mass of grey matter found on either side of the mid-line at the rostral end of the brain-stem. It is divided into a number of nuclei that send fibres to the cortex. It plays a major role in projecting sensory information to the cortex. It also affects electrical activity in the cortex and provides relays such that the cerebellum and basal ganglia can relay information to the motor cortex.

### 2.3 Epileptic seizures : anatomical brain areas and connecting pathways

The details of the anatomical parts of the brain and the processes involved in epileptic seizures is an area of on-going research. The advancement of imaging techniques and the increasing knowledge of the synaptic systems in the brain has yielded significant information. Meldrum (1988) reviewed this information and discussed the anatomical basis for a number of seizure types.

Meldrum's discussion of partial seizures included both focal motor seizures and those seizures involving the limbic system. The anatomy of focal motor seizures takes two forms; either involving cortical regions and transcallosal pathways resulting in interhemispheric spread, or the other common pathway via the brain-stem nuclei, i.e the thalamus and basal ganglia.

Seizures involving the limbic system are most commonly initiated simultaneously in the hippocampus and amygdala, and to a lesser degree purely in the hippocampus or amygdala. Excitability in the limbic system is also influenced by output from the basal ganglia.

The secondary generalisation of complex partial seizures is thought to follow one of three paths; a) by callosal spread, or b) via the thalamus or c) by the mid-brain reticular formation.

Meldrum reports that there are less available data on the neuroanatomy of generalised seizures, but does state that there is evidence for the involvement of the thalamic nuclei in generalised epilepsy. Thus, generalised epilepsy is viewed as being the response of hyper-excitabile cortical neurons to thalamocortical discharges.

Meldrum summarises the key brain areas involved in seizure transmission as follows :

1. The basal ganglia (includes the relays in the habenula, thalamus and medial septum) are an important relay system for focal and generalised seizures with motor manifestations, and also influence seizures originating from the limbic system.

2. The relays involved in cortical discharge are the striatum, the globus pallidus, the substantia nigra, the mesencephalic locomotor region, further reticular relays and the spinal cord.

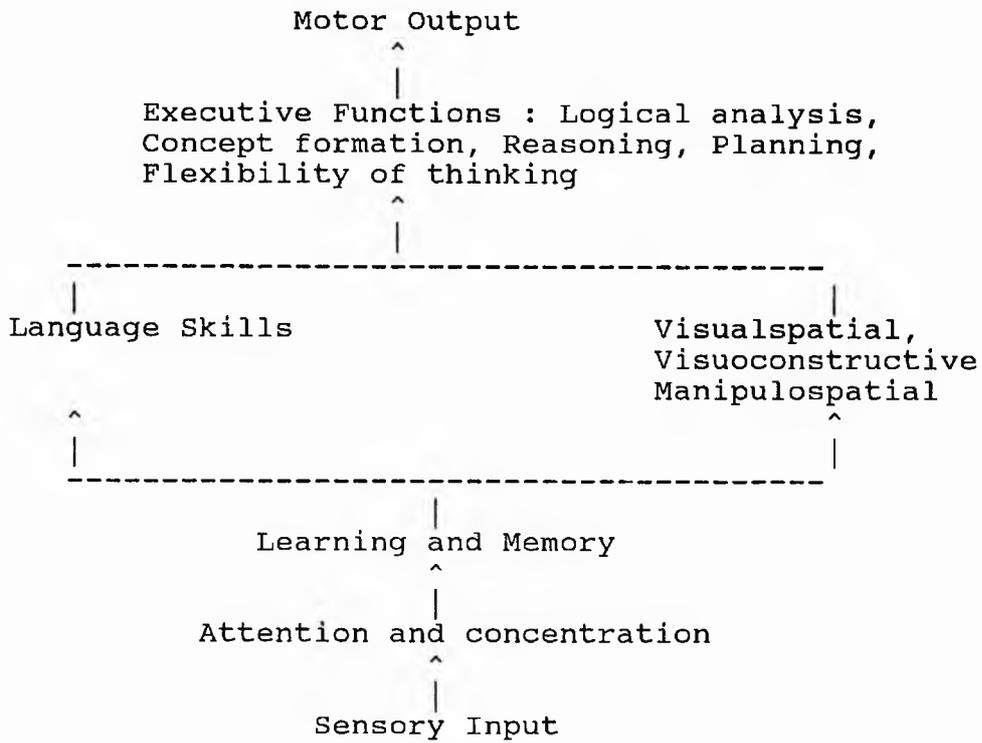


Fig 2b Conceptual model of the behavioural correlates of brain functioning (from Bennett 1988b)

#### 2.4 Epileptic seizures and cognitive processes.

The involvement of different parts of the brain in both seizure spread and a range of cognitive functions, leads to the question to what degree do epileptic seizures affect and/or impair these functions?

Bennett (1992) reviewed the effects of different types of epilepsy on specific areas of cognitive functioning. The review contained a wealth of information some of which is presented in this section. However, the review did not make clear whether the author was discussing the effects on cognitive functioning during seizures or the effects on cognitive functioning because the individual suffered from particular types of seizures. Hence, this review will endeavour to differentiate between these two factors.

To carry out the review, Bennett adopted a model of cognitive functioning devised by Reiton and Wolfson (1985). The model contains many of the areas of cognitive function commonly identified by cognitive psychologists and neuropsychologists. It is a process model (as opposed to a anatomical model) and contains the areas of sensory input, attention, memory, language skills, spatial skills, executive functions and motor output (See figure 2b for further details). It presumes that information enters at the sensory input stage, moves through the various stages and appropriate information exits at the motor-output stage.

Bennett brings together evidence that epileptic seizures and epileptic activity effects these areas of cognitive functioning. A small amount of this evidence will be presented here.

#### 2.41 Sensory Input

In absence seizures, which last between five and fifteen seconds and occur particularly in children, sensory information is often neither attended to nor registered during the time the seizure lasts.

#### 2.42 Attention and Concentration

Loss of awareness is a central characteristic of many seizure types including complex partial seizures. In addition, it has been found that individuals with epilepsy may suffer impairments in attention and concentration at times other than when experiencing seizures. The types of impairments observed appear related to seizure type. Generalised seizures give rise to more impairments of sustained attention compared to focal seizures (for example, Lansdell and Mirsky, 1964). Focal seizures are more likely to lead to difficulties in selective attention (for example, Stores, 1973).

#### 2.43 Learning and Memory

Memory deficits have been associated with specific seizure disorders, even when subjects have not suffered

overt seizures at the time of testing. Delaney, Rosen, Mattson and Novelly (1980) compared groups of subjects with epilepsy originating in either the right and left temporal lobe, with subjects who had unilateral frontal lobe epileptic foci and a normal control group. The study revealed significant impairments of verbal memory in the left-sided group, significant impairments of non-verbal visual memory in the right-sided group, and no differences between the normal control group and the frontal lobe group.

#### 2.44 Language Skills

Once again individuals who had suffered from complex partial seizures, particularly those with a temporal lobe focus have displayed impairments in language skills. In a study by Mayeux, Brandt, Rosen and Benson (1980) language deficits (especially dysnomia) were prominent in those patients with a left temporal focus.

#### 2.25 Visuo-spatial skills

A number of studies have shown that subjects with right temporal lobe epilepsy show visuo-spatial impairments; for example, Helmstaeder, Pohl, Hufnagel and Elgar (1991) compared subjects with left and right temporal lobe epilepsy and a control group and found that the subjects with right temporal lobe epilepsy were more

impaired on tests of visual construction making more visuo-spatial errors than the other two groups.

Andrewes, Puce and Bladin (1991) measured the post-ictal performance i.e. up to one hour post seizure, of eight subjects with temporal lobe epilepsy, on verbal and visuo-spatial recognition tests. The right temporal lobe epilepsy subjects showed deficits in the visuo-spatial recognition tasks whereas the left temporal lobe subjects were impaired on the verbal tasks.

#### 2.26 Executive Functions

It is very likely that a person with impairments in some of the areas already discussed will have impairments in executive functioning, as the many basic functions have to be intact in order for the executive functions to operate. However, there are a number of tests designed to measure specific executive functions, for example tests measuring planning and sequential thinking.

Hermann, Wyler, and Richey (1988) found that patients with complex partial seizures were impaired on the Wincosin Card-Sorting Test (a test of frontal lobe functioning). The view put forward was that epileptic activity from the temporal lobes was being transmitted to the frontal lobes and that this activity was causing the impairment. It was not clear whether this impairment was the result of the on-going epileptic activity or the result of permanent damage caused by the epilepsy.

### 2.27 Motor-Output

Slow reaction times and psychomotor speed are not uncommon in individuals with epilepsy (for example Brodie, McPhail, Macphee, Larkin and Gray, 1987) even when not suffering from overt seizures.

In summary, Bennett identified a number of areas of cognition in which there is a considerable amount of evidence that specific types of epileptic seizure may have detrimental effects on specific areas of cognitive functioning.

### 2.5 Interseizure activity and cognitive functioning

The discussion of epilepsy and cognitive functioning has concentrated on the effects of overt seizures on cognitive functioning and the long term effects of different types of seizure on cognitive functioning. However, there is a large amount of abnormal brain activity that does not result in overt seizures. Does this activity affect cognitive functioning and could this activity be part of the explanation as to why cognitive failures are seen, at times when there are no overt seizures?

To address this issue, one must first monitor the abnormal electrical activity. Two main classes of electrical activity can be recorded from electrodes, placed on the scalp. These are the on-going electrical potentials

as recorded by the electroencephalograph (EEG), and the event-related potentials (ERPs) which as their name implies are coupled to specific sensory, motor or cognitive events. The monitoring of these two types of activity gives rise to particular patterns of computerised and/or graphical recordings and this information that can be helpful in interpreting brain activity.

What are the effects of abnormal epileptiform activity as recorded by the EEG, on sensory and cognitive test performance? A number of researchers, including early studies by Tizard and Margerison (1963a) and Mirsky and Van Buren (1965) have identified various tests as being sensitive to epileptiform activity. These included choice reaction time tasks, signal detection speed tasks, and short term memory tasks. There are problems with much of the early research. Firstly, few studies documented the overt behaviour of their subjects, and this behaviour may have affected the EEG patterns obtained; and secondly, some of the subjects may have been suffering absence seizures at the time of testing, so it may not have been interseizure activity which impaired the cognitive performance.

Aarts, Binnie, Smit, and Wilkins (1984) carried out a study in which subjects were continuously monitored by video-recorder, in order to identify behavioural activities and overt seizures, and thus were able to discard data of subjects having overt seizures.

Aarts and his colleagues developed a method for measuring "Transitory cognitive impairment" (TCI) using visual and verbal short term memory tests. The subjects were connected to an EEG and the activity obtained was categorised as either epileptiform activity or non-epileptiform activity. The number of correct responses on the memory tasks was recorded for both categories of EEG activity. The most interesting finding was that the epileptiform discharges that were most disruptive to performance i.e causing "TCI", were those occurring during stimulus presentation. At such times, the number of errors was significantly greater than baseline levels. There were negligible differences between the error rates when discharges occurred as subjects were responding to stimuli. Also right-sided epileptiform activity had greater impairment on the visual test, whereas left-sided activity produced more errors on the verbal test.

#### 2.6 The effects of cognitive functioning on the epileptic brain

One aspect not considered by Aarts et al (1984) was that performing the tests themselves might influence epileptiform activity. Wilkins (1986) speculated that just as visual stimulation in photosensitive epilepsy may induce epileptiform activity, perhaps under certain circumstances cognitive activity could also induce epileptiform activity. Indeed, in an earlier publication, Wilkins (1981) described

a patient whose generalised seizures were reliably precipitated by him completing mental arithmetic. Electroencephalographic monitoring revealed that there were significant increases in paroxysmal activity on completion of a variety of spatial and arithmetical tasks.

Fenwick (1981) suggested a class of seizures that could be triggered by the action of the mind which he called "psychogenic seizures". In a more recent publication, Fenwick (1992) describes a study at the Maudesley Hospital in which 25 out of 76 patients were able to generate their own seizures at will, and also cites a number of case studies in which cognitive activity by individuals reliably triggered epileptic seizures.

### 2.7 Temporal factors associated with epilepsy in relation to cognitive functioning.

Many of the studies on epilepsy and cognitive functioning have concentrated on individuals with severe conditions and epilepsy that is difficult to manage. There appear to be a number of factors (including seizure type as discussed earlier) relating to the epileptic condition that increase the probability of cognitive impairment.

Dodrill (1992) reviewed a number of epilepsy variables that relate to cognitive functioning. The first factor that he identified was age of onset, with the general finding that the later the onset of the disease, the better outcome for cognitive functioning. Likewise, Dikmen and Matthews

(1977) and O'Leary, Lovell, Sackellares, Berent, Giordani, Seidenberg and Boll (1983) have shown that age of onset of the disease is an important variable, regardless of type of epilepsy, whereby early onset of the disease gives rise to poorer performance on a variety of tests of intelligence and other adaptive abilities.

Factors related to age of onset are the duration of the disease and the cumulative effects of recurrent seizures. Although a small number of seizures did not, normally, result in any mental deterioration, the effect of more than a hundred seizures or the effect of prolonged seizure activity (as in status epilepticus), gave rise to impaired intellectual, emotional and psychosocial functioning (Dodrill, 1986).

Dodrill (1992) also cited the number of medications taken by the individual as relevant to mental abilities, which is presumed by Dodrill to be a measure of the severity of the disease.

Smith, Craft, Collins, Mattson and Cramer (1986) have shown that individuals with generalised tonic-clonic seizures tend to have slightly poorer mental abilities than those with partial seizures only. Individuals suffering from more than one seizure type have also been shown to have slightly lower abilities when compared to individuals suffering from only one seizure type (Seidenberg, Beck and Geisser, 1986).

One of the most interesting points raised in the Dodrill (1992) article is the importance of aetiology of epilepsy as a factor related to cognitive functioning. Dodrill argues that with the availability of the new imaging techniques many smaller lesions are being found in individuals with few if any detectable cognitive impairments. However, for many individuals in which brain-damage is identified or for whom the onset of epilepsy is post-traumatic, the evidence supports, not surprisingly, that these individuals are very likely to show cognitive impairments (for example, Fowler, Richards, Berent and Boll, 1987). In such cases, it would seem very difficult to identify those cognitive impairments caused by epilepsy from those caused by the brain-damage that precipitated the onset of the epilepsy.

Thus, duration of the disease, age of onset, frequency of seizures, types of seizures and aetiology of the disorder are all factors deserving scrutiny when choosing subject samples and analysing data relating to possible cognitive impairments of subjects with epilepsy. These factors will require monitoring, particularly in all between-subjects design to ensure matched subject groups.

In summary, factors relating to the epileptic condition that may affect cognitive performance include :

1. Presence and extent of cerebral damage.
2. Age of onset of the disease.
3. Duration of the disease.

4. Frequency of seizures.
5. Type of seizures.
6. Amount of interseizure activity.
7. Timing of cognitive assessment post seizures.

Treatment may also affect the cognitive functioning of individuals with epilepsy. The possible effects of treatment, particularly in relation to anticonvulsant medication is the focus of the next chapter.

CHAPTER THREE  
ANTICONVULSANT DRUGS : ACTIONS, SIDE-EFFECTS AND  
COGNITIVE FUNCTIONING.

3.1 Actions and side-effects of ACDs

Once epilepsy has been diagnosed, the major means of treatment is via one or more anticonvulsant drugs (ACDs), including, carbamazepine (CBZ), sodium valproate (VPA) and phenytoin (DPH), or less commonly, one of the barbiturates. Most patients (approximately 80%) are rendered seizure free using ACDs. However, for a sizeable minority (approximately 20%) the seizures remain uncontrolled. When there is incomplete control, the clinician may wish to alter drug dosage and/or change the ACD prescribed. The clinician often has to decide whether to add another ACD or to substitute a different ACD to the original. The available evidence supports the view that substitution is more beneficial than adding further drugs (Schmidt, 1982a). However, the procedure for substitution is more complex and the clinician may view the procedure as risky in terms of increased frequency of seizures, if only in the short-term. Hence, a significant number of patients with uncontrollable seizures will be taking two or more ACDs. Of course, it may be that even with careful substitution, a clinician may have to resort to polytherapy to achieve maximum control.

Each particular drug has desired effects (efficacy) and unwanted actions (toxicity). In relation to efficacy it

is generally found that drugs effective against tonic-clonic seizures are also active against partial seizures. A number of studies have been carried out to compare the efficacy of individual ACDs. Mattson, Cramer, and Collins (1985) found that CBZ and DPH were more effective than phenobarbitone, whilst primidone was the least effective of the four drugs. Unfortunately, VPA was not included in this study. Studies that have included VPA, for example Turnbull, Hawel, Rawlins and Chadwick (1985) and Callaghan, Kenny, O'Neil, Crowley and Goggin (1985), showed that VPA was as effective as CBZ and DPH. However, prescribing practice for partial and generalised seizures in adults may favour CBZ and DPH before VPA (Eadie and Tyrer, 1989). Further details about these three drugs, including information on biochemical structure and pharmacokinetics, can be found in appendix 1.

<u>Table 3a Main anticonvulsant drugs</u>		
<u>Drug</u>	<u>1) Dose range (mg)</u> <u>2) Optimum blood serum concentration (mg/ml)</u>	<u>Adverse effects</u>
CBZ	1. 300-1600 2. 6-12	Drowsiness, dizziness, rashes, visual disturbances, leucopenia
DPH	1. 150-600 2. 10-20	Drowsiness, ataxia, hirsutism, gum hypertrophy, acne, facial coarsening
VPA	1. 400-2600 2. 50-100	Nausea, weight gain, tremor, alopecia, bleeding tendency

The aim for the clinician is to maximise efficacy and to minimise toxicity. The choice of which particular drug, the dosage of the drug and the drug regime are dependent on several factors summarised in table 3a (from Davidson, 1983). A number of points in table 3a need to be elaborated:

1. The three major ACDs prescribed by most physicians are carbamazepine (CBZ), phenytoin (DPH), and sodium valproate (VPA) which has led most of the studies in the recent literature on cognitive performance and ACDs being concerned with these three drugs.

2. It is important to note that the half-life of a particular drug is very variable across individuals, and this is an important reason for measuring blood serum level concentrations. The other reason is to monitor drug compliance. If a subject has not been taking their prescribed medication, blood serum concentration will be negligible. However, the value in measuring blood serum concentrations in terms of useful information obtained does vary across the three drugs. Serum monitoring is generally viewed to be of significant value for DPH, to be useful for CBZ, but the benefit of VPA monitoring is less clear and may be of little value (Rimner and Richens, 1988).

3. The information given in table 3a is valid for single drug regimes (monotherapy). If more than one drug is taken (polytherapy), drug-drug interactions are common, whereby the absorption, metabolism, or excretion of any

particular drug may be altered. This in turn may modify the therapeutic effects of any one drug. However, most recent research has concentrated primarily on individuals on monotherapy. The main aim of the studies in this thesis is to investigate the effects of ACDs (taken in concentrations falling within the "therapeutic range") on cognitive functioning. Hence, the subjects will, for the most part, be on monotherapy.

4. A number of possible side-effects for each of the ACDs are summarised in table 3a. Although, the focus of this thesis is to explore cognitive effects associated with ACDs, the prescribing clinician must take into account the physical side-effects. Hence, any effects on intellectual performance will be only one of the factors influencing prescribing practice.

-----  
 Table 3b : A summary of the research investigating the  
cognitive and behavioural side-effects of ACDs.

Drug	Author(s)	Study : Subjects and main findings
-----		
DPH		<u>Volunteers :</u>
	Booker et al (1967)	: No significant effects;
	Idestrom et al (1972)	: Poor concentration
	Harward et al (1970 and 1973)	: Modest improvements in performance.
	Stephens et al (1974)	: Improvements in performance
	Smith and Lovey (1972 and 1975)	: Impairments in memory and processing
	Thompson and Trimble (1981)	: Impairments in motor, memory and processing
		<u>Clinical subjects :</u>
	Dodrill et al (1977)	: Poor performance (compared to CBZ)
	Thompson and Trimble (1982 and 1983)	: Impairments in motor, memory and processing.
	Andrewes et al, (1984 and 1985)	: Impairments in memory and concentration compared to CBZ
	Gay et al (1985)	: Low rates of responding in learning tasks (Subjects were mentally-handicapped).
-----		
CBZ		<u>Volunteers :</u>
	Meinardi, (1972)	: Trends towards difficulties in talking
	Thompson and Trimble (1981)	: Impairments in motor tasks
		<u>Clinical subjects :</u>
	Puente (1976)	: Improvements in performance
	Schain (1977)	: Improvements in performance
	Dodrill et al (1977)	: Marginal effects
	Thompson and Trimble (1982 and 1983)	: Impairments on motor tasks
	Andrewes et al (1984 and 1986)	: Better performance in memory and concentration compared to DPH
	Brodie et al, (1987)	: Impaired psychomotor performance
-----		
VPA		<u>Volunteers :</u>
	Boxer, (1976)	: Hypnotic effects
	Thompson and Trimble (1981)	: No effects
		<u>Clinical subjects</u>
	Sonnen, (1975)	: No effects
	Sommerbeck et al (1977)	: Impairments in cognitive, motor and perceptual tasks
	Thompson and Trimble (1982 and 1983)	: Impairments in speed of mental processing.
	Gay et al, (1985)	: No effects on mentally handicapped subjects.
-----		

### 3.2 Review : ACDs and cognitive functioning.

Lee (1984) reviewed the research literature on the adverse effects of ACDs on cognitive functioning. A summary of his review (to 1981) and more recent studies (to 1987) are presented in table 3b. The table shows the studies investigating the effects of the three major drugs, CBZ, VPA and DPH. The table includes types of subject sample, i.e. volunteers or clinical populations, and the main findings of the study in relation to cognitive functioning.

The studies vary widely in type of subject and type of tests employed. The type of subjects range from normal volunteers, often undergraduate students, for example, Thompson and Trimble, (1981), to mentally-handicapped individuals suffering from epilepsy (Gay, 1985). Studies have used both adults and children, with different severities of epilepsy. Also some studies have chosen subjects recently diagnosed with epilepsy (new referrals), for example, Andrewes, Tomlinson, Elwes and Reynolds (1984), whereas others have used people suffering from chronic intractable epilepsy, for example, Brodie, Mcphail, Macphee, Larkin and Gray (1987).

The range of tests has included standard Intelligence tests such as the Weschler Adult Intelligence Scale (WAIS), and standard neuropsychological batteries of tests, with both of these batteries being employed by Dodrill and Troupin (1977). More vague tests including, measuring "hypnotic" effects (Boxer, 1976) and subjective reports of

"difficulties in talking " (Meinardi, 1972), have also been used to investigate the effects of ACDs. More recently, tests of psychomotor ability have been included in batteries of tests (Brodie et al, 1987). Thus, a wide range of measures have been employed and their validity and relationship to cognitive functioning often appears somewhat tenuous. Furthermore, the terminology to describing the effects is also vague, for example "processing"; this makes it difficult to interpret the different findings.

The results reported have varied from modest improvements in performance for example, Stephens, Shaffer and Brown (1974), to none or only marginal effects, for example Dodrill and Troupin (1977), to a range of impairments, for example Thompson and Trimble (1983). Such a wide range of types of subjects, tests and results in the literature, makes it very difficult to summarise the effects of the drugs on cognitive functioning. Nevertheless, leaving the relative merits of each of the studies aside, a simple "head-count" across the studies reveals more studies reporting impairments with DPH and VPA than with CBZ.

The next section will endeavour to discuss the most pertinent methodological issues in relation to studies of ACDs and cognitive functioning and to describe in more detail the more methodologically rigorous studies.

### 3.3 Methodological issues relevant to investigations.

Gram (1982) published an extensive review of controlled trials in the epilepsy literature (including those investigating cognitive functioning) and identified several important features whilst assessing the studies. Gram stated that a controlled trial is one using a within-group design, in a double-blind, placebo-controlled fashion, and is statistically evaluated. Of course, the main advantage of such a design is that many pertinent variables such as I.Q., age and type of seizures are held constant as subjects act as their own controls on these variables.

One important factor stressed by Gram, is that many of the early studies used fixed-schedule doses of drugs in their studies, for example Booker, Matthews and Slaby (1967). As discussed in the previous section, blood plasma serum levels should be used, wherever possible, because of the variable half-life of ACDs.

However, it is not always possible to meet these stringent demands using a clinical population. As Stores, (1978a), pointed out :

" The review that follows does not consist therefore exclusively of findings from well-controlled studies - it would be a very short review indeed if that were so."(p278).

Between-groups design are less powerful because there are problems associated with the heterogeneity of the groups of subjects and difficulties associated with matching groups of subjects. If groups are not adequately matched, it is possible to make two types of error, a "type 1" error - whereby spurious results are obtained due to factors other than the ACD medication effects; or a "type 2" error - whereby important effects are not discovered due to the large variability within the groups.

Although the preferable design, there are difficulties with the cross-over, within-subject design. Gram pointed out that a cross-over design has often been employed without the inclusion of a wash-out period. The duration of the wash-out period should be in proportion to the half-life for the drug under investigation, to avoid any carry-over effects of the drug. It may be preferable to include a wash-out period for research purposes, however, in clinical populations this would result in patients not receiving appropriate ACD medication for periods of time, which may be unacceptable to clinician and patients. It may be more feasible to use wash-out periods with volunteer subjects,

who do not suffer from epilepsy. Alternatively, it may be possible to use a wash-out period for subjects with epilepsy, for whom appropriate ACD medication has not been identified. However, the reasons for individuals changing medication can vary and it is possible that subject bias could be introduced to the design; this bias being dependent on the reasons for the change of medication.

-----  
 Table 3c : Summary of the studies investigating cognitive  
 side-effects of ACD medication  
 -----

Study (Subjects)	Drug	Impairment
Dodrill and Troupin (1977)	DPH vs CBZ	DPH : concentration and and problem solving
Thompson and Trimble (1981,82,83) (Chronic epilepsy and volunteers)	PolyT & DPH  VPA  Clobazam  CBZ	Memory, mental and motor speed and processing.  Mental speed and processing  Mental speed and processing  Motor speed
Andrewes et al, (1984 and 86) (New referrals)	DPH vs CBZ	DPH : Memory and concentration
MacPhee et al (1986) and Brodie et al, (1987) (Volunteers & chronic epilepsy)	DPH CBZ VPA	Psychomotor slowing Psychomotor slowing Psychomotor slowing

-----  
 Key : polyT : Polytherapy i.e subjects on more than one ACD  
 -----

### 3.4 Methodological detail of investigations

A small number of studies employing objective measures of cognitive functioning, monitoring serum-concentrations of ACDs and analysing data statistically are summarised in the table 3c.

At first glance, the table reveals the effects of the ACDs as very wide ranging. The list of impairments include attentional, cognitive, perceptual and motor. However, a more detailed analysis of each study is required to allow one to ascertain exactly what each research team meant by the psychological terms employed. Also, whereas the Thompson and Trimble found few impairments associated with CBZ, Brodie et al (1987) found significant motor slowing in subjects on CBZ. To explore these differences and to assess the severity of the impairments for a particular subject or group of subjects, the studies will be described in more detail.

Dodrill and Troupin (1977) devised a neuropsychological battery of tests that included the WAIS, parts of the Halstead neuropsychological battery and other neuropsychological tests of memory, attention and language function. This battery was administered to a group of subjects with chronic epilepsy using a double-blind cross-over design comparing CBZ and DPH. No significant findings were obtained using the WAIS or the Halstead neuropsychological tests. However, a number of significant

differences were obtained on some of the other measures, for example the Stroop test, and were always in favour of CBZ. This study raises the obvious question of which tests should be used to measure ACD effects. Standardised tests of intelligence will reflect, in part, years of learning and are thus unlikely to be sensitive to the more recent effects of ACDs. Neuropsychological batteries of tests have been developed on quite severely impaired populations, for example the head-injured population and, thus, may not be sensitive to less severe impairments.

Thompson and Trimble endeavoured to identify tests that would be sensitive to quite subtle changes in cognitive abilities. They pointed out that clinical impressions and subjective accounts by patients with epilepsy suggested that problems arose in the areas of memory, mental speed and concentration. Thompson and Trimble devised a battery of tests to look at the effects of ACDs on these aspects of cognitive function. They administered this battery to normal volunteers taking ACDs for short periods of time as well as subjects with chronic epilepsy. Their studies included comparisons of individual drugs to placebo, reductions in polytherapy, substitution of one ACD to CBZ, and reductions of serum level concentrations of ACDs.

Their first study, using eight normal volunteers, will be described in more detail to provide an impression of the type of study carried out by Thompson and Trimble. Subjects

were given placebo or DPH (3 x 200mg tablets daily), for a two week period, after which they were given the reverse tablet i.e. DPH or placebo for a further two weeks. Hence, the study was a double-blind, cross-over design.

Testing was carried out on three occasions :-

1. Baseline measurements, prior to drug or placebo administration.
2. At the end of the first treatment session i.e. after two weeks.
3. At the end of the second treatment session i.e. after four weeks.

Blood samples were taken at the end of the second and third treatment sessions so that ACD serum levels at the time of testing could be measured.

The battery of tests was made up of the following psychological measures :-

1. Memory tests involving immediate and delayed recall of 120 slides and 120 words, followed by a Yes-No recognition test of the slides and words.
2. The Stroop test, a test of concentration, involving a timed naming task using cards on which the words red, green or blue were printed in ink of conflicting colour.
3. A perceptual speed task, in which the time taken to recognise visual stimuli, presented via a 2-channel projection tachistoscope was measured.

4. Decision-making tasks, in which the subjects were asked to make fast responses to questions concerning the colour or the category of living/non-living, of objects presented on slides.
5. A perceptuo-motor task i.e. measurement of simple reaction time.
6. Motor task, in which the subjects were asked to do a tapping task.
7. Subjective feelings were measured using Lishman's (1972) adaptation of McNair and Lorr's (1964) mood adjective Check-list (MACL), which gave ratings for depression, anxiety, fatigue, and aggression.

Table 3d : Summary of results obtained from  
Thompson and Trimble studies

Tests	Subjects (volunteers or epileptic subjects)	1) Volunteers : DPH vs placebo	2) Epileptic : ACD to CBZ	3) Epileptic Reducing ACD
-----				
Memory : pictures				
Immediate Recall		NS	P < 0.05	NS
Delayed Recall		P < 0.05	P < 0.05	P < 0.05
Recognition		NS	NS	NS
-----				
Memory : words				
Immediate Recall		P < 0.05	P < 0.01	NS
Delayed Recall		NS	P < 0.001	NS
Recognition		NS	NS	NS
-----				
Concentration				
Stroop : time		NS	NS	NS
errors		P < 0.05	NS	NS
-----				
Visual scanning				
task : speed	/		P < 0.01	P < 0.05
with Auditory task				
: speed	/		P < 0.01	P < 0.05
Total No. errors	/		NS	P < 0.05
Total No. scanned	/		P < 0.001	P < 0.05
-----				
Mental speed :				
Perceptual speed				
: words		NS	P < 0.05	P < 0.001
: pictures		NS	P < 0.05	NS
-----				
Decision-making				
task : Colour		P < 0.01	P < 0.01	P < 0.01
: category		P < 0.025	P < 0.01	P < 0.05
Visuo-motor resp.		NS	/	NS
-----				
Motor Speed				
dominant hand		P < 0.05	P < 0.01	P < 0.01
non-dominant		NS	P < 0.01	P < 0.001
both hands :		NS	P < 0.001	P < 0.001
-----				

In later studies, a visual scanning task was also included in the battery.

The scoring procedure involved subtracting the pre-treatment scores from those obtained in the drug and placebo sessions. With the exception of the MACL scores, three-way ANOVA was computed on the difference scores for each test, using the following three factors :-

1. Treatment effects.
2. Session effects.
3. Individual differences.

The MACL data was analysed using non-parametric statistics i.e. Wilcoxon T Tests.

The results of a selection of Thompson and Trimble studies are presented in table 3d. Column one in table 3d presents the results of the study described above, i.e. volunteers taking either DPH or placebo. Column two summarises the results obtained from a clinical population who had one of their ACD drugs changed to CBZ, for example from DPH to CBZ. Column three summarises the results from a study in which subjects on polytherapy had the number of prescribed drugs reduced.

Summarising across these studies and similar studies carried out by the authors, but not included in table 3d, reveals that where significant differences were found, they tended to show impairments with high numbers of ACDs taken, and DPH gave rise to more impairments than VPA or CBZ. The decision-making task appeared particularly

sensitive to ACD changes, but there was also a range of impairments associated with other tests.

Later studies (not included in table 3d) investigated the reduction of serum concentrations of ACDs on cognitive functioning and found that on some tests, for example visual scanning and memory tests, higher serum concentrations tended to produce more impairments. However, as the subjects in this study were on a range of ACDs, it is not possible to identify differences between the drugs.

In summary, Thompson and Trimble reported a number of drug effects, and interpreted their results as revealing a number of specific impairments in various areas of cognition for different ACDs. The strong points of their research included :

1. Used a within-subject design such that subjects acted as their own controls. Also, where possible they used a randomised cross-over design.
2. When a between-groups design was used, the groups were matched for age, I.Q., and factors relating to their epilepsy.
3. The drug serum levels were measured and where applicable and ethical, the subjects were on monotherapy.
4. In their later studies, wash-out periods for the drugs taken by volunteers were used.

The weak points (in my view) include :

1. The researchers specified that they chose their tests on the basis of problems encountered by patients and clinicians, but it is not clear to what degree these tests have "ecological validity" i.e. how much test performance relates to the degree or type of problems identified by subjects in their every-day life.

2. There is no reason to suppose that the psychological processes involved are acting independently of each other, or indeed that the psychological processes they have identified do exist independently of each other. However, neither the test design nor the statistical analyses carried out on the data take account of this possibility. Thus, independent analyses of variance were carried out on almost all the data, instead of a multivariate analysis of variance that could take more account of the possible interactions and number of measurements obtained.

3. As the researchers did not discuss a theoretical basis onto which one could interpret the results, it is very much up to the reader to interpret the results as best s/he can.

This last point leaves a great deal of scope for the reader. Thus, if one studies the methodology and the results obtained by Thompson and Trimble, one interpretation is that they were in fact measuring a more general cognitive deficit, that of information processing ability. Thus, subjects were asked to perceive and

process the information in such a way as to produce the correct output in a short a time as possible. Tasks relating to the subjects knowledge of the world, or their autobiographical memory were not used.

-----  
 Table 3e New referrals with epilepsy - a comparison of  
 CBZ and DPH (Andrewes and Reynolds, 1984).  
 Psychological Measures. Significant Findings  
 (in favour of CBZ)  
 -----

1. Short-term memory scanning	P < 0.05
2. Word-list learning	NS (Non-significant)
3. Memory for prose	NS
4. Delayed recognition of pictures	NS
5. Memory questionnaires	NS
6. Decision-making task	NS
7. Tracking task	P < 0.05
8. Mood questionnaire	NS

-----

Andrewes et al (1984 and 1986) compared the effects of CBZ and DPH on new referrals with epilepsy, using a between-group design, in which the groups were matched on a number of epilepsy variables including seizure type and duration, as well as age and I.Q. Table 3e summarises the tests administered and the results obtained in their first study.

The memory-scanning task and the tracking task produced significant differences in favour of CBZ. It is, noticeable that many tasks including the decision-making task used in the Andrewes' study, did not produce any significant differences, unlike the Thompson and Trimble decision-making task. Although, labelled the same, these

significant differences, unlike the Thompson and Trimble decision-making task. Although, labelled the same, these two tasks are in fact very different, and hence, the precise experimental paradigm used in a particular study may influence greatly whether impairments are seen.

Macphee, Goldie, Roulston, Potter, Agnew, Laidlaw and Brodie (1986) investigated the relationship between concentration of CBZ, as measured by serum-level monitoring, and the presence of impairments. This study used normal volunteers taking a single dose of CBZ. The tests used included a critical flicker threshold measure, choice reaction time measures, a card-sorting task, the Simple-Simon memory game, and a tapping task. Impairments were identified at particular times after the medication was taken, which highlights another relevant factor i.e. the degree of impairments due to medication may vary during the course of a day as blood concentrations vary.

Brodie et al (1987) have completed some pilot work using tasks similar as the above study, to investigate the effects of different drugs in clinical populations. They have found psychomotor impairments present in the epilepsy population, but no differences between the individual drugs. There are some drawbacks to the design of this study, the most serious of which is the poor matching of subject groups. Nevertheless, it would be interesting to see if the results would be replicated with more carefully matched groups. One interesting difference between the Brodie and the Thompson and Trimble work concerns the results they obtained on the

tapping tasks. The task used by the Brodie team consisted of asking the subject to tap on a calculator for 60s, whereby the calculator recorded the number of taps. However, no impairments were found using this task. Thompson and Trimble used a different task whereby the subjects were asked to press alternately on two keys that were placed 17.5cm apart for three 15s. sessions, and impairments were noted using this task. Yet again different paradigms that purport to be measuring the same capability have produced different results. A model of cognition and/or motor actions which could account for these differences would be valuable in this context.

As with the studies carried out by other research teams in the area, the research carried out by Brodie et al (1987) can be criticised for not having any well-defined criteria to select the tasks they employed. Such problems also emphasise the difficulty of generalising the results from the experimental data to the problems encountered in everyday life, i.e which if any of the results are indicative of performance in everyday life?

The discussion so far indicates the following factors as relating directly to experimental design :

1. Subject factors i.e. in relation to epilepsy variables.
2. Drug regime and blood serum-level monitoring.
3. Between or within subject design.
4. Test battery employed.

### 3.5 ACDS, the EEG, and cognitive functioning

The relationship between epilepsy, brain anatomy and cognitive functioning was discussed in chapter two. The use of the EEG in exploring the relationship between epileptiform activity and cognitive functioning was also discussed. As ACDs affect the incidence and severity of epileptic seizures, one might expect to see changes in the recorded EEG in relation to ACDs. Can any of these changes also be related to changes in cognitive functioning ?

The work done in this area is sparse. Wilkus, Dodrill and Troupin (1978) used EEG analysis to compare CBZ and DPH in a double blind cross-over design using subjects suffering from complex partial and generalised seizures. The effects of CBZ on the EEG were to produce an increase in diffuse slow rhythms and an increase in generalised epileptiform discharges, which did not occur when the subjects were taking DPH. These changes also correlated with increasing serum concentrations of the CBZ.

Harding, Alford and Powell (1985) studied the effects of VPA on sleep EEG rhythms, reaction times, and visual evoked potentials. Under high-drug conditions there appeared to be a increase in delta activity during sleep and a decrease in rapid eye activity.

Binnie, Kasteleijn-Nolst Trenite and De Korte (1986) investigated the effect of the main-line ACDs on the photosensitivity of subjects with epilepsy, who had previously shown a photoconvulsive response. The results

revealed a decrease in photosensitivity for all the major ACDs.

In relation to epilepsy, the main EEG identified waveforms have provided the primary avenue of investigation. However, it is possible that Event Related Potentials (ERPs) may be of value in trying to explore the relationship of the epilepsy, ACD medication and cognitive functioning.

ERPs are always coupled with specific sensory, motor, or cognitive events. The ERPs most associated with cognitive processes, such as attention are the N1 and P2 waves, which vary systematically with the direction of attention. As well as the N1-P2 waves, if the subject is asked to detect a target item, the ERP contains a P3 wave (also known as the P300).

At the time of writing this section (see next section on recent literature) no investigation of ACDs, cognitive functioning and the N1-P2 and P3 waves had been carried out, although researchers such as Pfefferbaum, Wertegrat, Roth and Kofell (1984) have used the P3 wave to investigate differences in performance on auditory and visual rapid decision tasks to investigate several clinical groups, including dementia, depression and schizophrenia. The results revealed that all three groups showed changes in P3 latency (increased) and amplitude (decreased) with the largest changes in the dementia group.

In conclusion, one can summarise that although complex to use and interpret, EEG monitoring may provide

a further tool for investigating the effects of epileptiform activity on cognitive functioning and ACD effects on such activity. Furthermore, ERP methodology may provide a tool for investigating the effects of epileptiform activity and ACDs on cognitive performance related evoked potentials.

### 3.6 Review of recent literature on cognitive functioning and ACDs.

The hypotheses and design of the experimental work presented in this thesis are based on the information presented in this review thus far, as well as that presented in chapter two. However, a more recent body of literature is now available and this literature informed the interpretation and discussion of the results of the experimental work described in the thesis.

Thompson (1991) wrote a review article on the memory functioning of patients with epilepsy. This article provided an over-view of the possible factors that may produce memory impairments in patients with epilepsy. The factors identified are those which were described in chapter two, for example type of epilepsy and interseizure activity. Thompson also reviewed the effect of treatment i.e. ACDs on memory functioning. She described different sets of studies, differing primarily on the subject sample chosen. In relation to studies carried out on normal volunteers (many of which were carried out by herself), she acknowledged several points that may have had a bearing on the results obtained.

Firstly, the doses of ACD, particularly of CBZ (600 mg), given to the volunteer subjects could be viewed as lower than the doses prescribed to patients with epilepsy. Secondly, the experiments were investigating the immediate effects of the drugs and not the long-term effects of the medication as taken by patients with epilepsy. Thirdly, the influence of ACDs on healthy brains may be different to the effects of the drugs on a seizure-prone brain.

Thompson also reviewed those ACD studies which included patients with a long term history of epilepsy and found that it is those subjects on polytherapy and with high levels of medication that produce the more dramatic effects on cognitive functioning. Those studies involving subjects with newly diagnosed epilepsy appeared not to produce such dramatic effects. Thompson interpreted this finding as being due to any negative effects of ACDs on cognitive functioning being off-set by improved seizure control. However, it could also be hypothesized that newly diagnosed subjects with epilepsy are more likely to be prescribed low doses of medication, as in the Andrewes et al (1984) study, rather than the very high levels of medication found in some polytherapy subjects, and at these low doses ACD medication do not produce impairments in cognitive functioning.

Thompson also discussed the nature of memory, pointing out the term memory is used in a wide variety of contexts and the meaning may differ in the different circumstances. It is interesting to note that the way

forward for Thompson is to investigate the effects of epilepsy on memory by using tools that endeavour to measure everyday memory losses. These tools include observational and questionnaire methods.

Smith (1991) also reviewed the literature on the cognitive effects of ACDS. One of the interesting points raised in this review was the need to be cautious in interpreting results. To illustrate this point, Smith cited the re-analysis by Dodrill (1991) of his 1975 study comparing CBZ and DPH which showed that if reaction times were partially out of the test scores obtained in the study, the impairments of higher cognitive functioning attributed to DPH disappeared. Regardless of these types of possible errors in interpretation of data, Smith still endorsed the main finding of most recent studies that CBZ tended to show fewer impairments than DPH. Smith also reported that there had been fewer studies carried out on subjects on VPA. Those that had been carried out tended to find few effects of VPA on cognitive functioning, although this may be less so with higher levels of blood serum concentrations.

Studies in which there are few significant findings may not always be reported in the published literature. However, Meador, Loring, Huh, Gallager and King (1991) described a study in which fifteen subjects with epilepsy participated in a study comparing the effects on cognitive functioning of the three ACDS, CBZ, DPH and phenobarbitone. The study was a within-subjects design, with each subject taking each of the drugs for a three

month period. The study is interesting for two specific points. Firstly, a large battery of tests was administered, including measures of memory, motor and reaction time tasks, and on only one measure was there a difference between the three drug conditions. The performance of subjects when on phenobarbitone was significantly impaired compared to the other two drug conditions on a digit symbol task. The CBZ and the DPH conditions were not significantly different on any of the measures. Secondly, this study did measure the P300 response as discussed in the previous section. There was no significant difference in either the latency or amplitude of the P300 between the three drug conditions.

Dodrill and Troupin (1991) investigated a hypothesis suggested by Meador et al (1991) that differences in the performances between DPH and CBZ in the Dodrill and Troupin (1977) study may in part be due to the much higher serum levels of DPH compared to CBZ. They re-analysed their data having removed those subjects with very high levels of DPH. The results of this re-analysis showed no difference between the two drug groups, except for one motor task, which continued to show a lower performance for the DPH group.

Dodrill and Troupin go on to speculate as to the reasons for the differences in findings in studies particularly with regard to DPH. Firstly, most subjects undergo changes in their medication for clinical reasons, and thus represent a sub-set of that whole drug group, i.e. those subjects doing badly on their medication. This

sub-set of subjects may introduce biases into the data, not accounted for in the original exclusion criteria for studies. Also, many studies report very few significant findings compared to the number of analyses carried out (see chapter two in this thesis for examples). With so few significant findings one needs to be cautious about interpreting results.

This more recent body of literature is less conclusive that there are significant differences between the three main ACDs, and in particular throws doubt on the view that DPH compares unfavourably to the other two drugs in relation to effects on cognitive functioning.

## CHAPTER FOUR

### STUDY ONE: INVESTIGATION OF THE COGNITIVE PERFORMANCE OF SUBJECTS WITH EPILEPSY ON ANTICONVULSANT MEDICATION (DUNDEE STUDY)

#### 4.1 Introduction

This first study was carried out at the Dundee Royal Infirmary, with suitable subjects being identified by consultant neurologists, Dr.D.Davidson and Dr.R.Roberts.

The aim of the study was to assess the sensitivity of particular tests on the cognitive performance of subjects suffering from epilepsy, with special regard to the possible effects of their medication. The tests were chosen on the basis of the literature discussed in chapter three.

The test batteries of researchers, including Thompson and Trimble (1981, '82 and '83) and Andrewes et al (1984 and '86) were described in detail in chapter three. These batteries differ, but one common area of testing was that of memory. Thompson and Trimble originally chose memory tests because patients suffering from epilepsy described having memory difficulties. However, giving subjects laboratory based memory tasks does not provide data that are easy to relate back to an individual's everyday life. Two tests, the Rivermead Behavioural Memory test (Wilson, Cockburn and Baddeley, 1985) and part of the Sunderland and Harris memory questionnaire (Sunderland, Harris and Baddeley, 1983) have been developed with the aim of linking

tests and everyday difficulties. They are included in the test battery for this study. These tests purport to have a greater "ecological validity", thus allowing easier identification of individuals every-day memory problems. Hence, if they were to be shown to be of use in this area, they are tests that could be used as clinical as well as research tools.

Also included in both the Thompson and Trimble work and the Andrewes et al work were tasks that had large visuo-spatial and/or motor components. These tasks included the category-decision and visual-scanning tasks in the Thompson and Trimble battery and the tracking task in the Andrewes et al battery. Hence, the battery of tests for this study included tests that have a large visuo-spatial component, one of which is an adaptation of Thompson's and Trimble's category-decision task.

The study employed a between-groups design, and therefore tests of general intellectual ability were included to see if there were comparable levels of intellectual functioning across the groups.

The battery of tests was administered to four groups of clinical subjects on either carbamazepine (CBZ), phenytoin (DPH), sodium valproate (VPA) or polytherapy (POLYT) and also to a control (CTL) group. As the design of the study was a between-groups comparison, the groups were matched for age, sex and various aspects of their epilepsy.

In all, fifty-three subjects with epilepsy and ten CTL subjects completed the test battery.

#### 4.11 Hypotheses.

The hypotheses for the study were based on the literature available before 1987, as presented in chapters two and three. The hypotheses were as follows :

1. There would be significant impairments of performance of the subjects with epilepsy, compared to the CTL subjects across the test battery. A large number of studies investigating the effects of epilepsy on cognitive functioning identify a number of factors that would make impairments more probable. These factors are described in chapter two in sections 2.5 (interseizure activity) and 2.7 (temporal factors). These factors, plus the possibility of impairments due to ACD medication, support this hypothesis.

2. Within the group of subjects with epilepsy, the subjects on polytherapy would show greater impairments compared to subjects on monotherapy. This hypothesis is supported by the work of Thompson and Trimble (1982) that showed that subjects on larger numbers of ACDs were more impaired on cognitive tests than when those subjects were on lower numbers of ACDs. Further studies by Gillham, Williams, Weidman, Butler, Larkin and Brodie (1987) also support the view that subject

groups on polytherapy will show more cognitive impairments.

3. Within the group of subjects on monotherapy, those subjects on DPH would show greater degrees of impaired performance than subjects on VPA or CBZ. This hypothesis is supported by the work of Thompson and Trimble in a range of studies which indicated that the number of impairments associated with CBZ and VPA were fewer than DPH. Other studies including Andrewes et al (1984 and 1986) also supported the view that DPH showed more impairments compared to CBZ.

#### 4.2 Subjects

##### 4.21 Criteria for identifying subjects

To be included in the study the subjects had to meet the following criteria :

- i) The age of the subject was between 15 and 55 years.
- ii) The subject was free of any gross brain pathology, or history of neurosurgery.
- iii) Anticonvulsant blood serum concentrations of those subjects on ACD medication, fell within the optimum therapeutic range as described by Davidson (1983) :

Anticonvulsant : Optimum blood serum level

in  $\mu\text{mol/l}$ , and  $\mu\text{g/ml}$  (in brackets)

a. CBZ	:	20 - 50 ( 6 - 12 )
b. DPH	:	40 - 80 ( 10 - 20 )
c. VPA	:	350 - 700 ( 50 - 100 )
d. PB (Phenobarbitone)	:	80 - 180 ( 15 - 40 )

iv) The subject was not suffering from any diagnosed psychiatric disturbance, for example depression.

v) The subject was not taking medication other than anticonvulsants.

Similarly, the CTL subjects were between 15 and 55 years old, not on any medication, and not suffering from any psychiatric illness. Most of the CTL subjects were relatives or friends of the clinical subjects who had participated in the study.

Verbal consent for participation in the study was obtained through the responsible consultant and written consent was subsequently obtained from all subjects.

#### 4.22 Classifying of epilepsy variables

The clinical subject groups were monitored with regards to the following epilepsy variables :

##### a. Type of seizure.

The type of seizure was identified by the Consultant neurologists. Following the International classification of seizures (1981), as discussed in chapter two, and taking into account the views of the Consultant neurologists, three types of seizure were identified :

- i. Generalised tonic-clonic seizures.
- ii. Complex partial seizures.
- iii. Complex partial -> secondarily generalised.

Hence, subjects with other types of seizure were not included in the study.

##### b. Aetiology of the epilepsy.

Indications of the aetiology of the seizures were noted, particularly if the seizures were of temporal lobe origin, or had a focus in one of the hemispheres.

##### c. Age of subject at the onset of the disease (years).

##### d. Duration of the disease (years).

##### e. Frequency of the seizures (as measured by the subject).

Frequency of complex partial and tonic-clonic seizures were assigned to one of the following categories :-

- i. Several, i.e. greater than three, in the previous week (frequency 1).
- ii. Several, i.e. greater than three, in the previous month (frequency 2).
- iii. Several, i.e. greater than three, in the previous six months (frequency 3).
- iv. Infrequently, i.e less than three, in the previous six months (frequency 4).
- v. None recently, i.e. none in the previous six months (frequency 5).

Subjects who had had a recent seizure, i.e within the three days prior to testing were also identified.

#### 4.23 Subjects Identified

63 subjects participated in the study, of whom 53 had a diagnosis of epilepsy and ten were CTL subjects. Of the 53 subjects with epilepsy, 14 were on CBZ monotherapy, 13 were on VPA monotherapy, 13 on DPH monotherapy and 13 on polytherapy. Table 4a shows the mean age and numbers of male and female subjects in each group. There were slightly more women in the study (N=35) compared to men (N=28) but this difference was spread across the drug and CTL groups. The mean age of all the subject groups was between 30 and 40 years with similar standard deviations, supporting the view that the subject groups were well-matched for age.

<u>Table 4a Details of subject groups</u>			
<u>Subject Group</u>	<u>No. in group</u>	<u>Age (yrs) Mean (S.D.)</u>	<u>Sex (M/F)</u>
CTL	10	35.8 (12.3)	5M, 5F
CBZ	14	39.1 (12.9)	5M, 9F
VPA	13	31.6 (13.7)	7M, 6F
DPH	13	37.4 (11.0)	7M, 6F
POLYT	13	31.5 (12.9)	4M, 9F

#### 4.3 Rationale of the tasks used in the test battery

This section describes the background and reasons for the inclusion of each test in the test battery. The procedure for administering the tests is described in section 4.5.

##### 4.31 Wechsler Adult Intelligence Scale-Revised (WAIS-R), Wechsler (1981).

Sub-components of the WAIS-R can be administered to measure a subject's intellectual ability, although care must be taken in choosing appropriate sub-components. Some parts of the WAIS-R have been shown to be relatively impervious to general cerebral impairment (Babcock, 1930) and are thus seen as providing an appropriate tool to measure premorbid intellectual levels, in the face of possible cerebral damage. Sub-components of the WAIS-R that

"hold-up" in such situations are Vocabulary, Information, Picture Completion, and Object Assembly.

To obtain a measure of both verbal and performance abilities, the Vocabulary and the Picture Completion tests were selected and administered to all subjects.

#### 4.32 Category-Decision Task.

In the battery of tests employed by Thompson and Trimble (1981, 1982 and 1983), the category-decision task was particularly sensitive to effects of ACDs. The task is a time-based measure requiring the subject to respond as quickly as possible to questions concerning the colour or category of an object presented visually on a computer screen.

For this present study a pen-and-paper version of the category-decision task was devised, as no computer was available. The same categories of colour and animate/inanimate objects were used as in the Thompson and Trimble task, and the times to complete all the trials in a particular condition were recorded.

#### 4.33 Perceptual Maze Task (Elithorn, Jones, Kerr and Lee, 1964).

This task was one of several tasks included to measure spatial and perceptual skills. This particular task is thought to assess perceptual and intellectual skills and involves a considerable amount of visual scanning to

complete the test. The test has been employed to diagnose cerebral damage, especially in the right hemisphere (Sweetland and Keyser, 1983).

4.34 Benton revised visual retention test (Benton, Glithorn, Fogel, and Kerr, 1963).

This test also measures visuo-spatial abilities. The task is used to screen for memory impairments as well as being a tool for identifying particular visuo-spatial errors, when subjects repeatedly make specific types of errors. It has been used widely in experimental research (Sweetland and Keyser, 1983).

There are four parallel forms, so allowing re-testing. Form "D" was employed in this study.

4.35 Rey-Osterrieth Complex Figure Test,  
(Bennet-Levy, 1984)

This test is the third measure of visuo-spatial abilities and the scores obtained provide two types of measure :

a) A copy score :- This score reflects the accuracy of the original copy of the Rey-Osterreith figure and is viewed as a measure of the visuo-constructive ability.

b) Recall scores :- These scores measure the amount and the quality of the original information retained for either short-term or long-term periods.

Hence, poor performance on this test could be for one of two reasons, either poor encoding of information, or poor retrieval of information.

#### 4.36 Sunderland and Harris Questionnaire (Sunderland, Harris and Baddeley, 1983)

Sunderland et al (1983) were concerned that laboratory tests may say little about how memory operates in everyday life. To address this issue, Sunderland et al (1983) developed questionnaires and check-lists that were both cheap and simple to use, and could be completed both by the subject and a relative of the subject. Sunderland et al (1983) used the questionnaires to compare normal controls and subjects with closed-head injuries. The responses to the questionnaire by the controls and the subjects with head injuries were then compared to the standard laboratory test performances of the same subjects.

In this present study, the 15 most frequently cited items of reported memory loss, of both the controls and subjects with head injuries were compiled into a shorter questionnaire which was completed by all the subjects and 33 relatives in this study.

#### 4.37 The Rivermead Behavioural Memory Test (RBMT) (Wilson, Cockburn and Baddeley, 1985).

The RBMT was developed in part from the Sunderland et al (1983) questionnaire. The RBMT is a short battery of

memory tests, and was included in this study for two reasons :

a) As the battery is easy to use and has four equivalent versions of the tests, it might provide a useful screening tool, possibly at an out-patients' clinic.

b) The test endeavours to have high ecological validity, but to also maintain the benefits of objectivity and rigour. Evidence supporting this claim is provided by work carried out at the Rivermead Rehabilitation Centre, where the performances on the RBMT and other standard memory tests are compared to the number of observed memory lapses of subjects with head-injuries, attending the centre. The highest correlation between observed memory lapses and test performance was with the RMBT, with a correlation of 0.75.

The following quotation of Wilson et al (1985) provides a flavour of the purpose of the test :

"The RMBT was developed to detect the impairment of everyday functioning,.....The test attempts to bridge the gap between laboratory based measures of memory, and assessments obtained by observation and questionnaires."P5

#### 4.4 Protocol for Study One : Order of presentation of tests

The tests described in the rationale section were administered to all subjects and were completed in the following order:

1. WAIS-R Vocabulary and Picture Completion test.
2. Category-Decision task.
3. Perceptual Maze task.
4. Revised Benton Visual Retention Test.
5. Tasks 1 to 4 of the Rivermead Behavioural Memory Test (RBMT).
6. Rey-Osterrieth Figure : copy and immediate recall.
7. Tasks 5 to 12 of the RBMT.
8. Rey-Osterrieth Figure : delayed recall.
9. Memory Questionnaire.

The time of testing was varied and subjects were assigned to one of the following categories :

- i. 9am until 12pm.
- ii. 12pm until 3pm.
- iii. 3pm until 6pm.

Whenever possible, after the testing session, a blood sample was taken from the subject so that a blood serum analysis could be carried out to provide accurate measures of circulating anticonvulsant levels at the time of testing.

#### 4.5 Procedure : Administration of tests in battery

##### 4.51 Sub-components of Wechsler Adult Intelligence Scale-Revised, (Wechsler 1982), (WAIS-R).

The procedure followed was that described in the WAIS-R Handbook (1982).

##### a. Vocabulary test.

The vocabulary list consisted of 35 words of increasing difficulty. The subject was asked the meaning of each of the words in turn and his/her response was recorded verbatim by the experimenter. If the subject had five consecutive failures, the test was discontinued.

When it was not clear whether the subject knew the meaning of a word the experimenter asked for further elaboration.

Each item on the list was scored as a "2" for a correct answer, a "1" for a partially correct answer, or a "0" for an incorrect answer. Hence, the maximum score was 70. The raw score was then converted to an age-scaled score, with a maximum score of 20, a mean of 10 and a standard deviation of three points for the normal adult population.

(For further details of the test : see WAIS-R manual (1982), P70-71.)

b. Picture Completion test.

The materials for this test consisted of twenty pictures presented individually on cards. All the pictures were incomplete in some observable way. The subject was asked to specify what was missing from each picture. Each card was shown for a maximum of twenty seconds, and the pictures were of increasing difficulty.

After five consecutive failures the test was discontinued. Hence, the maximum score was 20 and the scores were converted to age-scaled scores, with the mean of the scale being 10 and the standard deviation for a normal population being 3.

(For further details : see WAIS-R manual (1982), P 63-64).

4.52 Category-Decision task

The computerised task employed by Thompson and Trimble (1981, '82 and '83) was converted to a "pen and paper" version. The task consisted of practice conditions and three experimental conditions. Each of the experimental conditions was completed twice, and the subject was asked to complete all the conditions as quickly as possible.

In the practice task, the subject was presented with eight pairs of two by two centimetre squares on a sheet of paper, with one of each of the pair of squares lying opposite a star, (\*), sign (See figure 4a). The subjects

were asked to place a line through the boxes that were placed opposite the "\*" sign as quickly as possible.

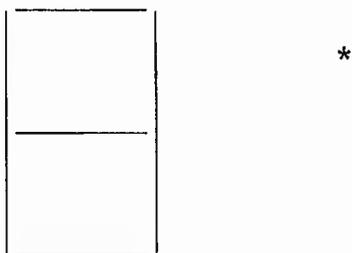


Figure 4a : An example item from the  
category-decision task

After the practice task, the subjects proceeded to do the three test conditions. In all conditions, the time taken to complete each section was measured by the experimenter using a stop watch.

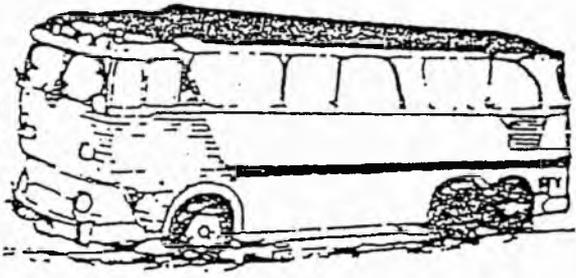
19. 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
--	--

Figure 4b: An example item from the category-decision task, condition two.

Condition one

The subject was told that 20 pairs of squares would be presented (8 pairs of squares per page, therefore, 2 1/2 pages in all). The subject was asked, as in the practice task, to place a line through the square that lay opposite the "\*". The subject was asked to complete the task as quickly as possible, as the experimenter would be timing the task.

Condition two

The subject was told that 20 objects would be presented (8 objects per page, therefore, 2 1/2 pages in all). The list of possible objects is shown in appendix two. With regard to each of the objects, the subject was asked to answer the following question; "Is the object presented on a shaded background ?" If the answer was "YES" the subject was told to place a line through the "YES" square, and if "NO" to place a line through the "NO" square. The words "YES" and "NO" were placed beneath the empty squares and were always presented in the same order i.e the top square was a "YES" square and the bottom square was a "NO" square. Figure 4b shows an item from the test with the lay-out of "YES" and "NO" squares.

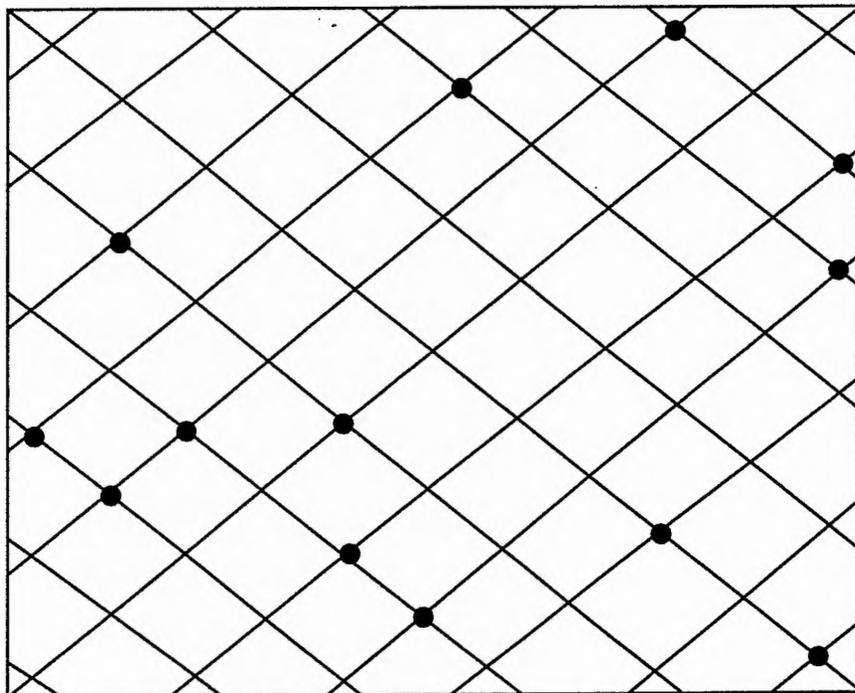
The subject was shown an example of the task and was asked to do the task as quickly as possible .

Condition three

20 objects were presented in the same manner as in condition two. However, on this occasion, the subject was asked the question, " Is the object animate, i.e. either an animal or a plant? ". Again, if the answer was "YES" or "NO", the subject was told to place a line through the appropriate square. The subject was shown an example of the task and was told to complete the task as quickly as possible.

Conditions one to three were repeated, such that each subject completed the task twice. The order of presentation of the test conditions was varied in a Latin-square design, i.e for one third of the subjects the order of the conditions was one, two and then three; for another third of the subjects it was condition two, three and then one and for the final third of the subjects it was condition three, one and then two.

The times taken to complete each of the conditions and the number of errors were recorded by the experimenter.



**Figure 4c: An example of a perceptual maze.**

#### 4.53 Perceptual Maze task

The test material was composed of dot patterns superimposed on a lattice background. An example of the task is shown in figure 4c.

As well as being shown an example of the task, the subjects were given the following instructions (written and verbal). The subject was told that he/she would be presented with dot patterns, one at a time, and of increasing complexity. In order to complete each of the patterns, the subject had to follow the path that completed the maximum number of black dots. At the bottom left corner of each dot pattern there would be a number that states the maximum number of dots that could be connected, on that particular dot pattern. The subject had completed the task when the specified number of dots had been joined. The subject, however, had to follow two rules whilst looking for the path :

i. The subject had always to remain on the black path lines, and must not cross the white spaces.

ii. The subject must always move in a forward direction; thus, at any intersection, the subject could move on either the path to the right or to the left.

The subject began his/her path somewhere on the bottom line, and tried to find the correct path within two minutes.

Before attempting the test patterns the subjects completed two practice patterns; the results of these two tasks were not included in the analysis. If a subject required further explanation concerning the tasks, it was given at this point.

On the test patterns, the subject was allowed to fail one pattern, i.e. not complete one path in the allotted time. Hence, the test was discontinued when the subject failed on a second pattern.

The dot patterns increased in complexity in such a way that the number of dots required to complete a particular path ranged from 5 to 15, and the number of distractor dots increased in proportion to the increasing number of path dots.

If the subject began to break one of the two rules this was immediately corrected by the experimenter during the task.

The times taken to complete the dot paths and the dot pattern at which the test was discontinued were recorded by the experimenter.

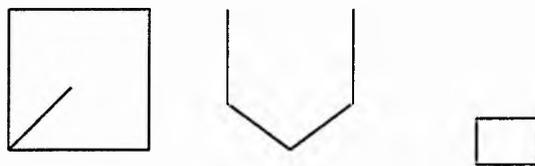


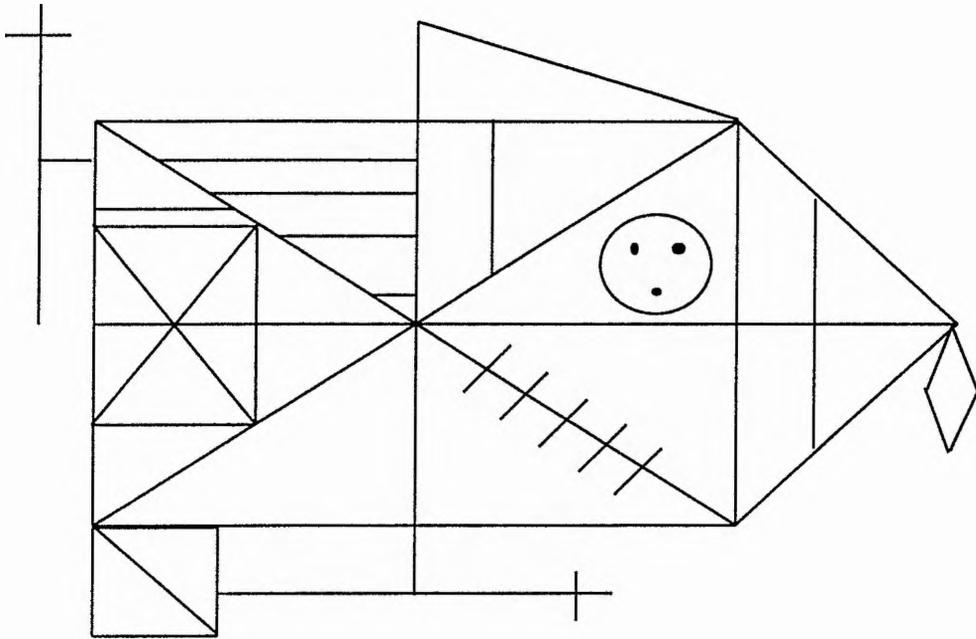
Figure 4d: Item D7 from the Benton Visual Retention Test.

#### 4.54 Revised Benton Visual Retention Test.

Version D of the Revised Benton Visual Retention Test was administered. The subject was told that he/she would be shown, individually, 10 simple drawings. The subject was presented with each one for 10 seconds, and was then asked to wait for 15 seconds, before drawing the shapes from memory. These drawings were marked by number and type of errors as specified by the Benton handbook marking scheme. An example of one of the Benton shapes is shown in figure 4d.

#### 4.55 The RBMT and the Rey-Osterrieth figure.

These two tasks were combined into one because the ability of the subjects meant that they did not normally require twenty minutes to complete the RBMT, and hence, it was very difficult to administer the prospective items of the test. By combining the Rey-Osterrieth figure with the items of the RBMT this difficulty was overcome. Also, the items of the RBMT provided the distracting tasks between the immediate and the delayed recall of the Rey-Osterrieth figure. The combination of these two tasks took the following protocol :



**Figure 4e: A copy of the  
Rey - Osterrieth complex figure**

i) The prospective memory test items, i.e items one to three, of the RBMT were administered. These were presenting a portrait with a to-be-remembered name, hiding one of the subject's belongings, and setting the timer.

ii) The Rey-Osterrieth figure, as shown opposite in figure 4e, was first copied and then immediately drawn from memory.

iii) Task four to twelve of the RBMT were then completed. These were recognition of pictures and photographs, immediate and delayed recall of prose, immediate and delayed recall of a route around the room, and the orientation questions. Recall of items one to three was then tested.

iv) The Rey-Osterrieth figure was drawn from memory for a second time, so providing a measure of delayed recall of Rey-Osterrieth.

#### 4.56 Memory Questionnaire

The questionnaire used in this study was an adaptation of the questionnaire devised by Sunderland et al (1983) and consisted of 15 items.

The questionnaire was completed by the subject, and the subject was asked to take a copy of the questionnaire away and ask a relative or close friend to independently complete the questionnaire on the subject's memory. Both the subject and the relative were asked to consider the

subject's memory over the previous six months, and to rate the subject on the 15 items on the questionnaire. If a particular item occurred to the subject very frequently, the number "4" was circled for that item, if occurring quite often a "3", occasionally a "2", and if the item never happened a "1" was circled. The relative completed the questionnaire in the same way but always considering the subject's behaviour.

The subjects and their relatives were also given the questionnaires in a check-list form, i.e. 7 copies of the questionnaire numbered day one to day seven. The subject and the relative were asked to monitor the subject's behaviour over a seven day period, and to record the number the items that occurred to the subject on each of the seven days. They did this by recording a tick (or more than one tick, if the subject made the same error more than once) next to the appropriate item on that day. Hence, the relative's and subject's questionnaires and check-lists were taken home by the subject after completion of the test session.

## CHAPTER FIVE

### DUNDEE STUDY ONE : RESULTS

#### 5.1 Introduction

Patients and their relatives attending out-patients at the Dundee Royal Infirmary participated in this study. 63 subjects (53 subjects with epilepsy and 10 controls) completed the test battery described in the previous chapter and summarised below :

1. Wais-R Vocabulary Test.
2. Wais-R Picture Completion Test.
3. Category-Decision Task.
4. Perceptual Maze Task.
5. Revised Benton Visual Retention Test.
6. Rey-Osterreith Figure.
7. Rivermead Behavioural Memory Test.
8. Memory Questionnaire.

Analysis of variance (ANOVA) was employed across each of the tests to compare the four drug groups (CBZ=14, VPA=13, DPH=13 and POLYT=13) and the control (CTL) group (N=10). This set of ANOVAs comprised the main body of results, with significant findings being further analysed using the Newman Keuls technique.

The Scheffé test, a conservative post-hoc test, more suitable for comparisons in which groups differ greatly in

size was used to compare the control group (N=10) and the epilepsy group (N=53), and also the monotherapy group (N=40) and the polytherapy group (N=13). For clinical interest, two further sets of ANOVA were carried out to compare controls versus subjects with epilepsy, and subjects on monotherapy versus subjects on polytherapy. These analyses provided a picture of the pattern of results for these comparisons, although the results must be interpreted cautiously because of the differences in sizes between the groups; hence the use of the Scheffé test as described above.

The data relating to the clinical epilepsy variables will be described, followed by the results of the group comparisons.

## 5.2 Clinical Data

Variables assessing the type and severity of the epilepsy disorder and its treatment were monitored for all the subjects with epilepsy. The type of seizure, the frequency of seizures, the age of onset and the duration of the condition and history of brain damage for each subject are shown in appendix three and the individual drug doses and blood serum levels are presented in appendix four.

Seizure type was classified as recorded in the subject's medical notes. Information on whether the subject suffered from more than one type of seizure; in particular, may have suffered absence seizures was not available, in an



months, four (28.6%) subjects had a seizure frequency of less than three seizures in the previous six months, and seven (50%) subjects had had no seizures in the previous six months. The seizure frequency of one subject was unobtainable.

Of the VPA subjects, seven (53.8%) had tonic-clonic seizures, three (23.1%) had complex partial seizures and three (23.1%) had complex partial, secondarily generalised, with the diagnosis of one subject being unobtainable.

In relation to seizure frequency, two (15.4%) subjects had had more than three seizures in the previous three months, one (7.7%) had had more than three seizures in the previous six months, two (15.4%) had had fewer than three seizures in the past six months, and eight (61.5%) had had no seizures in the past six months.

In the DPH group, ten (76.9%) subjects had tonic-clonic seizures, one (7.7%) subject had complex-partial seizures and one (7.7%) subject had complex partial, secondarily generalised. The diagnosis of one subject was unobtainable.

In terms of frequency, two (15.4%) subjects had had more than three seizures in the past six months, one (7.7%) subject had had less than three seizures in the previous six months, and nine (69.2%) subjects had had no seizures in the past six months. The frequency for one subject was unobtainable.

In the POLYT group, six (46.2%) subjects had tonic-clonic seizures, three (23.1%) had complex partial seizures and three (23.1%) had complex partial, secondarily generalised. The diagnosis of one subject was unobtainable. In terms of frequency, one (7.7%) subject had had more than three seizures in the previous week, four (30.8%) subjects had had more than three seizures in the previous month, four (30.8%) subjects had had more than three seizures in the previous six months, one (7.7%) had had less than three seizures in the previous six months, and one (7.7%) subject had had no seizures in the previous six months. The frequency for one subject was unobtainable.

In summary, most subjects had either tonic-clonic or complex partial seizures secondarily generalised. The numbers were spread evenly across the groups except for the DPH group which had a predominance of tonic-clonic seizures. Most subjects had had very few seizures recently, although the frequency was higher in the POLYT group subjects, justifying the taking of more than one type of ACD. Only one subject had very frequent seizures, i.e more than three the previous week. Hence, it was not possible to look at the effects of recent seizures on performing the tests as there were insufficient data. Indeed, there were only two subjects who had suffered a seizure in the three days prior to testing.

Table 5b : Age at onset and duration of the epileptic condition (No. of years)

Drug Group	Age : Mean (S.D.)	Duration : Mean (S.D.)
CBZ	22.6 (15.84)	15.9 (16.33)
VPA	22.5 (14.72)	7.7 (4.97)
DPH	24.5 (13.87)	13.0 (11.28)
POLYT	9.4 (9.28)	18.8 (13.10)

Table 5b presents the mean age of onset of the disorder, which is very similar for the three monotherapy groups, both in terms in mean and standard deviations, but very different for the polytherapy group, with a mean age of onset of 9.4 years and a standard deviation of 9.28.

The duration of the condition is more variable, with the VPA group being the smallest (mean of 7.7 years and standard deviation of 4.97), the POLYT group being the largest (mean of 18.8 years and standard deviation of 13.10) and the CBZ and DPH groups being similar and falling between the other two groups. The data for five subjects were unobtainable i.e not available in the medical notes.

Table 5c : Dose and blood serum concentration of medication of three monotherapy groups

Drug Group	Dose (mg) : Mean (S.D.)	Concentration ( $\mu$ mol/l) : Mean (S.D.)
CBZ	500 (235.3)	26.1 (9.32)
VPA	1100 (633.8)	226.0 (47.93)
DPH	289 (93.8)	48.6 (34.23)

Table 5c presents the mean drug doses and serum concentrations for the three monotherapy groups as recorded at the end of the testing session. The means for each of the groups fell within the therapeutic optimum levels for each of the drugs. However, in terms of individual subjects, two were below the optimum level in the CBZ group, one subject was above the optimum level in the VPA group, and one was below the optimum range in the DPH group. With regard to the serum concentration, two subjects were below the optimum level in the CBZ group, and one was above and two below in the DPH group. The doses for five subjects were unavailable i.e not recorded in the notes, as were the serum levels for fifteen subjects (See appendix four).

The POLYT group were taking a combination of ACDs, including the three drugs under investigation. In terms, of therapeutic levels, most fell in the therapeutic range for any one drug, with only one subject falling below the range for CBZ, and none being above this range. However, the data for four subjects were unobtainable. The data for the serum levels also revealed that most subjects' concentrations fell within the therapeutic range, with one subject falling below this range in the case of CBZ and DPH and two subjects falling below with VPA. The data of five subjects were unobtainable. Interactions between the various drugs are possible, such that it is more difficult to know the therapeutic range for each of the drug combinations.

In summary, the vast majority of subjects' drug concentrations, where data were available, fell within the recommended therapeutic range. However, it must be highlighted that many (N=20) serum levels were not available as the results from blood analyses were not entered into the medical notes.

### 5.3 Quantitative Analyses

The quantitative analyses will be described in detail for the five groups comparisons. The results from most of the tests will be analysed by one-way ANOVAs comparing groups, and will be presented in tables. Where there was a within-subject factor of condition, two-way ANOVAs will be carried out, with a between-subjects factor of group and a within-subjects factor of condition. Where appropriate post-hoc analyses, i.e. Newman Keuls tests and Scheffé tests are employed.

A brief section at the end of the results will include ANOVAs comparing the subjects with epilepsy (N=53) to the control subjects (N=10) and also the monotherapy subjects (N=40) to the polytherapy subjects (N=13). The design of this study renders these comparisons less orthodox because of the differences in the sizes of the groups and they are included only for clinical interest.

### 5.31 Missing data

There were no missing data points in this set of data, so the issue of accommodating missing data for the comparisons did not arise.

-----  
Table 5d : Analysis of tests of intellectual ability across  
the five groups data (mean-scaled scores)

Test	Subject group : Mean (S.D.)				
	CTL	CBZ	VPA	DPH	POLYT
Intellectual Ability (Combined Score)	10.4 (3.10)	10.2 (2.33)	8.4 (1.61)	9.1 (2.16)	7.4 (2.43)
Vocabulary	10.1 (3.11)	10.1 (2.50)	8.3 (1.84)	8.8 (2.34)	7.3 (2.46)
Picture Completion	10.7 (3.45)	10.4 (2.79)	8.5 (2.42)	9.3 (2.32)	7.5 (2.86)

-----

-----  
Table 5e : Results from the tests of intellectual ability  
across the five groups

Test	Five groups : F ratio (Df) and significance level	
Intellectual Ability (Combined Score)	F = 3.34 (4,58)	P < 0.05
Vocabulary	F = 2.96 (4,58)	P < 0.05
Picture Completion	F = 2.87 (4,58)	P < 0.05

-----

### 5.32 Comparison between drug and control groups

The five groups (CBZ=14, VPA=13, DPH=13, POLYT=13 and CTL=10) were analysed using ANOVA. Each of the tests in the test battery was analysed separately.

The results will be presented both to provide a picture of the performance of the drug groups and to describe the effect of conditions and sub-parts of the tests on subject performance.

### 5.33 Five group analyses of tests of intellectual ability

A measure of intellectual ability was attained using the mean of the scores from the Vocabulary and the Picture Completion test. Three one-way ANOVAs were carried out, each of the two tests being analysed separately, and then a third analysis carried out on the combined scores. The mean scores and standard deviations across the five groups for the tests of intellectual ability are summarised in table 5d. The CTL and CBZ group obtained the highest means, followed by the DPH group, the VPA group, with the POLYT group obtaining the lowest scores. The standard deviations were largest in the CTL group, smallest in the VPA group, and similar in size in the other three groups. The data were analysed using ANOVA, which revealed significant between group effects in all three analyses; for the combined scores ( $F_{4,58} = 3.34, P < 0.05$ ), for the

Vocabulary task ( $F_{4,58} = 2.96, P < 0.05$ ) and for the Picture Completion task ( $F_{4,58} = 2.87, P < 0.05$ ) (See table 5e).

#### Post hoc Analysis

As all three measures of intellectual ability were significantly different at the  $P < 0.05$  level, a Newman Keuls test was used on each set of the results. In the combined scores analysis, the POLYT group had significantly poorer performance at the  $P < 0.05$  level compared to the CBZ group, the CTL group and the DPH group. There were no other significant differences between the groups.

The Newman Keuls analyses also revealed the POLYT group to be significantly poorer in performance ( $P < 0.05$ ) on the Vocabulary test compared to the CTL and the CBZ group and poorer than the CTL group ( $P < 0.05$ ) on the Picture Completion test. No other groups were significantly different.

In summary, the POLYT group performed significantly worse than the CTL group, and also worse than the CBZ and the DPH groups on some of the measures of intellectual ability. These results support the hypothesis that the POLYT group would perform significantly worse than the CTL and monotherapy groups.

Scheffé test

The Scheffé test was used to compare all those subjects with epilepsy, i.e. the four drug groups combined (N=53), with the CTL group (N=10), and also all those subjects on monotherapy, i.e. the CBZ, the VPA and the DPH groups combined (N=40) were compared to the POLYT group (N=13), on scores of intellectual ability. No significant differences were found in these set of analyses. Hence, these analyses supported the null-hypotheses that are no significant differences in performance between the CTL and epilepsy groups, and none between the monotherapy and polytherapy groups.

-----  
Table 5f Mean total times for the category-decision task  
for the five groups

Test	Subject group : Mean (S.D.)				
	CTL	CBZ	VPA	DPH	POLYT
-----					
Category-Decision Task (Total time in secs)					
Condition 1	17.2 (2.35)	18.5 (6.24)	20.9 (5.08)	23.9 (9.22)	25.8 (10.20)
Condition 2	20.9 (4.67)	22.6 (6.83)	27.6 (9.53)	28.1 (11.64)	32.3 (12.08)
Condition 3	24.6 (7.53)	23.6 (7.18)	31.4 (7.71)	29.9 (9.27)	34.8 (15.18)

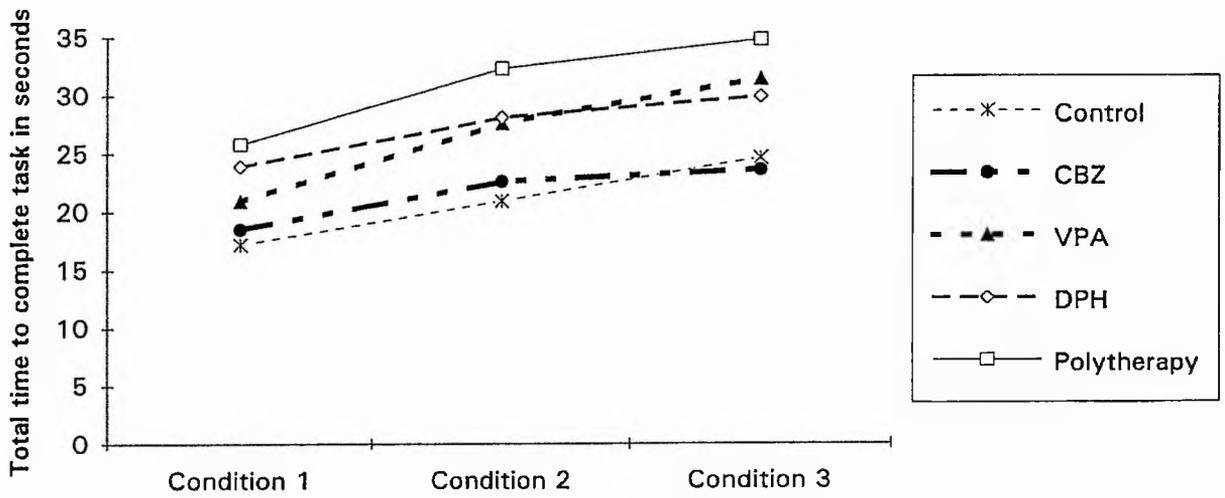
-----

-----  
Table 5g ANOVA of the category-decision tasks for the five  
groups

Test	Five groups : F ratio (Df) and significance level		
-----			
Category-Decision Task			
Effect of groups	F = 3.07	(4,58)	P < 0.05
Effect of condition	F = 71.32	(2,116)	P < 0.001
Interaction (Group by condition)	F = 1.38	(8,116)	P > 0.1

-----

Figure 5a: Graph of mean response times of five groups in the category-decision task



#### 5.34 Results from the Category-Decision task

The category-decision task was completed twice by the subjects and the total time to complete each set of 20 trials was recorded, as well as the number of errors.

Two subjects did not follow the procedure correctly i.e. did not immediately turn over the pages to continue doing the task, on their first attempt at the task. Hence, the data used for the analysis were the data from the second attempt at the task, which all subjects completed correctly. The mean total times for each of the three conditions of the task were compared in a two-way ANOVA with a main effect of groups and a within-subjects factor of condition.

The means and standard deviations for this task are presented in table 5f. In general, the means for the CTL group and the CBZ group were the fastest, followed by the VPA group, the DPH group and finally the POLYT group. For example, the means for the five groups for condition one were 17.2 (CTL), 18.5 (CBZ), 20.9 (VPA), 23.9 (DPH) and 25.8 seconds (POLYT), respectively, with increasing time representing poorer performance as shown graphically in figure 5a. The standard deviations followed the same order with the largest standard deviations occurring in the POLYT group and the smallest in the CTL group. The "F" ratios, the degrees of freedom and the significance levels are presented in table 5g and reveal a group main effect (F

4,58 = 3.07,  $P < 0.05$ ) and an effect of condition ( $F_{2,116} = 71.32$ ,  $P < 0.001$ ).

The number of errors was also monitored. The number of errors was small with the majority of subjects making no errors. Table 5h summarises the total number of errors for each of the groups across each of the conditions. It is interesting to note that there was not great variability in number of errors across the conditions.

-----

Table 5h : Total number of errors recorded for the five groups in each condition of the category-decision task

Group	Condition 1	Condition 2	Condition 3
CTL	1	0	0
CBZ	1	0	2
VPA	1	2	1
DPH	1	2	2
POLYT	6	5	2

-----

The data from the error scores were not analysed statistically due to the small number of errors. However, the larger number of errors obtained by the POLYT group is apparent.

#### Post hoc Analysis

The significant findings in the category-decision ANOVA were further analysed using Newman Keuls test. The analysis of the main effect of groups revealed that the POLYT group performed significantly poorer compared to the CTL group and the CBZ group ( $P < 0.05$ ). There were no other group differences. These analyses again show some support

for the hypothesis that the POLYT group would show impairments compared to other groups.

The effect of condition was also analysed using Newman Keuls test and revealed that all three conditions were significantly different from each other ( $P < 0.01$ ), with the tasks increasing in difficulty from condition one to three.

#### Scheffé test

The Scheffé test was used to compare all those subjects with epilepsy, i.e. the four drug groups combined, with the CTL group, and also subjects on monotherapy to the POLYT group, on the results from the category-decision task. No significant differences were found in this set of analyses. Hence, these analyses support the null-hypotheses i.e. that there are no significant differences between the groups.

In summary, the results revealed poorer performance by the POLYT group compared to the CTL and CBZ group. There were also significant effects of conditions but no test condition by group interactions.

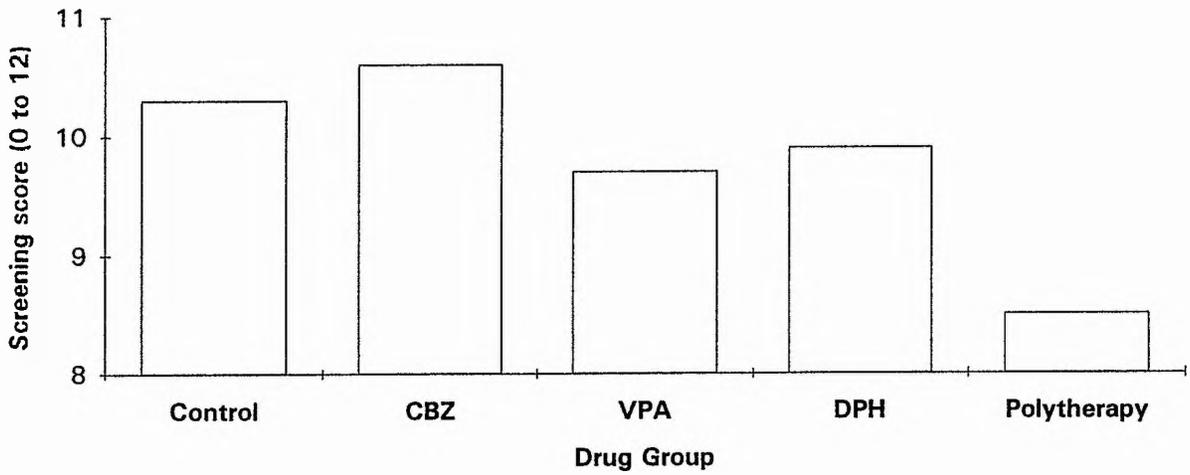
Table 5i: Mean scores on the RMBT and memory questionnaire for the five groups

Test	Subject group : Mean (S.D.)				
	CTL	CBZ	VPA	DPH	POLYT
Rivermead Behavioural Memory test					
Screening Score	10.3 (1.42)	10.6 (1.16)	9.7 (1.55)	9.9 (1.77)	8.5 (2.44)
Profile Score	66.9 (5.67)	67.0 (8.47)	62.1 (8.63)	64.9 (7.30)	58.3 (9.52)
Prose Recall					
Immediate : Raw score	9.45 (2.62)	9.68 (3.89)	7.89 (3.27)	8.70 (2.66)	6.46 (2.98)
Delayed : Raw score	8.45 (1.88)	8.25 (3.51)	6.85 (3.67)	7.26 (2.47)	5.73 (3.55)
Memory Questionnaire (Raw scores)	23.4 (8.46)	29.4 (8.04)	29.6 (10.99)	27.4 (13.85)	31.9 (11.31)

Table 5j ANOVA of the RMBT and the memory questionnaire for the five groups

Test	F ratio (Df) and significance level	
Rivermead Behavioural Memory test		
Screening Score	F = 2.57 (4,58)	P < 0.05
Profile Score	F = 2.50 (4,58)	P = 0.051
Prose Recall		
Effect of Condition	F = 1.89 (4,58)	P > 0.1
Group by condition	F = 43.23 (1,116)	P < 0.001
	F < 1	
Memory Questionnaire	F < 1	

**Figure 5b: Graph of mean screening scores for five groups on the RMBT**



### 5.35 The Rivermead Behavioural Memory Task (RMBT) and Memory Questionnaire

These two tests were included in the battery to provide a measure of memory impairments related to everyday life.

The RMBT produced two scores for each of the groups. The profile score was obtained from the sum of the raw scores on each of the sub-components of the RMBT, and these raw scores were converted to the screening scores. The RMBT contains, as one of its sub-components, a prose recall task. This standardised verbal memory task has been analysed individually as a comparison to the visuo-spatial memory tasks in the test battery.

The profile and screening scores were analysed by two separate one-way ANOVAs, whereas prose recall was analysed by a two-way ANOVA with a main effect of groups and a within-subjects factor of immediate versus delayed recall.

The pattern of means across both the screening and the profile scores revealed the CBZ group obtaining the higher scores, followed by the CTL group, the DPH group, the VPA group and finally the POLYT group (see table 5i and figure 5b). The standard deviations were once again largest for the POLYT group, followed by the VPA and DPH group and smallest for the CBZ and the CTL group (See table 5i). The ANOVA revealed a significant between groups difference in the screening score analysis ( $F_{4,58} = 2.57, P < 0.05$ ) and

a trend in the profile score ( $F_{4,58} = 2.50$   $P = 0.052$ ) (See table 5j)

#### Post hoc Analysis

Newman Keuls analysis was carried out on the screening data and showed the POLYT group performing significantly worse compared to the CTL group ( $P < 0.05$ ). No other significant differences found. This result supported the hypothesis that the POLYT group would perform worse than the CTL group.

#### Scheffé test

The Scheffé test was used to compare all those subjects with epilepsy and the CTL group, and also subjects on monotherapy to the POLYT group, on the screening score results. No significant differences were found in this set of analyses, thus supporting the null-hypotheses i.e. that there are no significant differences between the groups.

The prose recall analysis revealed a similar pattern of means and standard deviations to the screening and profile scores, but the ANOVA revealed no group differences. There was, not surprisingly, an effect of condition ( $F_{4,58} = 43.23$ ,  $P < 0.001$ ), with subjects performing less well on the delayed recall part of the task. There was no group by condition interaction.

The memory questionnaire scores that were obtained from the subjects at the time of testing were analysed

using a one-way ANOVA, which revealed an "F" ratio of less than one, and so no further analysis was carried out.

Only 33 (58%) of subjects returned the postal questionnaires and check-lists. Hence, there were not sufficient questionnaires completed by relatives, nor enough seven day check-lists to include in a between-groups analysis, and so, no analysis was carried out on these data.

-----  
Table 5k Mean scores on the visuo-spatial tasks for  
the five groups

Test	Subject group : Mean (S.D.)				
	CTL	CBZ	VPA	DPH	POLYT
Perceptual Maze Task	3.8 (1.99)	3.9 (1.77)	3.2 (1.57)	3.3 (1.79)	2.7 (1.11)
-----					
Benton Visual retention test					
Score	8.1 (2.03)	7.1 (2.40)	7.3 (2.81)	6.2 (2.54)	5.8 (3.65)
No.errors	2.40 (3.03)	4.07 (4.58)	4.23 (5.20)	7.00 (6.47)	6.39 (6.53)
-----					
Rey-Figure					
Part 1	35.4 (1.08)	34.8 (1.16)	33.9 (3.57)	32.7 (5.15)	31.7 (5.73)
Part 2	25.0 (5.02)	24.9 (6.30)	23.7 (9.32)	22.5 (8.65)	20.5 (9.39)
Part 3	25.7 (4.23)	23.2 (7.09)	24.6 (8.39)	20.6 (10.37)	19.8 (8.88)

-----  
Table 5l ANOVA of the visuo-spatial tasks for  
the five groups

Test	F ratio (Df) and significance level	
Perceptual Maze Task	F = 1.14 (4,58)	P > 0.1
-----		
Benton revised visual retention test		
Score	F = 1.34 (4,58)	P > 0.1
No.errors	F = 1.49 (4,58)	P > 0.1
-----		
Rey-Figure		
Effect of Group	F = 1.20 (4,58)	P > 0.1
Effect of Condition	F = 163.0 (2,116)	P < 0.001
Interaction (Group by Condition)	F < 1	

-----

### 5.36 Visuo-spatial tasks

Three tasks requiring visuo-spatial cognitive processes were included in the battery. All three produced a similar pattern of means and standard deviations. The CTL group and the CBZ tended to have the better mean scores and the smaller standard deviations, with the VPA and the DPH groups falling in the middle, and the POLYT group obtaining poorer means and larger standard deviations. These means and standard deviations are summarised in table 5k. Each of the three tests was analysed using ANOVA; a one-way ANOVA for the Perceptual Maze tasks scores, two one-way ANOVAs for the Benton Visual Retention task, (one for the scores and one for the number of errors as it was possible to score a high number of errors on any one of the ten trials) and a two-way ANOVA for the Rey-Osterreith figure, with a within groups factor of conditions. None of these analyses revealed any significant differences between the groups (See table 5l). There was, not surprisingly, an effect of condition in the Rey-Osterreith figure task ( $F_{4,58} = 163.0$ ,  $P < 0.001$ ), i.e the subjects found the complex figure more difficult to draw from memory, than to copy, but there was no group by condition interaction.

### 5.36 Summary

In general, the CTL and CBZ group means were in direction of better performance than the VPA and DPH means which in turn were better than the POLYT group. The standard deviations, however, were in the opposite direction with increasing standard deviations corresponding with lower performance means.

There were significant impairments for the polytherapy group compared to the CTL and CBZ groups on the tests of intellectual ability, the Rivermead behavioural memory test screening score (with a trend obtained on the profile score), and on the category-decision task. No group by condition interactions were obtained. No significant differences were found on the visuo-spatial tasks, nor on the memory questionnaire. Hence, there was some support for the hypothesis that the POLYT group would show impairments compared to CTL group and some of the monotherapy groups. However, there was no support for the hypotheses concerning differences between the monotherapy groups themselves, and in comparison to the CTL group, as no significant differences were obtained between these groups.

Figure 5c: Graph of spread of individual mean response times for condition two of the category decision task for five groups

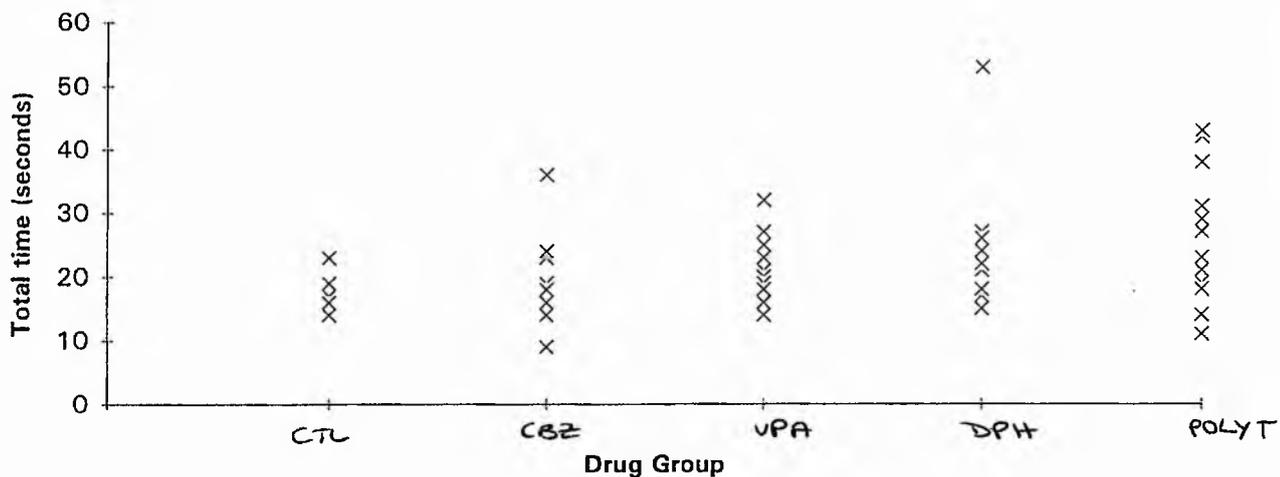
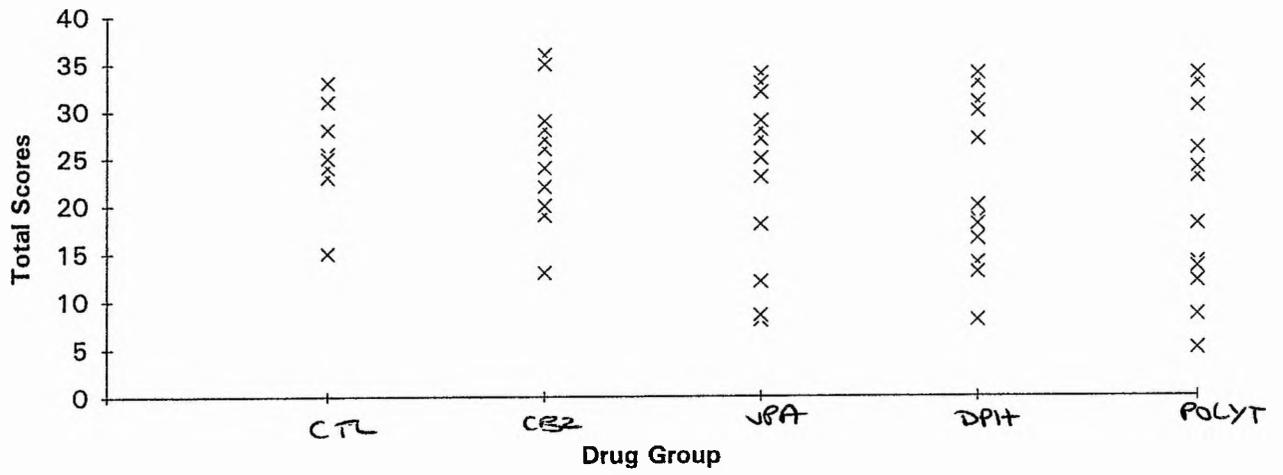


Figure 5d: Graph of the spread of Rey-Osterreith figure scores for five groups



#### 5.4 Further analysis

The comparisons between the groups using ANOVA yielded few significant differences between the five groups, with the exception of the POLYT. However, there were consistent patterns of data. The CTL and CBZ groups consistently obtained higher mean scores compared to the VPA and DPH groups, and these two groups consistently obtained higher mean scores than the POLYT group. It was also noticeable that the groups with the lower mean scores tended to have larger standard deviations. This pattern is shown on the category-decision task, for example on condition one the mean times and standard deviations (shown in brackets) for the CTL, CBZ, VPA, DPH and POLYT groups were 17.2s (2.35), 18.5s (6.24), 20.9s (5.08), 23.9s (9.22) and 25.8s (10.2) respectively. Figures 5c and 5d show graphically the spread of scores on both the category-decision task and the Rey-Osterreith task.

On many of the tests, the analysis using ANOVA supported the null-hypothesis i.e. that ACDs have no effects on cognitive functioning and there are no significant differences between the drug and CTL groups. However, as ANOVA compares the amount of the variance across the groups to that within the groups, these large standard deviations would have reduced the possibility of finding between-group differences.

-----  
 Table 5m    Ranked mean Z-scores for subjects  
                   across test battery  
 -----

Subj	Drug	Z-score	Rank	Subj	Drug	Z-score	Rank
18	CBZ	1.49	1	29	VPA	-0.55	33
49	CTL	0.92	2	31	DPH	-0.57	34
08	CBZ	0.89	3	10	VPA	-0.58	35
15	CBZ	0.88	4	25	CBZ	-0.59	36
50	CBZ	0.80	5	09	VPA	-0.65	37
45	POLYT	0.75	6	41	POLYT	-0.77	38
56	CTL	0.54	7	64	DPH	-0.82	39
40	CTL	0.37	8	65	DPH	-0.83	40
52	DPH	0.20	9	27	CTL	-0.85	41
57	CTL	0.19	10	26	DPH	-0.88	42
44	DPH	0.16	11	53	VPA	-1.03	43
42	VPA	0.16	11	13	VPA	-1.04	44
12	CBZ	0.15	13	67	VPA	-1.09	45
61	DPH	0.15	13	34	POLYT	-1.09	45
23	CBZ	0.14	15	16	CTL	-1.11	47
28	CTL	0.14	15	20	CBZ	-1.17	48
46	CTL	0.12	17	55	POLYT	-1.26	48
21	CBZ	0.11	18	30	VPA	-1.38	50
35	CTL	0.08	19	47	CBZ	-1.54	51
51	CTL	0.08	19	60	DPH	-1.54	51
17	VPA	0.04	21	06	DPH	-1.73	53
14	CBZ	0.01	22	43	POLYT	-1.83	54
39	VPA	-0.01	23	59	POLYT	-2.08	55
54	VPA	-0.03	24	36	POLYT	-2.39	56
22	CBZ	-0.19	25	48	VPA	-2.52	57
58	DPH	-0.24	26	68	POLYT	-2.60	58
11	VPA	-0.25	27	33	POLYT	-2.66	59
32	POLYT	-0.27	28	19	CBZ	-2.74	19
07	CBZ	-0.40	29	63	POLYT	-2.76	63
24	POLYT	-0.46	30	66	POLYT	-3.87	62
62	DPH	-0.53	31	38	DPH	-4.80	63
37	DPH	-0.54	32				

-----

Given that there were large standard deviations on some tests for some of the drug groups, are there individuals within the drug groups who could be identified as out-liers compared to the CTL group? If so, who are these individuals and can any reasons be identified as to why they performed as out-liers?

In order to answer these questions, the z-scores for each of the subjects on each of the tests were computed using the standard deviations of the CTL group. The mean of the of z-scores for the tests was used to rank the performance of each subject on the tests. Table 5m shows the mean z-score across the tests for each subject and the rank order of the subjects, with rank 1 obtaining the highest z-scores and rank 63 the lowest.

The range of z-scores was from 1.49 to -4.80, with 21 subjects obtaining a mean z-score above zero and 42 subjects obtaining an mean z-score below zero. The lowest z-score obtained by a control subject was -1.11 which was ranked at 47. Hence, 16 epilepsy subjects obtained lower z-scores than the lowest scoring control subject and eight of these subjects scored z-scores that were more than double that of the lowest control subject in the direction of poor performance, i.e. larger than -2.22. These subjects are identified as out-liers.

One possible way to reconcile this observation with the lack of significant differences in the ANOVAs, is to suggest that although the majority of subjects did not show

significant impairments on the test battery, such that there were no overall group differences, there were a number of clinical subjects who did perform very poorly on the battery of tests.

One possible reason for the poor performance of some clinical subjects is explored by looking at the eight subjects who performed poorly across the tests compared to the CTL subjects. The clinical characteristics of these subjects will be described to explore possible avenues why these subjects performed so poorly.

#### 5.41 Details of individual subjects

Of the subjects on monotherapy, three subjects were identified as out-liers on the z-score analysis. The clinical details of these three subjects are described below:

Subject number 48 was a 52 year old woman who suffered from complex partial, secondarily generalised seizures. The first seizure occurred when she was 47 years old, i.e the duration of the disorder was five years, but she had suffered no seizures in the past six months. This subject was taking VPA, and although the dose was not recorded in the medical notes her serum level at the time of testing was 399  $\mu\text{mol/l}$ , which is at the low end of the therapeutic range.

Subject number 38 was a woman aged 50 years, for whom epilepsy was diagnosed when she was 47. This individual suffered from generalised tonic-clonic seizures but she had

suffered none in the previous six months. She was taking 200 mg of DPH daily and the serum level of her medication at the time of testing was 62  $\mu\text{mol/l}$ , which is in the middle of the therapeutic range.

Subject number 19 was a 52 year old woman. The details of her epilepsy could not be found as her medical notes were missing. However, she reported having suffered no seizures recently, and her serum level of CBZ at the time of testing was 31  $\mu\text{mol/l}$  which is in the middle of the therapeutic range.

Five subjects performing as out-liers were identified in the POLYT group. The clinical details of these subjects will be described.

Subject number 33 was a 22 year old woman who suffered from generalised tonic-clonic seizures. The first seizure occurred when she was thirteen years old, and hence the duration of the disease was nine years. The subject still suffered seizures but these occurred at a frequency of less than three per six months. The subject was on daily doses of 600 mg DPH and 1500 mg VPA and had serum levels at the time of testing of 44  $\mu\text{mol/l}$  DPH and 205  $\mu\text{mol/l}$  VPA, which are well within the therapeutic range for these ACDs.

Subject number 36 was a 38 year old woman who had suffered complex partial seizures since the age of nine years. This subject still suffered from regular seizures which occurred at a frequency of more than three per month. She was on daily doses of 325 mg DPH and 60 mg

Phenobarbitone. Unfortunately, the serum levels of the medication at the time of testing were not available.

Subject 59 was a 34 year old man who had suffered generalised tonic-clonic seizures for three years. This subject still suffered from regular seizures at a frequency of greater than three per month. This subject was on a combination of CBZ and Clobazam. The dose of CBZ 700 mg and the serum level at the time of testing was 41  $\mu\text{mol/l}$  which is in the middle of the therapeutic range. The dose and serum levels of the clobazam were unavailable.

Subject number 63 was a 20 year old woman who had suffered from complex partial seizures from early childhood. She had not suffered from any seizures in the past six months. This subject took CBZ (400 mg daily) and phenobarbitone (60 mg) daily and her serum levels for these two drugs at the time of testing was 13  $\mu\text{mol/l}$  and 41  $\mu\text{mol/l}$  respectively, both of which are at the low end of the recommended therapeutic range.

Subject number 66 had suffered from complex partial seizures for a number of years (her medical notes did not provide more precise information on the age of onset of her condition). She was still suffering from regular seizures i.e. more than three per week. Her medication consisted of 1000 mg of CBZ and 800 mg of VPA daily. The serum levels of these drugs at the time of testing was 49  $\mu\text{mol/l}$  and 408  $\mu\text{mol/l}$  respectively. Hence, the level of CBZ was at the top

of the therapeutic range whereas the VPA was at the lower end of the therapeutic range.

The clinical details of these subjects does not point any one clinical factor that might throw some light as to why these individuals performed so poorly on the test battery. They showed a range of presentations in terms of seizure type, duration of disorder and frequency of recent seizures. The subjects on POLYT tended to suffer from higher seizure frequencies, so justifying the need for POLYT.

The ACD doses and serum levels tended to be well within the recommended therapeutic ranges.

One interesting factor is that seven of the eight individuals were female. 30 of the 53 subjects with epilepsy in this study were female, although it is still somewhat surprising that so many of this group of out-liers were female. There is, however, a large amount of clinical data that is unknown with regard to these individuals, for example the possibility of cerebral damage or the presence of interseizure activity, both of which may be related to cognitive performance.

Table 5o Mean scores for the epilepsy versus CTL groups  
(Mean scores combined across conditions of tests)

Test	Subject Group : Mean (S.D.)	
	CTL	Epilepsy
Intellectual Ability (Age-scaled score) (Combined score)	10.2 (3.11)	8.8 (2.34)
Category-decision Task (in secs) (Combined score)	21.6 (4.96)	26.5 (10.21)
Rivermead Behavioural Memory Test Screening Score	10.3 (1.42)	9.7 (1.88)
Sunderland and Harris Questionnaire	23.4 (8.46)	29.4 (10.93)
Perceptual Maze Task (No. mazes completed)	3.8 (1.99)	3.3 (1.61)
Revised Benton Retention task (No. correct)	8.1 (2.03)	6.6 (2.87)
Rey-Figure (Combined Score)	28.9 (4.32)	26.1 (7.34)

Table 5p Results from the epilepsy vs CTL groups analysis

Test	Two groups : F ratio (Df) and CTL versus Epilepsy significance level	
Intellectual Ability (Combined score)	F = 2.70 (1,61)	P > 0.1
Category-decision Task (Combined Score)	F = 3.37 (1,61)	P = 0.072
Rivermead Behavioural Memory Test Screening Score	F = 2.88 (1,61)	P > 0.1
Sunderland and Harris Questionnaire	F = 2.69 (1,61)	P > 0.1
Perceptual Maze Task	F < 1	
Revised Benton Retention Test	F = 2.48 (1,61)	P > 0.1
Rey-Figure	F = 1.62 (1,61)	P > 0.1

### 5.5 For Clinical Interest : Control versus clinical subjects

The performance on the tests of the subjects with epilepsy (N=53) was compared to the CTL group (N=10) using ANOVA. Most of the analyses were one-way ANOVAs with a between-groups factor of epilepsy versus non-epilepsy. For those tests with different conditions, two-way ANOVAs were carried out with a between groups factor of epilepsy versus non-epilepsy and a within-groups factor of condition.

Table 5o contains the means and standard deviations for the combined mean scores for the two groups across all the tests. (Note that as there were no group by condition interactions found in the monotherapy versus polytherapy analyses, for those tasks where there were more than one condition, the combined means and standard deviations across all conditions are presented).

The results of the ANOVA analyses, in terms of "F" ratios, degrees of freedom and levels of significance across these three tests are presented in table 5p

Comparing the CTL group to all the subjects with epilepsy combined as one group produced a pattern of results in which the means of the CTL group were generally the direction of better performance compared to the clinical group. The standard deviations were generally larger for the clinical group. However, the differences between the means, when analysed by ANOVA, were not significant, with only the category-decision task showing a

trend i.e  $P < 0.1$ , in the direction of impaired performance of the clinical group. There were no significant group by condition interactions.

-----  
Table 5g Mean scores for the tests for the monotherapy  
versus polytherapy groups

(Mean scores combined across conditions of tests)

Test	Subject Group : Mean (S.D.)	
	MONOT	POLYT
Intellectual Ability (Age-scaled score) (Combined score)	9.26 (2.15)	7.39 (2.43)
Category-decision Task (in secs) (Combined scores)	25.1 (8.62)	31.0 (12.63)
Rivermead Behavioural Memory Test Screening Score	10.08 (1.51)	8.54 (2.44)
Memory Questionnaire	28.88 (10.90)	31.00 (11.31)
Perceptual Maze Task	3.4 (1.71)	2.7 (1.11)
Revised Benton Retention Task (Score)	6.9 (2.57)	5.8 (2.65)
Rey-Figure (Combined Scores)	26.8 (6.31)	24.0 (7.42)

-----  
Table 5r Results of the monotherapy versus polytherapy  
analysis

Test	F ratio (Df) and significance level	
Intellectual Ability (Combined Score)	F = 6.06 (1,51)	P < 0.05
Category-decision Task (Combined score)	F = 4.10 (1,51)	P < 0.05
Rivermead Behavioural Memory task Screening Score	F = 7.38 (1,51)	P < 0.01
Memory Questionnaire	F < 1	
Perceptual Maze Task	F = 2.38 (1,51)	P > 0.1
Revised Benton Retention Task (Score)	F = 1.21 (1,51)	P > 0.1
Rey-Figure Effect of Group	F = 1.71 (1,51)	P > 0.1

5.6 For clinical Interest : Monotherapy versus  
Polytherapy groups

The subjects with epilepsy were divided into two groups, those on monotherapy (N=40) and those on polytherapy (N=13). The performance of the two groups was analysed using ANOVA (a one-way ANOVA, with one factor of groups, for those tests without conditions and a two-way ANOVA with factors of groups and conditions, for those tests with conditions).

The monotherapy group had means in the direction of better performance, and also smaller standard deviations than the polytherapy group. The means and standard deviations are presented in table 5q. (Note that as there were no group by condition interactions found in the monotherapy versus polytherapy analyses, for those tasks where there were more than one condition, the combined means and standard deviations across all conditions are presented).

The results were analysed by ANOVA and several of the comparisons produced significant findings. The polytherapy group performed significantly worse on the combined intellectual ability score ( $F_{1,51} = 6.06, P < 0.05$ ), on the category-decision task ( $F_{1,51} = 4.10, P < 0.05$ ) and on the Rivermead Behavioural Memory Test screening score ( $F_{1,51} = 7.38, P < 0.01$ ). However, neither the memory questionnaire nor the visuo-spatial tasks showed

significant differences. Table 5r presents the group effect "F" ratios, degrees of freedom and significance levels.

#### 5.6 Summary

A number of interesting features and results arose through the course of this study. These points will be summarised below with further discussion taking place in the main discussion chapter (see chapter eleven) :

1. The number of subjects in the five groups was smaller than anticipated, in spite of the fact that the study ran for 18 months. Identifying suitable subjects in a busy hospital setting was not as straight-forward as was anticipated at the out-set.

2. The test battery was easy to run, and the data easy to collect, which was reflected in the lack of missing data points. The only exception to this were the postal check-lists and questionnaires, which were removed from the analysis.

3. The clinical information concerning the subjects with epilepsy revealed a set of subjects that had a long duration of epilepsy but who had reasonably well-controlled seizures. There was only one subject, in the POLYT group who reported getting three or more seizures in a week and a small number reported getting several in one month (again mostly in the POLYT group).

4. The analysis of results did not produce a great number of group differences and hence, tended to support

the null-hypotheses that the subjects with epilepsy were not impaired, irrespective of the ACD taken. Where differences were found they tended to show poorer performance by the POLYT group. The tests that did reveal these differences were the tests of intellectual ability, the RMBT and the category-decision task. Neither the visuo-spatial tasks nor the memory questionnaire revealed differences between the groups.

5. A further analysis using mean z-scores was carried out, and showed a number of subjects with epilepsy performing very poorly. However, the clinical information available did not indicate a possible reason for these poor levels of performance.

The findings of this study and their implications will be discussed in chapter eleven.

## CHAPTER SIX

### COGNITIVE FUNCTIONING : THEORY AND APPLICATION

#### 6.1 Introduction

The literature on the cognitive impairments associated with ACDs has been described in chapter three. Turning to this literature, what can be gleaned from the published work as to the nature of these impairments?

Trimble and Thompson (1983) made the following distinction between :

"Cognitive function, traditionally measured by psychological tests and reflective of an individual's ability to deal meaningfully with information in their world, and behaviour, which reflects more a person's success, or otherwise, in handling interpersonal relationships." S55.

Taking this viewpoint, they developed a battery of tests that included measures of memory, attention, retention of new information, speed and accuracy of perceptual registration, decision-making and manual speed. Unfortunately, Thompson and Trimble did not discuss the rationale behind these categories of cognitive function. Furthermore, they did not consider a particular skill that may underpin, or affect performance in another area, for example perceptual registration may underpin category-decision tasks.

Andrewes, Tomlinson, Elwes and Reynolds (1984) used the two terms of cognitive function and mental function inter-changeably and claimed that the tests chosen for their assessment were :

"Tests chosen for their ability to isolate particular cognitive functions according to theoretical research." P23.

However, the particular cognitive functions isolated were not specified. Hence, our understanding of the precise nature and extent of these impairments is hampered by the different types of assessments employed. The lack of a theoretical framework and justification for the tests used makes for poor understanding of the results obtained; for example, terms such as "memory" and "attention" are often used to describe what certain tests are measuring. It is difficult to know what these concepts mean in terms of either psychological theories and/or relevance to everyday functioning. To avoid this pitfall, it is necessary for researchers to employ robust psychological theories and the appropriate experimental paradigms.

Difficulties in choosing appropriate theories of cognition are numerous. The extensive and diverse literature on cognition poses problems for the applied clinical researcher. There is a large range of terminology and types of experimental paradigms, but a lack of encompassing theories. Eysenck (1977) compiled the

following list of terms describing memory phenomena, which illustrates this point :

"We have iconic, echoic, active, working, acoustic, articulatory, primary, secondary, episodic, semantic, short-term, intermediate-term and long-term memories, and these memories contain tags, traces, images, attributes, markers, concepts, cognitive maps, natural-language mediators, kernel sentences, rational rules, nodes, associations, propositions, higher-order memory units, and features."P4.

Nevertheless, researchers investigating the effects of aging and of neurological damage on cognitive functioning have successfully employed theories and paradigms in the applied setting. Examples of such work will be described later in relation to choosing appropriate paradigms for the study described in chapters seven and eight of this thesis.

Regardless of the poorly specified rationale for the tests used in the ACD literature, some the tests have produced some interesting findings. Researchers' interpretations of their findings can provide guidance for choosing appropriate models and paradigms from the cognitive psychology literature.

Dodrill and Troupin (1977) compared CBZ and DPH, and identified certain types of tasks as being sensitive to different drugs. They interpreted their findings in the following way :

"Those tasks with clearly significant differences between drugs primarily involved higher level complex skills, requiring mental manipulation and they always favoured carbamazepine. Furthermore, there was a strong tendency for these differences to become apparent only on our most complex and demanding measures."P1027.

Thompson and Trimble (1983) made the following observations :

"Impairment of performance seemed to be related to the demands of the task.....the degree of slowing on the decision-making test appeared to be related to the type of decision required with slowing being most marked for the more difficult category judgements....

.....These decrements of concentration and mental slowing seem likely to be related to the poorer immediate recall for pictures and words. The presentation of memory stimuli was experimentally paced such that a reduction in attentional capacity or slowing would probably interfere with the adequate registration of stimulus items."P232.

Finally, Andrewes et al (1986) concluded that :

"The memory tasks showed the greatest differences between the groups."P131

From these interpretations, the following areas of cognition appear to be sensitive to the effects of ACDs :-

i. Attentional capacity, as identified by task demands and complexity.

ii. Recent memory function, with particular regard to types of material.

The following discussion on cognitive functioning will concentrate on those theories that take memory and/or attentional capacity as a central theme, and also those paradigms that explore aspects of task demands and complexity.

## 6.2 Cognition Functioning : Memory and Attention

### 6.21 Models of memory

Memory and attention are seen as the corner-stones of our ability to process information. Although closely linked, for the purpose of describing the theories underpinning these terms, they will be discussed as separate and independent entities.

The concept of memory has been influenced greatly by three theoretical models. Firstly, there was the "multi-store" approach of Atkinson and Schriffin (1968 and 1971). This model is now viewed as simplistic and is unable to explain neurological data of patients with intact long-term memory but poor short term memory (Shallice and Warrington, 1970). The second model was the "depth of processing" model ( Craik and Lockhart, 1972), incorporating the concept of a continuum of depth of processing of information. However, this framework is not supported by experiments on normal

subjects investigating the recency effect, nor by neuropsychological data which again tended to support the view of a dichotomous framework of long and short term memory (Baddeley, 1978).

The third approach is the "working memory" model (Baddeley and Hitch, 1974). This robust model is supported by much experimental data and has also been used with some success in applied settings. Hence, a more detailed overview of the model will be described.

#### 6.22 Working Memory Model

In 1974, Baddeley and Hitch set about constructing a model of memory that described how memory operated. The result of their deliberations was the concept of working memory. The working memory model included both a phonologically-based short-term memory similar to those of the old store models, named the articulatory loop, but also other components, notably the visuo-spatial scratch pad and a central executive. Baddeley and Hitch perceived the working memory system as :

"a system that allowed several pieces of information to be held in the mind at the same time and interrelated."p169

The model implied a system for the temporary holding of information during a range of cognitive tasks. Such a system could then be employed to read or understand a spoken sentence, or to carry out a reasoning task. This

general working memory system had a limited capacity, and hence a broad range of tasks would absorb a considerable amount of this capacity, and compete with the performance of other tasks.

To develop the model, they took as a starting point the component common to all short-term memory systems, that of a limited capacity, which is frequently measured using the digit span task. In the seventies, a number of experiments were carried out investigating the amount of residual memory available when performing, concurrently, a span task and another type of task, for example a verbal reasoning task. Although, performing a six digit span task considerably slowed performance on the reasoning task, there were still processes available to perform the reasoning task. It appeared that short-term memory processes and the processing required for the reasoning task over-lapped but were not entirely dependent on one limited capacity system. What other components made up this system and could these components be isolated from the rest of the system? Two such systems identified were the articulatory loop and the visuo-spatial sketch pad.

### 6.23 The Articulatory Loop

The articulatory loop is the term given to that part of the system that deals with short-term storage of items that are encoded and rehearsed in an acoustic manner. The capacity of the loop is often measured by a span task and

temporally is in the range of 2.5s i.e subjects can recall what they can say in 2.5s. Baddeley (1966) revealed that on many occasions subjects used the process of sub-vocal phonological rehearsal in order to prevent a trace from decaying; this rehearsal process is located in the articulatory loop. If this path of maintaining information is blocked by, for example, making the subject repeat a word aloud (a process known as articulatory suppression), then recall is impaired. The articulatory loop seems also to be involved in reading abilities, as shown by reading tasks in which the subject is asked to spot text errors. Articulatory suppression inhibits this process. Hence, it seems likely that the articulatory loop acts as a checking mechanism for preserving the order of information.

The acoustic nature of the loop explains why performance of the loop is detrimentally affected by items that are phonemically similar or of longer spoken duration (Baddeley, Thomson and Buchanan, 1975). Subsequent data, investigating the word length and phonological similarity effects, have led to a revision in the original articulatory model, as described in the next paragraphs.

As predicted by the original model, both the phonological similarity and the word length effects are abolished by articulatory suppression, when the to be remembered material is presented visually. However, if this material is presented auditorily, a clear word length effect and phonological similarity effect are still

observed (Baddeley et al, 1975). There is, nevertheless, one subtle and important difference between these two effects. If material is presented auditorily, and suppression is continued throughout input and output of the material, the word length effect is abolished (Baddeley, Lewis and Vallar, 1984, experiment 4). Under the same experimental conditions, the phonological similarity effect is still present, though somewhat reduced (Baddeley et al, 1984, experiment 1-3).

The revised model of the articulatory loop consists of two parts, an articulatory process for maintaining information by the process of rehearsal, and a phonological store that feeds into this articulatory control process. The phonological store is directly accessible by auditory presentation or by articulatory coding of visually coded material. Hence, the phonological similarity effect appears to be a product of this system, remaining present, with auditory presentation, even if articulatory suppression occurs throughout input and recall. The word length effect appears to be more a product of the articulatory process, being time-based and requiring verbal rehearsal to be maintained.

#### 6.24 Visuo-spatial sketch pad and other visual sub-systems.

Another sub-system of the working memory system is the visuo-spatial sketch pad which can generate and manipulate

visuo-spatial images, (Baddeley and Lieberman, 1980). This storage system can be disrupted by concurrent spatial processing, particularly where eye-movements and other bodily movements are involved (Quinn and Ralston, 1986). Philips and Christie (1977a and b) described a different type of visual system, that could be described as a visual pattern-based store that is maintained by active rehearsal of the pattern. It is not clear to what degree the visuo-spatial sketch pad and more visual stores are distinct components of a working memory system, or indeed if there are other types of visual stores not yet identified.

Far less work has been carried out in this area than in the verbal storage of information. Logie (1986) described a number of experiments in an attempt to identify experimental tasks that were primarily tasks using the visuo-spatial sketch pad and thus made minimal demands on either the central executive or the articulatory loop. He pointed out that in some of the earlier tasks, for example the "Brooks task" and the tracking tasks, the tasks are difficult to do and are therefore likely to be making use of the central executive. Ideally, Logie wished to identify visuo-spatial tasks that were the equivalent to articulatory suppression.

Logie carried out a number of experiments using variations in pattern-matching and picture presentation tasks which were used as secondary tasks that may affect recall of a primary task. The primary tasks either involved

learning a list of words by rote rehearsal or by visual imagery mnemonics. Hence, there was the possibility that the introduction of secondary tasks would differentially affect the performance on the primary tasks. The results of these experiments revealed that it was possible to obtain selective disruption on the visual mnemonic task by presentation of unattended pictures, whereas there was selective disruption of the rote rehearsal task by presentation of unattended speech. Hence, this set of experiments provided some paradigms for investigating the visuo-spatial sketch pad, separate from the other systems in working memory.

#### 6.25 Central Executive

Baddeley and Hitch (1974) thought that there must be an overall controlling mechanism that they called a "central executive". This central executive was seen as the core of the working memory system and was thought to embody much of the attentional mechanism. The central executive is served by other systems designed to do specific tasks. These include the articulatory loop and the visuo-spatial sketch pad.

As the central executive is perceived as central to the working memory model, it may have seemed odd not to have discussed this component earlier. However, theories of working memory have paid scant attention to this component and, until relatively recently, have chosen not even to

speculate on the characteristics of the central executive. Nevertheless, Baddeley has begun to develop his own view on the nature of the central executive. He has described two approaches in formulating ideas on the nature of the executive in his book "Working memory" (1986).

The first approach was to postulate that any process that was part of working memory but was outside particular "slave" systems, must fall within the realms of the executive. However, as the boundaries of the slave systems are not clearly defined, and as we do not know how many slave systems are yet to be discovered, this approach does not provide any clear idea of the nature of the central executive.

The second approach was to look at the executive as a type of supervisor or scheduler for the working memory system, which would relate directly to the control of attention. With this approach in mind, Baddeley turned to the literature on attention, hoping to be able to integrate concepts of memory and attention. Unfortunately, he found that many models of attention concentrated entirely on aspects of perception, and not on aspects of planning or scheduling of tasks. One model that Baddeley did find useful was the Norman and Shallice (1980) model of attention to action. A component of the model is the supervisory attentional system, with a limited capacity, that could be used in tasks that involve planning or decision-making, or where novel or poorly learned sequences

of acts were involved. The other major component of the Norman and Shallice model is the concept of a large selection of semi-automatic series of actions (schemata), that would be triggered into action on the presentation of particular stimuli. An example, of a well-learned and complex schemata is that associated with the skill of walking.

In Baddeley's view, such a model can account for much of the experimental data attributed to the central executive in working memory tasks. The model can be illustrated by its application to experiments using dual task paradigms. When the primary tasks includes tasks of reasoning, learning or comprehension and the secondary task is a span task, the effects are not as dramatic as expected. It could be postulated that part(s) of the primary tasks are already part of schemata, and hence not affected by the competition with the span task for the limited capacity supervisory system.

The model may also be of value in interpreting data from applied fields of neuropsychology and aging. For example, older adults appear reasonably unimpaired on standard measures of short term memory, but have problems when completing more complex tasks, manipulating and/or time-sharing between information, for example, in dichotic listening tasks (Broadbent and Gregory, 1965). Hence, applying the Norman and Shallice model to conceptualise the

central executive, these types of results could be viewed as deficits of the central executive.

In summary, the working memory model can be divided into a number of components, two of which are the verbal and visuo-spatial short term stores. There is a controlling mechanism, or central executive, that may be similar to that of the supervisory attentional system of the Norman and Shallice (1980) model of action.

By following the developments in the memory literature with regard to short-term memory, the point is now reached where there is at least some tentative integration of memory and attentional components of cognition. However, the complex model of Norman and Shallice does not provide paradigms for measuring attentional capacity, nor provide ways of investigating the effects of task complexity. To do this, it is necessary to study some of the literature on attention.

#### 6.26 Models of Attention

Attention has often been regarded as synonymous with consciousness and/or concentration. It is generally considered to be a mechanism by which a individual can select a portion of appropriate information. The information can be selected for various reasons, including relevance and also novelty to the individual.

Research on attention has provided the distinction between focused and divided attention. The research on

focused attention has concentrated on the selection mechanisms of attention, what information is attended to and what happens to the unattended information. Divided attention research has been primarily concerned with performance limitations, i.e. the processing limitations and the capacity of attentional systems.

Attention can thus be investigated at different levels, at a perceptual level or at a more cognitive level. Wickens (1980) compared two useful metaphors that capture the essence of this distinction. The first metaphor described attention as a type of searchlight (Wachtel, 1967). Thus, in focused attention this searchlight focuses on that topic on which one is momentarily concentrating. The second metaphor for attention is as a resource (Norman and Bobrow, 1975), which emphasises attention as having a certain capacity which can be used on one or more tasks and can therefore be divided. Hence, in divided attention tasks attention as a resource is investigated.

The literature considering attention as a resource provides a useful framework in considering the effects of ACDs for four reasons :

1. Provides a framework for measuring attentional capacity.
2. Provides ways of linking memory and attention together (as in the Norman and Shallice model).

3. Attempts to clarify issues surrounding task difficulty.

4. Provides methodologies, most notably dual-task paradigms and a discussion of the costs and benefits of these methodologies.

Perceiving attention as a resource has its origins in the theorising of researchers such as Moray (1967), who proposed that attention was similar to a general purpose computer, in that it had a limited processing capacity. Tasks differing in difficulty would make differing demands on this capacity. Hence, as the difficulty in one task increases, the capacity to maintain performance on another task decreases. Kahneman (1973) developed this view-point, in particular, he viewed attention as a flexible, shared processing resource with limited availability. Kahneman also proposed that physiological correlates, for example heart rate, could be suitable indices of resource mobilization. Two key elements in Kahneman's (1973) theorising were :

"the allocation policy and the evaluation of demands on the limited capacity. The evaluation of demands is the governor system that causes capacity (or effort) to be supplied as needed by the activities that the allocation policy has selected."P11

This type of theorising is similar to that of Norman and Shallice's Supervisory Attentional System, and consequently to the central executive of working memory.

The concept of resource is often translated experimentally in terms of "difficulty", with the rationale that more difficult tasks require greater amounts of resources. However, there are many examples of tasks interfering primarily via structure i.e. by the stages, codes or modalities of processing required, rather than by difficulty per se. Wickens (1976) found that performance on a manual tracking task was more impaired by a concurrent task requiring subjects to maintain constant pressure on a stick, than by an auditory signal detection task that the subjects perceived as being the more difficult secondary task. As well as this type of data, there is evidence for structural effects in the phenomena of task "difficulty insensitivity", in which secondary tasks interfere with some primary tasks but fail to do so with others.

Kahneman's (1973) theory had accounted for this type of data by proposing that although there was one undifferentiated pool of resources, there were also "satellite" structures, for example, ears, hands, or voice, that produced structural interference.

Two elements of this type of single resource theorising have been challenged by a number of researchers including Allport (1980). The first area of contention is that instead of one resource pool of attention there may be

several distinct pools, of which different tasks make differing demands on these pools. The second and related area is the necessity of conceptualising an overall governor or controller system. In Allport's view, the experimental data supports the requirement for several distinct resources, and Allport is not convinced that the behavioural data demands the necessity for an overall controlling mechanism. An alternative and influential way of accounting for the data is that of multiple resource theories according to Allport (1980). These theories argue that instead of one pool of undifferentiated resources, there are several with different capacities and uses. This framework had been argued very strongly by Navon and Gopher (1979), using performance operating characteristics (POCs) to describe dual-task performance data.

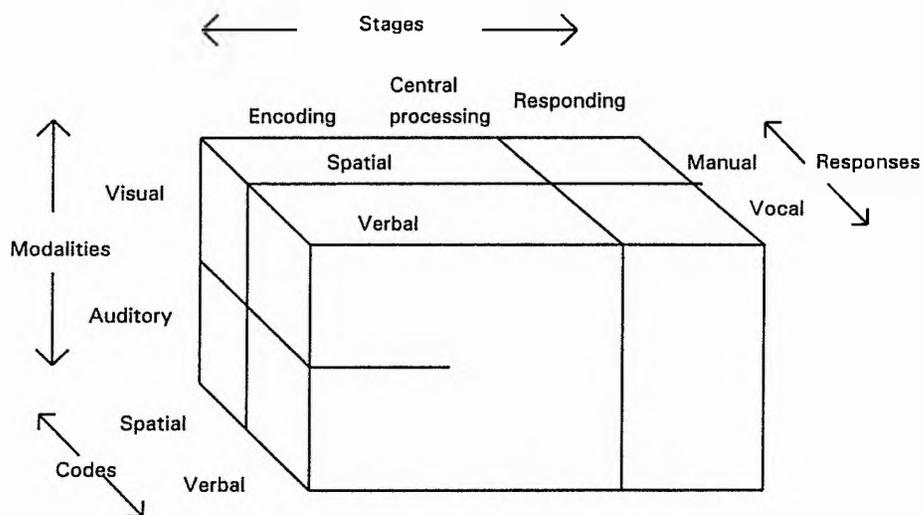


Figure 6a: The proposed structure of processing resources by C. D. Wickens (1980)

What are these different resources and how are they related? Not all the issues concerning attentional resources are resolved, but Wickens (1980) on consideration of a large portion of the literature produced a useful diagrammatic representation of the different groups of resources along three dimensions, as shown in figure 6a. Any particular task could demand different resources along any of the three dimensions of stages, modalities or processing codes.

With regard to stages, the evidence cited by Wickens (1980) pointed to different resource pools, one for perceptual and central-processing aspects of a task and another for response selection and execution of a task. Hence, secondary tasks affecting only perceptual or central-processing of a primary task will have little effect on success in responding to the primary task, whereas those affecting response selection and execution of a task will have a marked effect on the primary task.

In the case of modalities, according to Wickens, there is strong evidence that it is much easier to perform concurrent cross-modal tasks that use, for example, the visual and auditory modalities, than to perform concurrent tasks that use the same modality.

Finally, when considering processing codes, there is a large amount of evidence for separate verbal and spatial coding, examples of which were cited earlier in the

discussion of working memory. The relative ease with which tasks requiring vocal and manual responding can be performed, as opposed to concurrent tasks requiring the same type of responding, supports the view that outputs are also divided in terms of verbal and spatial codes, with vocal outputs using verbal resources and manual outputs using more spatial resources.

Performance along these dimensions has primarily been investigated using the dual-task technique. This technique has also been extensively used in the investigation of the working memory model. The basic task is for the subject to maintain adequate performance on a primary task whilst simultaneously performing a secondary task. An example from investigations into working memory is where the primary task is a verbal reasoning task and the secondary task is a verbal digit span task. As these two tasks are competing for at least some of the same resources there is a decrement in performance on the primary task when the secondary task is introduced.

Using this technique has some obvious benefits :

1. One can investigate resource capacity, by loading the secondary task, so that residual capacity is used up and the subject begins to have difficulties maintaining performance on the primary task.
2. One can investigate the effects of varying task difficulty (an area identified as interesting in the

ACD literature), by increasing the complexity of the secondary task.

3. One can investigate the nature of the attentional resources which are tapped, particularly as one secondary task can be applied across many different types of primary tasks.

There are disadvantages with the technique. A problematic area is the strategies used by the subject to perform the two tasks, particularly if the subject concentrates on the secondary task, so treating it as the primary task. When using this technique good instructions for the subject are very important.

### 6.3 Adapting techniques to the applied setting

One of the major aims of this theoretical chapter is to find ways of adapting theoretical ideas into paradigms appropriate for investigating the effects of ACDs on cognitive functioning. The following text describes in detail two paradigms that may be of value in this sphere.

Morris (1984 and 1986) noted that memory impairments are often one of the earliest signs of dementia. He was one of the first researchers to use the working memory framework and dual-task paradigms to investigate the memory impairments of individuals with mild senile dementia of an Alzheimer type (SDAT).

In his first set of studies, Morris (1984) compared a SDAT group and a matched group of elderly controls on tasks investigating performance of the articulatory loop. He found that although performance was significantly poorer for the SDAT group, the articulatory loop was functioning normally because this group showed normal word length and phonemic similarity effects indistinguishable from controls.

In a second set of studies, Morris investigated the hypothesis that the differences in performance of normal elderly and the SDAT groups were due to impairments in the central executive. The tasks employed were variations of the Brown-Peterson task. The basic procedure was as follows:

1. The subject was presented with a trigram (a set of three consonants) to be remembered for a designated interval.
2. The subject was asked to perform a secondary task during the retention interval.
3. The subject was asked to recall the three items of the trigram in the correct order.

The trigrams were presented visually by means of cards i.e a set of three consonants per card, for three seconds, and both the retention intervals and the secondary tasks were varied. The SDAT group (N=12) and the normal elderly control group (N=12) completed 96 experimental trials,

comprising six trials for each of four conditions over the four retention intervals (0, 5, 10, and 20s). The four conditions differed according to what was required of the subjects in the retention interval :

1. Unfilled retention interval :- in which the subjects were asked to concentrate solely on remembering the trigram. However, subjects were asked not to use vocal rehearsal.
2. Articulatory suppression :- in which the subject was asked to repeat aloud, at a steady rate, the word "the", for the duration of the retention interval.
3. Digit reversal :- in which the experimenter presented pairs of digits and the subject was asked to reverse the digits, for the duration of the retention interval.
4. Digit addition :- in which the experimenter presented pairs of digits which the subject was asked to sum, for the duration of the retention interval.

The number of articulations, digit reversals and additions were monitored by the experimenter. Performance was measured in terms of mean percentage of items recalled in the correct serial position for each delay period. Overall the SDAT group was clearly impaired. The differences between the groups seemed to increase with increasing task complexity and retention interval. However,

as the zero interval condition was included in these analyses, and most subjects from both groups performed at ceiling, this obscures the effects of interval delay. It is possible that the significant results were due to different performances for zero retention interval and having any retention interval, and that increasing the delay made little difference in the ratio of performance between the two groups. This view is supported by an analysis of the digit reversal and digit addition conditions which showed parallel performance for the two groups with increasing delay.

One very interesting finding was that concurrent articulation caused a significant decrement in performance when compared with the unfilled condition in the SDAT group, but not in the elderly control group. This is an important result, supporting the original hypothesis, i.e. that dementia results in a decrement in processing resources of the central executive. Normally, articulatory suppression would not take up enough of the resources to interfere very much with the primary task of remembering the trigrams. However, if the SDAT group has a depleted central executive, the simple task of articulatory suppression will consume a greater proportion of these resources and so less will be available for the primary task of remembering the trigrams.

However, another possible explanation is that the SDAT group are more prone to interference effects and the

articulations may produce abnormal interference. To discount this possibility, Morris carried out a third experiment, similar to the one just described, but with two conditions, articulatory suppression and tapping (in which the subject was asked to tap repeatedly on the testing table). The hypothesis for this experiment was that if the non-verbal tapping task produced a differential impaired performance for the SDAT group, it would be difficult to argue that such a task produced abnormal interference. The results revealed that the SDAT group, unlike the elderly controls, showed a significant decrement in performance in both the tapping and articulatory suppression conditions.

The overall conclusion from these set of experiments is that very simple distracting tasks produced substantial forgetting in the SDAT groups. These results are interpreted by Morris as evidence in support of a depleted central executive. However, the interpretation is derived by a process of elimination. As the articulatory loop is thought to be functioning normally and it would be difficult to explain the results in terms of structural interference, therefore it must be a central executive deficit. The studies do not attempt to investigate the central executive per Se, which may be due to difficulties in investigating a concept that is still rather vague.

The executive is generally conceived of as a controlling and scheduling device for distributing resources, and therefore tasks requiring scheduling and

changing direction of resources would presumably require a large amount of central executive functioning.

Weber, Burt, and Noll (1986) devised a task that required switching of resources between memory and perceptual attention. This type of switching might be required in a task such as reading and could be described as a task requiring extensive use of the central executive. Weber et al, devised a paradigm that allowed measurement of the switching time between perception and memory. The subjects for the study were 14 undergraduates who followed the following basic procedure of four experimental conditions.

1. Three consonants were presented visually and immediately recalled on clearing the screen (time to recall consonants was measured).
2. The subject was asked to read aloud as quickly as possible three consonants as they appeared on the screen (time to read consonants was measured).
3. Two sets of consonants are presented, first a set to be remembered, followed by a perceptual set (as in condition 2). The subject said the first of the perceptual consonants followed by the first of the memory items, followed by the second of the perceptual consonants etc. Hence, the subject recalled six consonants alternating between perception and memory and the total time to recall the six items was measured.

4. Sets of six consonants were presented to be either read aloud or recalled immediately.

The study followed this basic design, producing times for components of perception, memory recall and switching from perception and memory. The number of items presented was also increased, hence more resources were required for the perceptual and memory aspects of the tasks and less was available for the switching task so, producing significant increases in the switching times.

Weber et al (1986) interpreted the results as revealing a depletion in central executive resources, such that as the list length increased, the memory and perceptual aspects of the task required more resources, leaving less resources in the central executive, resulting in slower switching times.

Both the Morris (1984 and 1986) studies and the Weber et al, 1986 study are examples of ways of investigating resources using the theoretical framework of working memory. They have been described in detail as they provide tasks that will be incorporated into the test battery designed for the Glasgow study described in the next chapter.

#### 6.4 Summary

This chapter has endeavoured to integrate the results and interpretations found in the ACD literature, with aspects of theorising and research into cognition. The ACD literature indicated those areas of cognitive psychology research on which to focus. The cognitive psychology literature provided theoretical frameworks for understanding cognition, paradigms for investigating sub-components of cognition, and high-lighted some of the inherent problems in transferring some of this work to the applied setting.

Interweaving these two lines of research has led to the identification of working memory and attentional resource theory, as appropriate avenues to form the theoretical under-pinning of batteries of tests to investigate the effects of ACDs on cognitive functioning. It has also high-lighted the usefulness of dual-task paradigms as a possible methodology for investigating this area.

A battery of tests based on the contents of both this chapter and chapters two and three is described in chapter seven. The results obtained in this study are described in chapter eight.

## CHAPTER SEVEN

### STUDY TWO : MEASURING COGNITIVE FUNCTIONING USING A NEW TEST BATTERY

#### 7.1 : Aims of chapter

The aims of this chapter are two-fold. Firstly, the rationale for a new battery of tests based on the theorising in chapter six will be explained. Secondly, the methodology of how this battery of tests was employed to investigate the effects of anticonvulsant drugs on cognitive functioning will be described.

The second of these aims can be further elaborated :

1. To use psychometric tests based on a theoretical framework, to identify the nature of the cognitive impairments of persons taking anticonvulsant medication.

2. To design a study that, although primarily a between-groups design, could also incorporate within-subject comparisons, made possible when some of the subjects changed medication for clinical reasons.

3. To use a computerised battery of tests so that

- a) tasks requiring accurate and rapid timing could be included,
- b) a larger amount of data could be collected than in the more conventional "pen and paper" tests, and,
- c) possible experimenter bias would be minimised.

4. To follow up the work already begun in this area at the Glasgow Western Infirmary.

## 7.2 Introduction

The study was carried out at the Glasgow Western Infirmary, and involved 92 subjects with epilepsy and ten control subjects. Suitable clinical subjects were identified by consultant pharmacologist Dr.M.J.Brodie. They were divided into four groups on the basis of their medication. A battery of tests was administered to the five groups of subjects (including one control group). Whenever possible, the subjects completed the battery of tests on three occasions, and any changes in medication or seizure frequency were monitored. Therefore, a mixture of between-group and within-group comparisons were carried out.

The facilities at the Western Infirmary were such that there was good serum level monitoring of the anticonvulsant medications of subjects involved in the study. There was also access to relevant medical information, including details of EEG reports and computerised tomography (CT) scans. BBC microcomputers were available for administering tasks and collecting data.

### 7.21 Hypotheses

The hypotheses being investigated in this study were based on the information presented in chapters two, three and six. They were as follows :

1. Subjects with epilepsy would be significantly impaired on the test battery compared to the control

group. This hypothesis is supported by the information presented in chapter two and also by the work of Brodie et al., (1987) which had been carried out at the Western Infirmary.

2. Within the clinical subject population, the subjects on anticonvulsant medication would be more impaired than untreated subjects with epilepsy. This hypothesis is supported by the information presented in chapter three, which described the detrimental effects of anticonvulsant medication on cognitive functioning.

3. Within the subject groups on monotherapy, those on the drug DPH would show most impaired performance, particularly in comparison to those on CBZ and VPA. This hypothesis is supported by the work of Thompson and Trimble (1981, '82 and '83) which showed that the number of impairments associated with CBZ and VPA to be far fewer than with DPH.

4. From the discussion presented in chapter six, it is hypothesized that the impairments of performance will best be interpreted in terms of a depletion in cognitive resources and working memory. Hence, it is predicted that the pattern of impairments will be generalized across different resources and modalities, and will be greater when task complexity increases. Hence, performance will decline in proportion to test condition difficulty. Also, on the dual-task memory

tests it is predicted that different secondary tasks will impair the performance of the primary tasks to different degrees, as a function of the type of primary task (verbal, spatial or visual) as proposed by the working memory model.

### 7.3 Subjects

#### 7.31 Criteria for subject inclusion.

The criteria for subject inclusion was the same as in study one (chapter four), with regard to age of subjects (16 to 55 years), lack of gross brain pathology and/or neurosurgery, no other medication apart from anticonvulsants, medication in the optimum therapeutic range, and no evidence of psychiatric symptomatology.

Additional criteria were that the subjects should have an abnormal EEG but a normal CT scan.

The subjects with epilepsy were either taking CBZ, VPA, DPH or were not on any medication for their epilepsy (i.e. an untreated group, UT). The control (CTL) group were persons either known to the clinical subjects or persons working in the hospital, matched for age and numbers of males and females in the groups.

Consent for the subjects to participate in the study was obtained by Dr.M.J.Brodie.

The matching of subjects with epilepsy on features of their epileptic condition followed the same protocol as in

chapter four, with regards to types and frequency of seizures, age at onset and duration of their epilepsy.

### 7.32 Subjects identified

Possible subjects were identified by Dr. M.J. Brodie. Forms containing details about each subject's epilepsy were already in use at the clinic and provided relevant information on the variables of age, type of epilepsy, frequency of seizures, family history of epilepsy, presence of neurological damage (as seen on a CT scan) and EEG data. This information was employed in the screening of subjects to match groups.

Control subjects who neither took anticonvulsant medication nor had epilepsy were identified amongst the hospital staff and volunteers (friends and relatives of subjects with epilepsy).

Hence, five experimental groups were identified :-

1. Subjects with epilepsy taking CBZ monotherapy.
2. Subjects with epilepsy taking VPA monotherapy.
3. Subjects with epilepsy taking DPH monotherapy.
4. Subjects with epilepsy taking no anticonvulsants  
(untreated group, UT)
5. Control group of subjects (CTL)

-----  
Table 7a : Details of subject groups for study 2

Drug Group	No. of subjects	No. of subj. post screen	Age (mean/SD)	Sex (M/F)
CBZ	28	21	25.2 (5.37)	8 / 14
VPA	17	16	27.4 (10.48)	4 / 12
DPH	20	15	34.3 (10.91)	11 / 5
UT	28	22	22.6 (5.24)	8 / 14
CTL	11	10	27.2 (4.10)	5 / 5
TOTAL	102	84		

-----

The original sample of 102 subjects consisted of 91 subjects with epilepsy and 11 control subjects. However, for the between-group analyses, the data for 20 of the subjects were excluded for the following reasons :

- i. Abnormal CT scan or other indication of brain damage (N=11).
- ii. Normal EEG in the case of subjects with epilepsy (N=5).
- iii. Incomplete data (N=3), of whom one was a control subject.
- iv. On medications other than anticonvulsants (N=1).

Two subjects are represented twice in the analyses because they were included in the medicated and non-medicated groups. This arose because they actually began taking medication during the period of testing.

Hence, the final numbers of subjects in the epilepsy data sets were 74 and in the control data sets were 10. The subjects with epilepsy were made up of 52 subjects taking anticonvulsant medication and 22 not taking any anticonvulsant medication, the latter group being designated the untreated epileptic group (UT). Of those 52 subjects on medication, 21 were taking CBZ, 16 were taking VPA and 15 were taking DPH.

Table 7a table provides a summary of the details of the subjects included in the final analysis. The mean age of four of the subject groups was within five years of each other i.e from 22.6 to 27.4 years, but the mean age of the DPH group was somewhat older (34.3 years). The DPH

group was also different to the other groups in the numbers of male and female subjects in the group. This group had double the number of men in the group compared to female subjects, a ratio of eleven to five, whereas the other groups had either similar numbers of male and female subjects or had more female subjects in the groups.

The clinical data for each of the groups will be described in the results chapter under the heading of clinical data.

#### 7.4 Rationale for tests used in the test battery

The test battery was based largely on the theoretical framework of working memory and resource theory as described in chapter six and to a lesser degree was based on tests similar to those used in other studies, for example, by Thompson and Trimble (1981). The amount of testing was agreed with Dr.M.J.Brodie as being at a level that would not be too taxing for his patients.

A battery of tests incorporating dual-task paradigms was designed to investigate aspects of working memory and resource theory. Thus, the test battery included psychometric tests of intellectual abilities and mood, tests of motor skill of increasing complexity, and tests of verbal, visual and visuo-spatial working memory, which also increased in difficulty. These memory tests were specifically intended to test the "resource depletion" hypothesis. Tests of rapid decision making and attention-

switching were included to investigate the "central executive" in the working memory model.

The detailed rationale for each of the tests is described in this section, whereas the procedure for administering the tests is described in section 7.6

#### 7.41 Wechsler Adult Intelligence Scale-Revised (WAIS-R) Wechsler (1981).

The Vocabulary and the Picture Completion sub-components of the WAIS-R were administered based on the same rationale as in chapter four.

#### 7.42 Multiple Affect Adjective Check-list (MAACL), Zuckerman and Lubin (1965).

The aim of including this questionnaire was to ensure that the groups of subjects were matched on various aspects of their mood. The MAACL is quick to administer, requiring the subject to consider their mood at that particular time, and specifically measures levels of anxiety, depression and hostility. The MAACL has been used both for evaluation and research (Sweetland and Keyser, 1983).

#### 7.43 Motor tasks.

Two tapping tasks were included in the battery of tests. Both were based on tasks used by other researchers in the area, for example, Brodie et al (1986). The reasons for including such tasks have been discussed by Hindmarch (1980):

"The rate of finger tapping is one of the simplest of human motor activities and has been widely used to measure drug changes in motor performance."P196

#### 7.44 Reaction time tasks

A simple reaction time task was employed to provide a measure of subject performance on a perceptual input and motor output task, following the theoretical framework as described by Wickens (1980). This simple task did not require the memory or decision-making components of a working memory system. However, the task was made more complex by combining the simple reaction time task with the motor tapping task, so investigating the effects of task complexity on subject performance. As perceptual and motor performance are often part of memory and attention based tasks, the simple reaction time and motor tasks can separate out these different aspects of subject performance.

#### 7.45 Digit Span

The Digit Span task, presented and recalled auditorily, is a reliable measure of the articulatory loop system in the working memory model. The inclusion of the digit span in the WAIS-R battery means that normative data is available for this test.

#### 7.46 Memory tasks : Verbal, visual and spatial tasks

Three types of working memory tasks were included to explore the performance of subjects using different parts of the working memory system. All three tasks had a primary memory task and secondary tasks that were either verbal, visual or motor in nature.

The verbal memory task was based on the Brown-Peterson task, as adapted by Morris (1984). The visual task was based, in part, on the Revised Benton Visual Retention task (1963) and involved recalling complex shapes as described in chapter four.

The spatial task was designed by the author, as suitable, easy to use, spatial tasks investigating the working memory model were unavailable in the literature. The work of Logie (1986) only came to the attention of the author, after the design of the task included in this battery of tests. The author wished to include a measure of spatial memory that fulfilled the following requirements :

- a. A task that measured memory for spatial location, but did not involve skilled performance that would make extensive use of the "central executive", as based on the literature discussed in chapter six.
- b. A task that was quick to administer within a test battery. Hence, instructions should be easy to follow and carry out.
- c. A task that could be combined with the same secondary tasks as used with the verbal and visual memory tasks.

Given these requirements, the type of tasks used by Brookes (1967), for example, matrices of numbers in different locations, and the tasks developed by Baddeley and Lieberman (1980) involving tracking, did not fulfil these criteria. These tasks were difficult to do, involving complicated procedures and a level of skilled performance.

The scoring on all three memory tasks gave a minimum score of zero and a maximum of six on each condition. The exact nature of the scoring on the spatial task was based on the performances of five pilot subjects on the test.

#### 7.47 Category-Decision task

This task as employed by Thompson and Trimble (1981, '82 and '83) was particularly sensitive in detecting differences between subjects on different anticonvulsant drugs. The task is a time-based measure requiring the subject to respond rapidly to a question concerning the colour or category of an object presented visually. The task requires rapid decision-making and could thus be seen as a "central executive" task in the working memory framework. The task also increases in complexity, hence testing the effects of task complexity on subject performance.

The task is computerised, and therefore, differs from the category-decision task in chapter four.

#### 7.48 Attention-switching task

This task was adapted from that used by Weber et al (1986) and involves the subject switching from a primarily perceptual task to a memory task. Hence, the switching of resources between the two tasks could be seen as requiring extensive use of the "central executive" in the working memory model.

This group of tests was administered in the study using the following procedure:

#### 7.5 Protocol for study two

The tests were completed by all the subjects and are summarised as follows :

1. WAIS Vocabulary and Picture Completion tasks.
2. MAACL.
3. Finger tapping tasks.
4. Simple reaction time (SRT) with three conditions.
5. Short term memory span (Digit Span).
6. Trigram memory task.
7. Visual memory task.
8. Spatial memory task.
9. Category-Decision task.
10. Attention-Switching task.

This protocol was completed (where possible) by each of the subjects on one or more occasions at intervals of approximately eight weeks.

In order to minimize the effects of fatigue on tasks completed at the end of the testing session, the order of presentation of the tasks was varied and balanced across the groups, with equal numbers of subjects completing the tests in the following orders :

Order one : 1, 5, 9, 10, 3, 4, 6, 2, 7, 8.

Order two : 1, 5, 9, 10, 3, 4, 7, 2, 8, 6.

Order three : 1, 5, 3, 4, 9, 10, 8, 2, 6, 7.

Order four : 1, 5, 6, 7, 9, 10, 2, 8, 3, 4.

Order five : 1, 5, 7, 8, 2, 6, 3, 4, 9, 10.

Order six : 1, 5, 8, 6, 2, 7, 3, 4, 9, 10.

The subjects also completed the MAACL and were asked when they had had their last seizure and the nature of that seizure. After completing the whole battery, those subjects taking medication provided 20ml blood samples which were subsequently analysed for blood serum levels of anticonvulsants.

## 7.6 Procedure for study two

### 7.61 WAIS sub-components

This test was administered as in study one (chapter four) following instructions in the WAIS-R manual.

### 7.62 Multiple Affect Adjective Check-list (MAACL).

Each subject was presented with a list of 132 adjectives describing mood and feelings. The subject was asked to read the lists of words quickly and to place a cross (X) in the boxes next to all those words that described his/her mood and feelings at that time or, if appropriate, on that day. The subject was asked to identify all the appropriate words, even though some of them may seem very similar. The questionnaire was subsequently marked giving scores on three scales for anxiety, depression and hostility.

### 7.63 Motor task.

This task was divided into two parts.

a) The subject was asked to tap using the index finger of his/her hand (the hand was specified by the experimenter) on a response key for a period of 60s. The subject tapped as quickly as possible for the whole period and was asked not to stop tapping, once started.

b) The subject was asked to tap on two response keys alternately. The response keys were placed 17.5cm apart. Again the subjects only used one finger of the specified

hand and continued tapping as quickly as possible for the 60s.

The hand specification was balanced across the groups. The number of taps and the inter-tap interval were recorded on the BBC microcomputer.

#### 7.64 Simple reaction time (SRT)

This task was divided into three conditions. In all three conditions, the primary task remained the same i.e. the subject was asked to press the space-bar on the microcomputer as soon as he/she saw an orange light (cursor) appear in the middle of the blank screen. The light disappeared when the space bar was pressed. Before the cursor appeared it was preceded by a warning signal (a bleep produced by the microcomputer) and the bleep-cursor interval was varied (0.5 to 2.0s). The subject completed 10 practice trials and 20 experimental trials. The microcomputer recorded the response times to the onset of the light i.e. the time from when the cursor appeared to when the subject pressed the space bar.

Each of the three conditions had a different secondary task to be carried out by the subject, using their other hand, whilst simultaneously responding to the light:

- i) No distractor condition (Trials = 20)
- ii) The distractor task was the single key tapping task as carried out in section 7.63(a) (Trials = 20).

iii) The distractor task in this condition was the alternate key tapping task as carried out in section 7.63(b) (Trials = 20)

In all three conditions there were practice conditions to ensure that the subjects understood the tasks.

#### 7.65 Digit Span task

Both forward and backward digit spans were measured using the ascending staircase method. The procedure and lists of digits followed the WAIS-R Digit Span test.

#### 7.66 Trigram task

In this task there were five conditions. In all conditions, the primary task remained the same. This consisted of the subjects being presented with sets of three randomly generated consonants (trigrams) for five seconds, via the BBC microcomputer screen.

The subject was then told to wait for a ten seconds interval and after ten seconds the subject was asked to verbally recall the letters. The experimenter typed in the subject's responses. In each of the five conditions the subject was presented with two practice trials and six experimental trials.

The secondary (distractor) tasks were presented in the ten second waiting intervals. The five conditions were as follows :

- i) There was no secondary task, so the subject could concentrate solely on recall of the trigram,

although the subject was not allowed to verbally rehearse the trigram; however, covert rehearsal could still be taking place.

ii) The subject was asked to carry out articulatory suppression, i.e. the subject was asked to repeat aloud the word "the" during the ten second waiting interval, at a steady rate of approximately two articulations per second. The experimenter demonstrated the method of articulation before the subject commenced the practice trials. The subject began each period of articulation by saying aloud the word "the" at the beginning of each ten second interval. The number of articulations were counted by the experimenter pressing the space bar as the subject articulated the word "the". Hence, the number of articulations were recorded on the computer.

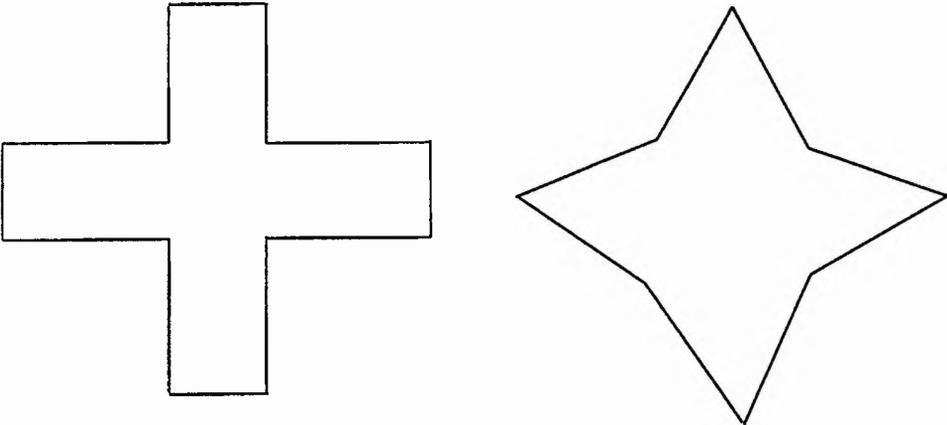


Figure 7a: Two examples of visual distractor shapes.

iii) The subject was asked to count backwards in multiples of threes beginning at 101 during the ten second waiting interval. Before commencing the practice trials, the experimenter demonstrated the method of counting backwards. The experimenter also said the first number, i.e. the last number from the previous trial, from which to start the counting at the beginning of each ten second interval.

iv) The subject was asked to copy on to paper some simple shapes that appeared on the screen during the ten second interval. Two of the shapes presented are shown opposite in figure 7a. The subject was told to continue drawing for the whole ten second interval, but that it was not necessary to finish all the shapes in the ten second interval. The same distracting tasks were presented in all the experimental trials.

v) The distracting task in this condition was a tapping task, in which the subject was asked to tap alternately on two response keys at a steady rate of approximately two taps per second, using the index finger of his/her preferred hand. The experimenter demonstrated the tapping rate before the subject commenced the practice trials.

The subject had to recall the trigrams perfectly before the experimenter scored a "1" on the computer, otherwise the subject scored a "0".

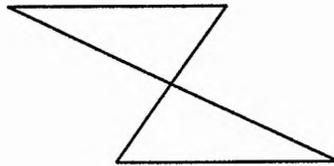


Figure 7b: An example of a primary task item in the visual task.

### 7.67 Visual task

The visual task was similar to the trigram task in its method of presentation. The primary task was always presented via the computer screen. It consisted of an abstract shape being presented on the screen for five seconds. There was then a ten second waiting period, after which the subject was asked to draw the shape from recall. There was a selection of eighteen types of shape, each of which could be shown at four different angles. Hence, there were 72 possible stimuli. The types of shapes that could be presented in any set of six trials were balanced such that the six shapes in any set of trials were different (not just the same shape seen from a different angle), and were regulated in the number of lines contained in the shapes. An example of the type of shapes presented is shown opposite in figure 7b. There were two practice trials and six experimental trials in each of the conditions. In this task there were four conditions, which varied in the nature of the secondary (distracting) task. The subject was always asked to concentrate on recalling the shape presented in the primary task. The four conditions were as follows :

- i) There was no secondary task and hence the subject was able to concentrate on recalling the primary shape after the ten second interval.
- ii) The subject was presented with distracting shapes in the ten second interval as in the trigram task (section 7.66, condition iv). Again, the subject was asked to copy the presented distractor

shapes for ten seconds, and after this interval to try to draw the primary task shape.

iii) In this condition, the secondary task was the articulation of the word "the", (see section 7.66, condition ii).

iv) In this condition, the secondary task was the tapping task (see section 6.66, condition v).

The primary shapes were scored by the experimenter. The shape had to be accurately recalled in order to be scored as correct, although the size of the shape was not of importance. The number of distractor shapes drawn in condition (b) was recorded by the experimenter, whereas the number of articulations and the taps were recorded by the computer.

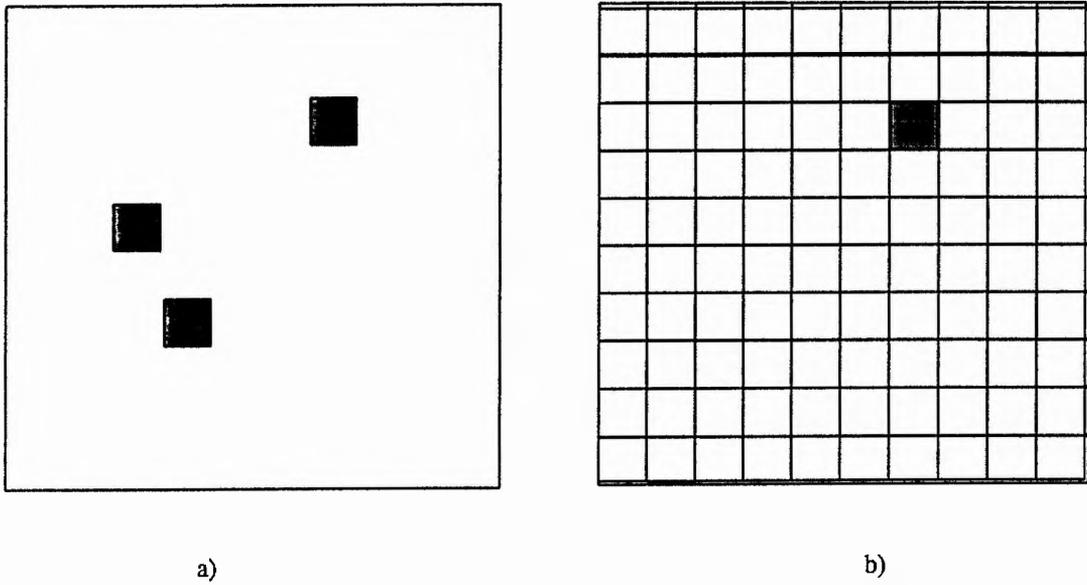


Figure 7c: Example of the spatial task, a) on presentation, and b) on recall.

### 7.68 Spatial task

This task was also similar to the trigram task. The primary task consisted of a large white square, 15cm by 15cm, being presented on the computer screen for five seconds. On each trial, somewhere within the large white square appeared three small, 1.5cm by 1.5cm, red squares for the five seconds period. During the presentation period, the subject was asked to concentrate on the position of the red squares. An example of the type of stimulus is presented opposite in figure 7c. After the post stimulus presentation waiting interval of ten seconds, a 15cm by 15cm width grid appeared on the screen containing one of the previously presented red squares. The subject was asked to point to the position of the two missing red squares. After the subject had pointed to two squares on the grid, the experimenter pressed the space bar, upon which the screen showed the correct position of the missing stimuli squares by filling two squares of the grid in yellow. If the subject had correctly pointed to the position of the missing squares, the subject received one point for each of the correct squares. Hence, the maximum score was two points, which was scored by the experimenter. If, however, the subject pointed to one of the adjacent squares to the correct one he/she received a score of 0.5 instead of one and if the subject pointed at other squares he/she received zero. Hence, the minimum score is zero and the maximum score was twelve, which was subsequently divided by two, to provide a score out of six. Again, there were two practice trials and six

experimental trials. The four conditions were as follows

:

i) There was no distractor, and so the subject could concentrate on recalling the locations of the red squares.

ii) The secondary task was the tapping task (as in section 7.66, condition v).

iii) The secondary task was concurrent articulation (as in section 7.66, condition ii).

iv) The secondary task was the drawing of shapes (as in section 7.66, condition iv).

The performance on the secondary tasks was recorded as in trigram task (see section 7.66).

#### 7.69a Category-Decision task.

The stimuli for this task were chosen from a selection of 43 digitized images presented via the computer screen. The list of images is presented in appendix two. The stimuli were the same objects that were used in the "pen and paper" version of this task, used in the Dundee study and described in chapter four. The images on the screen could be presented coloured red or green, and categorized as animate or inanimate.

There were three conditions in this task and 20 experimental trials for each of the conditions :

i) The subject was asked to respond to the colour of the object on the image, which was either "red" or "green". In this condition, one of the response keys was labelled "red" and the other was labelled "green". The

subject saw the prompt word "colour" on the computer screen, followed by either a red or green object.

ii) The subject was asked to respond to whether the image presented was either "animate" or "inanimate". The prompt word for this condition was the word "animate", and again the keys were labelled appropriately.

iii) The subject was randomly asked about the colour of the object or whether the object was "animate", with presentation of appropriate prompt words. The number of "colour" questions and "animate" questions was equal, i.e. ten trials of each.

In each condition, a word acting as a prompt for the appropriate response, i.e. what colour or whether animate or not, was flashed on the screen for 500ms, followed 500ms later by the image. The subject was asked to make the appropriate response by pressing one of the response keys as quickly as possible. Each of the keys was labelled using cards stating green, red, animate, inanimate and green/inanimate and red/animate depending on the condition of the task. The response time, i.e. the time between the appearance of the image on the screen and the subject responding on the key, was recorded by the computer. The subject was allowed to place his/her index fingers on the left and right response keys and these keys were labelled clearly for appropriate responding in each of the conditions. Both the order of presentation of the conditions and the responses assigned to the two response keys were balanced across the groups. For conditions (i) and (ii) there were three practice

trials and for condition (iii) there were five practice trials. All practice trials were completed before the experimental trials began. If a subject appeared not to understand the nature of the task, further practice trials and explanations were given by the experimenter.

#### 7.69b Attention-Switching task

The stimulus materials for this task were trigrams of letters as used in the trigram task (see section 7.66). There were three conditions, each containing two practice trials and ten experimental trials. If, however, the subject did not appear to understand the task, he/she was given extra explanations and practice trials by the experimenter. After the subject recalled the trigrams, the experimenter immediately pressed the space bar on the computer, and the response time, i.e. the time from presentation of appropriate response cue to the pressing on the space bar was recorded on the computer. Errors in recall were monitored by the experimenter, and the subject had to recall all letters in the correct order before being scored as correct. The three conditions were as follows :

- i) A trigram appeared on the screen. The subject was asked to read the trigram as soon as it appeared on the screen. After the subject had read the trigram, the experimenter pressed the space-bar (a reading task).
- ii) The subject was presented with a trigram on the screen for four seconds. After another four

second waiting interval an asterisk appeared on the screen. On seeing the asterisk (\*), the subject was asked to recall the trigram as quickly as possible (a working memory task). After recall, the experimenter immediately pressed the space-bar and another trigram appeared.

iii) A trigram to be memorised was presented on the screen for four second as in condition (i). After four seconds, another different trigram was presented on the screen. When this second trigram appeared, the subject was asked to recall as quickly as possible the first letter of the memorised trigram, and then to say the first letter of the one on the screen. He/she then recalled the second letter of the memorised trigram followed by the second letter on the screen etc. When the subject had said all six letters the experimenter pressed the space-bar.

When all the tasks had been completed, those subjects taking anticonvulsant medication were asked to provide a 20ml blood sample.

CHAPTER EIGHTGLASGOW STUDY : RESULTS8.1 Introduction

Subjects completed the test battery after attending the epilepsy clinic. The test battery was completed by 102 subjects, of whom 31 completed the test battery on one occasion, 35 on two occasions, 34 on three occasions and 2 subjects on four occasions. The sum total of completed test sessions was 211. Most of the analyses of these data were carried out on the results from the session one data.

The repeated testing of some subjects allowed for within-subjects analyses, to investigate performance across sessions. This was carried out on a small number of subjects who had had changes in their medication between the testing sessions, and also it was used to investigate the effects of recent seizures on test performance. Practice effects on the test battery were analysed using the data of subjects who completed the tests on three separate occasions.

Where possible, all subjects completed the test battery described in chapter seven which is summarised below:

1. WAIS Vocabulary and Picture Completion tasks.
2. MAACL (Mood Affect Adjective Check-list)
3. Finger tapping tasks.
4. Simple reaction time tasks.
5. Digit span.
6. Trigram memory task.
7. Visual memory task.
8. Spatial memory task.
9. Category-Decision task.
10. Attention-Switching task.

The data obtained were analysed primarily by analysis of variance (ANOVA), with a between-subjects factor of drug groups and, where appropriate, a within-subjects factor of condition and/or session (two-way ANOVA).

The main body of analysis was the comparisons across five groups (CTL N=10, UT N=22, CBZ N=21, VPA N=16 and DPH N=15). The results from these analyses will be described in detail, including post hoc analyses (using Newman Keuls and Scheffe tests) where indicated.

The Scheffé test was employed to compare the CTL group (N=10) to the group with epilepsy (N=74), and also the ACD group (N=32) to the Non-ACD group (N=52). The Scheffé test is a conservative post-hoc test, which allows for the combining of different subject groups to form new groups

and is suitable for comparisons between groups that differ greatly in size.

The data from the 71 subjects who completed the test battery on more than one occasion allowed for the following within-group comparisons (across test sessions) to be carried out :-

a. Change in level of ACD, i.e high versus low blood serum concentration of ACD (N=16 and consisted of CBZ N=9 and DPH N=7).

(Note, four subjects changed from higher to lower levels of medication, whereas twelve subjects changed from lower to higher levels of medication)

b. Presence of recently occurring seizure i.e. seizure occurring in previous two days, versus no recent seizure i.e. none in previous 14 days, (N=8)

c. Comparison of subject performance on the test battery across three sessions to identify practice effects, (N=23). These subjects had no changes in seizure frequency or medication.

Before describing the ANOVAs, the data pertaining to the clinical characteristics are described.

-----  
 Table 8.2a Summary of clinical data across four groups  
 with epilepsy

Drug	Type of Seizures			Seizure frequency			Age at onset (yrs)	Duration (yrs)
	T/C (No. of Subj.)	C/P (No. of Subj.)	C/Psg (No. of Subj.)	1	2	3	mean (SD)	mean (SD)
CBZ (N=21)	9	4	8	8	8	5	17.0 (7.8)	8.1 (7.4)
VPA (N=16)	7	2	7	5	3	8	16.8 (10.4)	10.5 (11.9)
DPH (N=15)	7	2	6	5	5	5	22.8 (15.3)	12.3 (11.6)
UT (N=22)	11	4	3	3	11	5	18.2 (6.7)	4.2 (6.0)

-----  
 Key : T/C : tonic-clonic; C/P : complex partial  
 T/Psg : complex partial, secondarily generalised

: Frequency 1 : high frequency  
 : Frequency 2 : medium frequency  
 : Frequency 3 : low frequency  
 -----

## 8.2 Clinical data

Variables assessing the degree and severity of the epileptic condition were monitored across the subject sample. The type of epilepsy, the frequency of seizures, the age of the subject at the onset of the condition and the duration of the disease are summarised for each subject in appendix five.

Table 8.2a summarises these variables for the four clinical groups (three drug groups and one untreated group).

The identified seizure type was that diagnosed by the Consultant neurologists in the medical notes. The information on the frequency of seizures was provided by the subject. There is the possibility that the seizure events described by the subject, for example "a dizzy spell" may not correspond to the single type of seizure identified using the medical notes. Hence, there is no screening of minor seizures, for example, absence seizures, in the frequency data.

Of the CBZ subjects, nine (42.8%) were diagnosed as having tonic-clonic seizures, four (19.0%) as having complex partial seizures and eight (38.1%) as having complex partial, secondarily generalised seizures. In terms of frequency of seizures, eight (38.1%) had more than three seizures in past six months, with eight subjects having more frequent seizures and five having less frequent seizures. The mean age of onset of the condition for the

CBZ group was 17.0 years with a standard deviation of 7.8 years, and the mean duration of the disease was 8.1 years with a standard deviation of 7.4 years.

The DPH subjects revealed a similar pattern in terms of types of seizures, with seven (43.8%) being diagnosed with tonic-clonic seizures, two (12.5%) with complex partial and six (37.5%) with complex partial, secondarily generalised. In terms of frequency, five subjects had a seizure frequency of greater than three in past six months, with five subjects having more frequent subjects and five having fewer seizures. The mean age at onset of epilepsy was 22.8 years with a standard deviation of 15.3 years, and the mean duration of the condition was 12.3 years with a standard deviation of 11.6 years.

The VPA group revealed seven (43.8%) subjects diagnosed with tonic-clonic seizures, two (12.5%) with complex partial seizures and seven with (43.85) complex partial, secondarily generalised. In terms of frequency, three subjects had a frequency of more than three seizures in the past six months, five had more frequent seizures than this, and 8 had fewer seizures. The mean age at onset of epilepsy was 16.8 years, with a standard deviation of 10.4, and the mean duration of the condition was 10.5 years, with a standard deviation of 11.9.

In the UT group 11 (55%) were classified as having tonic-clonic seizures, four (20%) as having complex partial seizures, three (15%) as complex partial, secondarily

generalised, one (5%) as having absence seizures and two were of uncertain type. In terms of seizure frequency, 11 had a frequency of more than three seizures in the past six months, three had had more frequent seizures than this, and five had had fewer seizures. The frequency of one subject was unknown. The mean age at onset of epilepsy was 18.2 years with a standard deviation of 6.7 years, and the mean duration of the condition was 4.17 years with a standard deviation of 6.0.

Inspection of the three drug groups revealed that most subjects had either tonic-clonic seizures or complex partial seizures, secondarily generalised. Few subjects had complex partial seizures alone. In comparison, the untreated clinical group had a greater proportion of tonic-clonic seizures and fewer complex partial, secondarily generalised.

In terms of seizure frequency, most of the drug group subjects fell in the high and medium frequency ranges, but most of the untreated group were in the medium frequency range. The age of onset was similar across the CBZ, the VPA and the UT group, but was later for the DPH group. In terms of duration, the UT group had a smaller duration of the

disease than the drug groups.

In summary, the three drug groups were reasonably well-matched on the epilepsy variables, but the UT group were somewhat different both in terms of seizure type (fewer complex partial, secondarily generalised) and a lower seizure frequency.

-----  
Table 8.2b Blood serum concentrations of anticonvulsant  
drugs for the three drug groups

Drug group	Concentration (mg/ml) Mean (SD)	No. Subjs. outside therapeutic range
CBZ (N=21)	9.3 (2.81)	3 above range 2 below range
VPA (N=16)	91.3 (36.9)	7 above range 3 below range
DPH (N=15)	25.8 (13.5)	10 above range 2 below range

-----

The blood serum concentrations of the anticonvulsant medications were monitored for the three drug groups. The individual subject drug data is presented in appendix six. The data for the three drug groups are summarised in table 8.2b. The mean concentration of CBZ for the CBZ group was 9.25 mg/ml, with a standard deviation of 2.81. Three subjects were above the optimum serum levels as designated by Davidson (1983) and two were below. The mean concentration of the VPA group was 91.3 mg/ml, with a standard deviation of 36.9. Seven subjects were above the optimum serum level and three were below. The mean concentration of the DPH group was 25.97 mg/ml, with a standard deviation of 13.5. Ten subjects were above the optimum serum level and two subjects were below this level. There were, therefore, many subjects falling above the optimum serum level of medication particularly in the VPA and the DPH groups.

### 8.3 Quantitative analyses

#### Drug groups versus untreated group versus control group comparisons

The main analyses comprised of between-groups ANOVAs across the five groups (CTL, N=10, UT, N=20, CBZ N=21, VPA N=17 and DPH N=16), with a within-subjects factor of condition. The analyses used the test data from session one.

The performance of subjects on the different tests and conditions is described to allow the reader to evaluate the pattern of performance on each of the tests.

The data from the analyses will be presented in tables which will contain the means, standard deviations, "F" ratios, degrees of freedom and level of significance for each of the individual ANOVAs.

---

 Table 8.3a Numbers of subjects in analyses
 

---

Test	Total No.	CBZ	VPA	DPH	UT	CTL
Intellectual Ability	84	21	16	15	22	10
Motor Task	84	21	16	15	22	10
Reaction time Task	84	21	16	15	22	10
Digit Span	84	21	16	15	22	10
Trigram task	84	21	16	15	22	10
Visual task	83	21	16	15	21	10
Spatial task	82	21	16	15	20	10
Distractor tasks :						
1. Articulations	84	21	16	15	22	10
2. Counting backwards	84	21	16	15	22	10
3. Shapes	83	21	16	15	21	10
4. Tapping	84	21	16	15	22	10
Category-decision task	58	20	9	8	11	10
Attention-switching task	61	20	9	11	11	10

---

### 8.31 Missing Data

Missing data points were treated in one of two ways in the analyses. If a subject did not complete a particular test, that subject's data were removed from the analysis completely. However, if a result from any individual trial was not recorded because of either experimenter error or technical reasons, the subject was given the mean score for the whole data set for that missing trial data point. The number of data points treated in this way was small, for example in the trigram task, the data of only three subjects out of a total 420 sets of data i.e. 84 subjects each completing five conditions of the tests, were treated in this way. In giving the mean trial score to missing data points, there is a small reduction in the probability of obtaining significant differences between the groups.

Unfortunately, due to an error in the computer programme for the category-decision and the attention-switching tasks, the correct response times for a large portion of data were not recorded. Hence, the data set for these two tests was reduced by approximately a third of the original data set.

The number of subjects included in each test analysis is presented in table 8.3a, showing a much reduced data set for the category-decision and attention-switching tasks. A complete data set consisted of 84 subjects.

### 8.32 Mood Affect Adjective Check-List (MAACL)

The results from the MAACL provided measures of anxiety, depression and hostility. The data from the MAACL was non-parametric and was therefore analysed using Wilcoxon signed ranks test.

The five drug groups were compared across the three mood variables. They were not significantly different on any of the three variables (all significance levels were  $P > 0.1$ ) Hence, the subjective feelings of negative mood states did not differ significantly across any of the groups, and no further analysis was carried out on this data.

Table 8.3b : Mean scaled scores for the tests of  
Intellectual ability across the five groups

Test	Subject group : Mean (S.D.)				
	CTL	UT	CBZ	VPA	DPH
Intellectual Ability (Combined score)	9.15 (1.69)	7.91 (1.98)	8.93 (1.96)	7.78 (1.94)	9.33 (2.32)
Vocabulary	9.70 (2.72)	8.27 (1.98)	9.24 (2.24)	7.81 (1.70)	9.47 (2.60)
Picture Completion	8.60 (1.80)	7.55 (2.40)	8.62 (2.59)	7.75 (2.75)	9.20 (1.72)

Table 8.3c Summary of ANOVA for the five groups on tests  
of Intellectual ability

Test	"F" ratio (Df) and significance level	
Intellectual Ability (Combined score)	F = 1.56 (Df 4/79)	P > 0.1
Vocabulary	F = 1.79 (Df 4/79)	P > 0.1
Picture Completion	F = 1.23 (Df 4/79)	P > 0.1

### 8.33 Tests of intellectual ability

Table 8.3b summarises the mean scaled scores and standard deviations across the five groups for the tests of intellectual ability. On the combined scores (mean of Vocabulary and Picture Completion), the DPH group had the highest mean (9.33), followed by the CTL group (9.15), then CBZ (8.93), the UT group (7.91) and finally the VPA group (7.78). The DPH group also had the largest standard deviation with the CTL group having the smallest.

Table 8.3c presents the "F" ratios, degree of freedom and levels of significance of the results of the three one-way ANOVAs across the five groups on the tasks of intellectual ability. There were no significant differences on these tests between the five groups. Therefore, any significant differences between groups, on further tests, should indicate specific cognitive impairments and not simply lower intellectual ability.

-----  
 Table 8.3d Mean total number of taps on motor tasks and  
mean response times on reaction time tasks for  
the five groups

Test	Subject group : Mean (S.D)				
	CTL	UT	CBZ	VPA	DPH
-----					
Motor tasks : Total No. of taps					
Condition one (no distractor)					
a) Single tapping	320.6 (37.6)	280.6 (55.7)	314.0 (64.3)	286.4 (61.3)	293.3 (40.7)
b) Double tapping	161.7 (25.6)	138.5 (36.2)	162.2 (35.6)	146.4 (30.5)	153.7 (32.0)
Condition two (with simple reaction time task)					
a) Single tapping	288.9 (66.5)	234.9 (59.1)	281.1 (59.5)	253.8 (72.8)	273.1 (52.4)
b) Double tapping	153.3 (36.1)	125.1 (37.3)	149.0 (35.6)	135.9 (29.1)	146.8 (33.0)
-----					
Reaction time tasks (in msec)					
Condition one (No tapping)	261.9 (30.6)	301.9 (61.1)	340.8 (157.1)	331.6 (81.5)	335.4 (101.6)
Condition two (Single tapping)	292.2 (44.1)	345.7 (65.7)	394.1 (203.0)	381.8 (107.0)	350.6 (90.3)
Condition three (Double tapping)	369.3 (52.0)	411.1 (81.4)	460.4 (198.3)	524.0 (324.5)	468.8 (120.1)
-----					

### 8.34 Motor tasks and Reaction Time tasks

The motor task consisted of two simple tapping tasks

- a) tapping one key for 60 seconds with the same finger and
- b) tapping two keys, alternately, for 60 seconds with the same finger.

The simple reaction time task consisted of the subject responding as quickly as possible to an orange cursor appearing on the computer screen.

The tasks were first carried out separately. The two tasks i.e reaction time task and motor tasks, were then carried out simultaneously. Dual-task methodology was used, whereby the subjects were asked to maintain their performance on the reaction time task i.e. the primary task, whilst endeavouring to carry out the tapping tasks i.e the secondary tasks. The subjects were first asked to complete the reaction time task with a secondary task of tapping on a single key with their free hand, and were then asked to carry out the reaction time task with a secondary task of tapping alternately on two keys with their free hand.

The response times in the reaction time tasks were measured in milliseconds and the tapping tasks were measured in the total number of taps recorded in 60 seconds.

Table 8.3d summarises the means and standard deviations for the tapping rates and response times across the conditions. The pattern of means across the tapping

tasks revealed higher tapping rates for the CTL group, followed in general by the CBZ group, the DPH group, the VPA group and lastly, the UT group. There was no obvious pattern in the standard deviations, with the exception of the CTL group having smaller standard deviations.

The effect of making the motor task more difficult, by introducing two keys to be pressed alternately, dramatically reduced the tapping rate compared to the original single tapping rate. The rate of tapping also slowed (by approximately 10%) when the tapping tasks were used as secondary tasks, with the reaction time tasks.

The mean response times in the reaction time task produced a consistent pattern of means in which the CTL group had the fastest response times, followed by the UT group, followed by the three drug groups. In general, the CTL group and the UT group also had smaller standard deviations compared with the three drug groups.

The effect of combining the reaction time task with the motor tasks served to slow down the reaction time tasks; for example, in the control group, the mean response time in condition one (no tapping task) was 261.9 ms, the mean response time in condition two (with single key tapping) was 292.2 ms and in condition three (with double key tapping) the response time was 369.3 ms.

-----  
 Table 8.3e Summary of ANOVAs across five groups for the  
motor and reaction time tasks

Test "F" ratio (Df) and significance level  
 -----

Motor tasks

Effect of Group	F = 2.14	(Df 4/79)	P = 0.083
Effect of Condition	F = 70.05	(Df 4/79)	P < 0.001
Effect of Keys	F = 786.00	(Df 4/79)	P < 0.001

Interactions

Group by Condition	F < 1
Group by keys	F < 1
Group by condition by keys	F < 1

-----  
 Reaction time tasks

Effect of Group	F = 1.86	(Df 4/79)	P > 0.1
Effect of Condition	F = 43.26	(Df 4/79)	P < 0.001
Interaction (Group by Condition)	F < 1		

-----

The "F" ratios, degrees of freedom and the levels of significance are presented in table 8.3e, for the two-way ANOVAs of the tapping and reaction time tasks. In both sets of analysis there was a within-subjects factor of condition as well as the between-groups factor. The analyses revealed no significant group effects, although there was a trend in the motor task ( $F(4,79) = 2.14, P = 0.083$ ). The effect of condition, i.e. the addition of the dual task, was highly significant in both motor and reaction time tasks, as was the effect of keys in the tapping task. For all these effects the level of significance was less than 0.001. These significant effects show that response times and tapping rates slowed as tasks became progressively more complex.

There were, however, no significant interactions between group and condition. Hence, increasing the task complexity did not have a larger detrimental effect on any one group's performance.

The analysis of the results for the reaction time tasks was repeated using corrected means for each subject, i.e. those individual response times that were more than three standard deviations from the mean score of the total subject sample were removed from each subject's score, and a new mean response time was computed. Analyses were also carried out using the uncorrected and corrected median scores. The same findings were obtained regardless of which particular analysis was carried out, with all "F" ratios

being more than one, but all significance levels being less than 0.1.

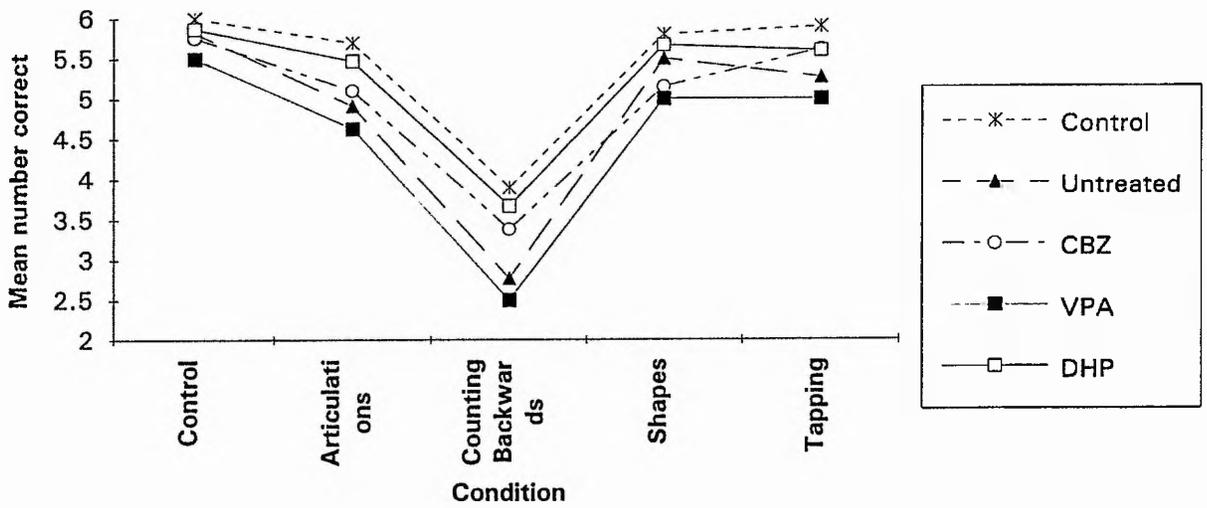
In summary, the results on these motor and perceptual tasks revealed no significant group differences, although there was a trend in the tapping tasks. There were significant effects of condition but no group by condition interactions. Hence, the lack of significant differences between the groups supports the null-hypotheses i.e. of there being no significant differences in performance between the control and clinical groups, and no significant differences between the clinical groups.

-----  
Table 8.3f Mean scaled score for digit span and mean  
score correct for trigrams for the five groups  
 -----

Test	Subject Groups : Means (S.D)				
	CTL	UT	CBZ	VPA	DPH
Digit span	12.00 (2.24)	11.87 (2.19)	11.00 (2.82)	10.98 (2.95)	10.13 (3.44)
Trigram task					
Condition one	6.00	5.82	5.76	5.50	5.87
Control	(0.00)	(0.40)	(0.44)	(0.73)	(0.35)
Condition two	5.70	4.91	5.10	4.63	5.47
Articulations	(0.48)	(1.11)	(1.34)	(1.71)	(0.99)
Condition three	3.90	2.77	3.38	2.50	3.67
Counting in "3s"	(1.45)	(1.69)	(1.56)	(1.90)	(1.88)
Condition four	5.80	5.50	5.15	5.00	5.67
Shapes	(0.42)	(0.74)	(1.06)	(1.03)	(0.49)
Condition five	5.90	5.27	5.62	5.00	5.60
Tapping	(0.32)	(0.83)	(0.67)	(1.27)	(0.51)

-----

Figure 8a: Graph of trigram data for the five groups in study two



### 8.35 Verbal Memory Tasks

The two verbal memory tasks were the digit span and the trigram task. Table 8.3f summarises the means and standard deviations for the five groups. In the digit span task the CTL group obtained a higher mean score than the other groups, followed by the UT group, the CBZ group, the VPA group, and the finally the DPH group. The UT group and the CTL groups had smaller standard deviations than the three drug groups.

In the trigram task, the CTL group once again obtained the highest mean scores, the next highest was the DPH group, followed by the CBZ group, the UT group and finally the VPA group (see figure 8a). The control group also had smaller standard deviations, but this may have been due to ceiling effects in some conditions. However, in condition three where few ceiling effects were observed, the CTL group still obtained the smallest standard deviations, followed by the CBZ group, the UT group, the DPH group and finally the VPA group.

Surveying the means across the five conditions of the trigram task, one observes that the highest mean scores were obtained with the no distractor condition, the next highest mean scores were with the tapping distractor task, followed by the drawing shapes condition, then with articulatory suppression, and the lowest mean scores were obtained with the counting distractor task; for example, in

-----  
 Table 8.3g ANOVA of digit span and trigram data for the  
five groups.

Test	"F" ratio (DF) and significance level		
Digit Span (Groups)	F =	1.80 (Df 4/79)	P > 0.1
Trigram task			
Effect of groups	F =	3.25 (Df 4/79)	P < 0.05
Effect of Condition	F =	110.01 (Df 4/316)	P < 0.001
Interaction (Group by condition)	F <	1	

-----

the CTL group the means for these five conditions were 6.0, 5.9, 5.8, 5.7 and 3.9 respectively.

The digit span task results were analysed by a one-way ANOVA, with a between-subjects factor of groups. No significant group effect was found on this analysis.

The trigram task was analysed by a two-way ANOVA, with a between-subjects factor of groups and a within subjects factor of condition. Main effects were found for groups ( $F(4,79) = 3.25, P < 0.05$ ), and for conditions ( $F(4,316) = 110.01, P < 0.001$ ). However, there was no significant group by condition interaction (see table 8.3g).

#### Post hoc Analyses

The main effect of groups on the trigram task was further analysed using Newman Keuls test. This analysis revealed a significant difference ( $P < 0.05$ ) between the CTL group and the VPA group, with the VPA group performing more poorly. No other group comparisons were significant.

-----  
Table 8.3h : Summary of Newman Keul comparisons for trigram conditions  
 -----

	CTL	Tapping	Shapes	Artic.	Counting
CTL		P < 0.05	P < 0.05	P < 0.01	P < 0.01
Tapping			N.S	P < 0.05	P < 0.01
Shapes				P < 0.05	P < 0.01
Artic.					P < 0.01
Counting					

-----

The effect of condition was also analysed using a Newman Keuls test. The control condition, i.e no

distractor, produced significantly higher scores compared to both the articulatory suppression and the counting distractor conditions at the  $P < 0.01$  level. The control condition was also significantly higher scoring compared to the tapping and drawing shapes condition at the  $P < 0.05$  level. The counting condition was significantly impaired at the  $P < 0.01$  level compared to the articulatory suppression, the tapping and the drawing shapes conditions. The articulatory suppression condition was significantly lower scoring, at the  $P < 0.05$  level, compared to the tapping and the drawing shapes conditions. These comparisons are summarised in table 8.3h.

The Newman Keuls analysis supported the hypothesis that the verbal distractor tasks interfered to a greater degree on the performance on the primary trigram task compared to the visual and motor secondary tasks. The visual and motor distractor conditions did, however, have an effect on performance compared to the control condition, with significantly lower scores being obtained on the primary task in these conditions.

Two further group comparisons were made (for clinical interest) using the Scheffe test.

1. CTL group (N=10) versus the group with epilepsy (N=74)
2. ACD group (N=52) versus non-ACD group (N=32)

Neither of these two analyses revealed significant differences between the groups.

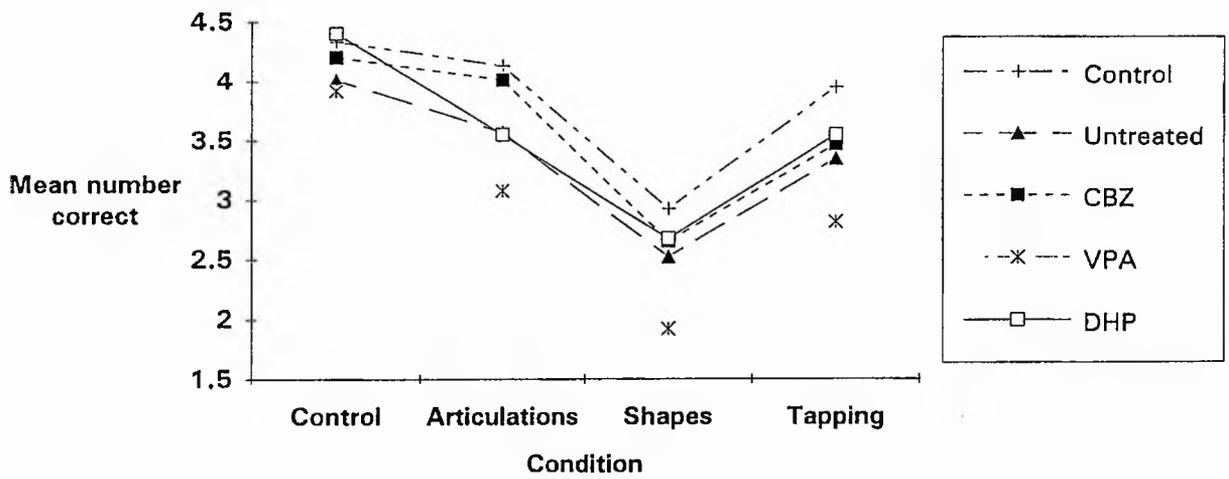
-----  
 Table 8.3i Mean score correct for the visual and spatial  
 tasks for the five groups

Test	Subject Groups : Means (S.D)				
	CTL	UT	CBZ	VPA	DPH
-----					
Visual task					
Condition one	5.30	5.05	5.00	4.57	4.93
Control	(0.68)	(1.05)	(0.95)	(1.26)	(0.99)
Condition two	5.20	5.10	4.71	4.19	4.42
Articulations	(0.79)	(0.94)	(0.96)	(1.17)	(1.29)
Condition three	3.60	3.38	3.62	2.75	3.13
Shapes	(1.90)	(1.23)	(1.24)	(1.29)	(1.77)
Condition four	5.00	4.48	4.52	3.63	4.67
Tapping	(1.16)	(1.24)	(1.21)	(1.45)	(1.29)
-----					
Spatial task					
Condition one	4.33	4.01	4.20	3.92	4.40
Control	(0.89)	(0.56)	(0.74)	(0.95)	(0.64)
Condition two	4.13	3.57	4.01	3.08	3.55
Articulations	(0.97)	(0.92)	(0.99)	(1.00)	(0.97)
Condition three	2.93	2.53	2.66	1.93	2.68
Shapes	(0.99)	(0.99)	(0.83)	(0.89)	(1.29)
Condition four	3.95	3.35	3.47	2.82	3.55
Tapping	(0.89)	(1.00)	(1.10)	(1.24)	(0.89)
-----					

-----  
 Table 8.3j ANOVA of visual and spatial task for the five  
 groups

Test	"F" ratio (DF) and significance level		
-----			
Visual task	F =	2.12	(Df 1/78) P = 0.082
(Effect of Group)			
Effect of Condition	F =	71.10	(Df 3/234) P < 0.001
Interaction	F <	1	
(Group by Condition)			
-----			
Spatial task	F =	2.94	(Df 1/78) P < 0.05
(Effect of Group)			
Effect of condition	F =	76.47	(Df 3/234) P < 0.001
Interaction	F <	1	
(Group by Condition)			
-----			

Figure 8b: Graph of the spatial memory task for five groups in study two



### 8.36 Non-verbal memory tasks

Table 8.3i summarises the means and standard deviations for the two non-verbal primary memory tasks across the five groups. The maximum scores on both the visual and the spatial memory tasks were six, and a number of subjects achieved the maximum score on some of the conditions.

The CTL group obtained the highest mean score on the visual memory task, followed by the UT group, the CBZ group, DPH group and finally the VPA group; for example the means on the condition one for the groups were 5.30, 5.05, 5.00, 4.93, and 4.57 respectively. The size of the standard deviations will have been affected by the ceiling effects obtained in some conditions. Looking across the conditions there was no observable pattern in the sizes of the standard deviations.

Surveying the means across the four different conditions, one finds a consistent pattern, with the highest being obtained in the no distractor condition, the next were in the articulatory suppression condition, followed by those in the tapping task, with the smallest means being obtained in the drawing shapes condition.

The means and standard deviations of the spatial memory task is also summarised in table 8.3i. There was a less clear pattern of size of means, although generally the CTL group obtained higher means than the other groups. There were fewer maximum scores on the spatial task and

generally lower scores than on the visual task. Once again there was no clear pattern of size of standard deviations. Indeed, the standard deviations appeared to be of a more similar size in all five groups (see figure 8b).

Surveying the effects of condition on the mean scores, a similar picture was revealed for the spatial task as for the visual task. Again, there was a consistent order of the means, with the highest scores being obtained by the no distractor condition, followed by the articulatory suppression, followed by the tapping condition and the lowest mean scores were obtained by the drawing shapes condition. Hence, on both primary tasks, the shape drawing distractor task produced the lowest means in the primary task data.

Both the visual and the spatial task were analysed using two-way ANOVAS, with a between-subjects factor of groups and a within-subjects factor of condition. Main effects of groups were found in the spatial task ( $F_{1,78} = 2.94$ ,  $P < 0.05$ ) and a trend was observed in the visual task, ( $F_{1,78} = 2.12$ ,  $P < 0.1$ ). There were also effects of conditions for both tasks,  $F_{3,234} = 71.10$ ,  $P < 0.001$  for the visual task, and  $F_{(3/234)} = 76.47$ ,  $P < 0.001$  in the spatial task (see table 8.3j).

There were no significant interactions between groups and conditions. Hence, increasing task difficulty did not affect the performance differentially, across the five groups.

-----  
 Table 8.3k Newman Keuls analysis of condition for the  
visual and the spatial tasks  
 -----

1. Visual Task

	CTL	Artic.	Tapping	Shapes
CTL		N.S.	P < 0.01	P < 0.01
Artic.			P < 0.05	P < 0.01
Tapping				P < 0.01
Shapes				

2. Spatial Task

	CTL	Artic.	Tapping	Shapes
CTL		P < 0.01	P < 0.01	P < 0.01
Artic.			P < 0.01	P < 0.01
Tapping				P < 0.01
Shapes				

-----

### Post hoc Analyses

The main effect of groups on the spatial task was further analysed using the Newman Keuls test. The performance of the VPA group was significantly poorer than the CTL group performance on the spatial task ( $P < 0.05$ ). There were no other significant differences.

The effect of condition for both the tasks was analysed by Newman Keuls test.

In the visual task the control condition performance was significantly better than the tapping and the drawing shapes condition ( $P < 0.01$ ). The articulatory suppression performance was also significantly better than the tapping task ( $P < 0.05$ ) and the drawing tasks ( $P < 0.01$ ). The tapping task produced significantly better performance compared to the drawing shapes task ( $P < 0.01$ ), as shown in table 8.3k.

The effects of conditions in the spatial task were analysed using Newman Keuls test, which revealed that comparisons between conditions were all significantly different at the  $P < 0.01$  level. The best performance on the primary spatial task was in the control condition followed by the articulatory suppression condition, the tapping task condition, and finally the visual condition. Table 8.3k summarises these findings.

The Newman Keuls analysis supported the working memory model and hence the design of the tasks, i.e. that the visual and spatial tasks would be more greatly affected by

the tapping and the drawing shapes secondary tasks than by the verbal articulatory suppression condition. In addition, the trigram task was significantly more affected by the articulatory suppression condition compared to either the tapping or drawing shapes conditions (see section 8.35). However, the pattern of performance on the visual and spatial primary tasks could not be differentiated by the performance of the primary tasks, on the tapping and shape conditions.

Two further comparisons, the CTL subjects (N=10) versus the subjects with epilepsy (N=74) and the ACD (N=52) versus the non-ACD (N=32) were made on both the two tasks using the Scheffé test. Neither of the analyses revealed significant differences between the groups.

In the three memory tasks (trigrams, visual and spatial) the subjects were requested to perform the secondary (distractor) task at a specified and constant rate across all three tasks. The following section presents the analyses of the performance of the groups on each of the secondary tasks across each of the memory tasks.

-----  
 Table 8.31 Mean Number of distractor tasks per second  
 across the three memory tasks for the five groups.  
 -----

Test	Subject Groups : Means (S.D)				
	CTL	UT	CBZ	VPA	DPH
-----					
Articulations					
A) Trigrams	2.27 (0.54)	2.26 (0.80)	2.75 (0.83)	2.50 (1.05)	2.39 (0.86)
B) Visual	2.46 (0.61)	2.30 (0.72)	2.71 (0.85)	2.30 (0.81)	2.44 (0.79)
C) Spatial	2.52 (0.89)	2.34 (0.84)	2.59 (0.82)	2.38 (1.08)	2.26 (0.90)
-----					
Counting backwards (Trigram task)	0.53 (0.21)	0.45 (0.17)	0.44 (0.15)	0.34 (0.22)	0.47 (0.18)
-----					
Shapes					
A) Trigrams	0.19 (0.06)	0.18 (0.06)	0.20 (0.05)	0.16 (0.04)	0.17 (0.07)
B) Visual	0.18 (0.05)	0.18 (0.06)	0.19 (0.07)	0.14 (0.04)	0.15 (0.07)
C) Spatial	0.19 (0.05)	0.17 (0.07)	0.19 (0.06)	0.14 (0.04)	0.15 (0.07)
-----					
Tapping					
A) Trigrams	2.03 (0.36)	1.87 (0.52)	2.19 (0.44)	2.21 (0.65)	2.12 (0.53)
B) Visual	2.01 (0.39)	1.85 (0.66)	2.17 (0.42)	1.90 (0.63)	2.01 (0.49)
C) Spatial	1.95 (0.35)	1.76 (0.59)	2.11 (0.50)	1.79 (0.57)	2.05 (0.58)
-----					

### 8.37 Distractor tasks

The subjects were required to carry out secondary distractor tasks in the different conditions of the memory tasks. The aim was that the performance on the secondary tasks should be constant across the tasks and the subject groups, and that any trade-off in performance should only occur in the primary memory tasks. This section assesses the extent to which the subjects were successful at maintaining secondary task performance.

The rate of articulatory suppression requested by the experimenter was two items per second. In general, the subjects achieved this as they performed at a rate of between 2 and 2.5 items per second as shown by the mean scores in table 8.31. This rate was maintained across the different memory tasks and across the five groups.

The counting backwards in threes condition only applied in the trigram memory task. It was more difficult to specify a rate of performance in this task, as the rate depended on the ability of the subject to count backwards in threes. The order of the means on this task revealed that the CTL group obtained the highest rate of counting, followed by the DPH group, the UT group, the CBZ group and finally the VPA group.

In the shapes condition, it was also more difficult to specify a rate of drawing. Nevertheless, a consistent rate of drawing was obtained across the three memory tasks, with the CTL group and the CBZ group drawing at perhaps a

marginally higher rate compared to the other three groups (see table 8.31)

The subjects were instructed to tap at a rate of two taps per second in the tapping condition on the memory tasks. In general, the groups were all able to tap at a rate close to this requested rate. However, across the three memory tasks the rate of tapping varied in a consistent manner, with faster mean tapping rates being obtained on the trigram task, followed by the visual task, and slowest tapping rates being obtained by the spatial task; for example the CTL group means were 2.03, 2.01 and 1.95 respectively. (See table 8.31)

In terms of standard deviations, few obvious patterns of results were obtained. In general, the control group had smaller standard deviations compared to the other groups, but this was not a wholly consistent pattern.

-----  
Table 8.3m ANOVA of the secondary tasks for the five groups

Test	"F" ratio (DF) and significance level		
-----			
Articulations :			
Effect of Group	F < 1		
Effect of Task	F < 1		
Interaction (Group by Task)	F = 1.74 (Df 8/158)		P = 0.092
-----			
Counting backwards :			
Effect of Group	F = 2.04 (Df 4/79)		P = 0.094
-----			
Shapes :			
Effect of Group	F = 2.01 (Df 4/79)		P > 0.1
Effect of Task	F = 10.98 (Df 2/158)		P < 0.001
Interaction (Group by Task)	F < 1		
-----			
Tapping :			
Effect of Group	F = 1.10 (Df 4/79)		P > 0.1
Effect of Task	F = 4.17 (Df 2/158)		P < 0.05
Interaction (Group by Task)	F < 1		
-----			

The distractor tasks were analysed using ANOVA and the results are summarised in table 8.3m. The articulatory suppression, shape drawing and tapping distractors were each analysed using a two-way ANOVA with a between-subjects factor of groups and a within-subjects factor of primary task.

There were no main effects for either groups or condition in the articulatory suppression. However, there was a trend in the groups by distractor interaction ( $F_{8,158} = 1.74, P < 0.1$ ).

There were no main effects of groups in either the shapes drawing or the tapping distractor tasks. However, in both, there was an effect of task for the shape drawing distractor ( $F_{2,158} = 10.98, P < 0.001$ ), and for the tapping distractor ( $F_{4,158} = 4.17, P < 0.05$ ). There were no group by distractor interactions.

The counting backwards distractor was analysed by a one-way ANOVA which revealed a trend towards a significant effect of groups ( $F_{4,79} = 2.04, P < 0.1$ ).

#### Post hoc Analyses

Although subjects were asked to maintain a constant performance on the distractors, there were effects of primary task for both the tapping ( $P < 0.05$ ) and the drawing shapes ( $P < 0.001$ ) distractors. These effects were analysed using Newman Keuls test.

The performance on the shape drawing distractor was significantly reduced on the visual task ( $P < 0.01$ ) compared to the performance of this distractor on the trigram task. The performance on the tapping distractor, on the other hand, was significantly reduced on the spatial task compared to the trigram task ( $P < 0.01$ ). There were no other significant differences.

This analysis supports the view that there is a difference in mode of operation in the spatial task compared to the visual task, and that the difficulty of combining motor and spatial tasks resulted in a reduced level of performance in the motor tapping distractor compared to the control condition. Likewise, the difficulty of performing on the primary visual task and the secondary shape drawing task resulted in reduced performance in the secondary drawing task compared to performance of the drawing shapes distractor on the trigram task.

In summary, the three dual-task memory tests showed some differences in performance, particularly between the CTL and the VPA group. There were several effects of condition as expected from the design of the tests. However, there were no interactions between group and condition of test.

This set of results, obtained from using working memory tasks, supported a model of working memory with separate verbal and visuo-spatial systems, and indeed to some degree indicate the possibility of separate visual and

spatial systems. However, there was no clear evidence that ACDs impair performance on these tasks, nor indeed that epilepsy per se results in impairments on these tasks.

-----  
Table 8.3n Mean response times for the category-decision and attention-switching tasks in milliseconds, for the five groups.

Test	Subject group : Mean (S.D)				
	CTL	UT	CBZ	VPA	DPH
-----					
Category-decision task (N=58)					
Condition one	552.9 (175.5)	551.9 (204.8)	540.8 (145.3)	731.1 (263.6)	682.0 (209.6)
Condition two	657.8 (114.4)	732.0 (220.0)	806.8 (270.5)	853.9 (390.8)	814.2 (305.3)
Condition three	904.3 (337.7)	930.9 (478.3)	1027.4 (486.1)	1397.9 (481.8)	1126.3 (498.5)
-----					
Attention-switching task (N=60)					
Condition one	1514.0 (324.8)	1372.1 (242.3)	1492.0 (490.9)	1726.1 (458.9)	1541.9 (382.6)
Condition two	1579.1 (227.8)	1534.8 (316.3)	1647.6 (350.6)	1874.0 (383.9)	1634.1 (415.8)
Condition three	4895.6 (932.8)	5108.2 (1308)	5361.2 (1586)	5109.4 (1794)	4803.4 (1450)
-----					

-----  
Table 8.3p ANOVA of category-decision and attention-switching tasks for the five groups

Test	"F" ratio (Df) and significance level		
-----			
Category-decision task			
Effect of Group	F = 1.91	(Df 4/53)	P > 0.1
Effect of Condition	F = 43.26	(Df 2/106)	P < 0.001
Interaction (Group by Condition)	F < 1		
-----			
Attention-switching task			
Effect of Group	F < 1		
Effect of Condition	F = 362.64	(Df 2/110)	P < 0.001
Interaction (Group by condition)	F > 1		
-----			

### 8.38 Category-Decision and Attention-Switching tasks

The means and standard deviations for the category-decision and attention-switching tasks are presented in table 8.3n. Each of the means presented is the mean group response time in milliseconds.

The pattern of means in the category-decision task revealed that the CTL group generally had the fastest response times, followed by the UT group, the CBZ group, the DPH group with the VPA group having the slowest times; for example, in condition three the times were 904.3, 930.9, 1027.4, 1126.3, and 1397.4 milliseconds, respectively. The standard deviations were generally smaller for the CTL group but of a similar size for the other groups.

The means of every group consistently increased across the three task conditions; for example, the CTL group means were 552.9, 657.8 and 904.3 respectively.

-----  
Table 8.3g Mean percentage of errors on category-decision  
task for five groups

Group	Mean percentage error score (%)		
	Condition 1	Condition 2	Condition 3
CTL	3.0	0.0	14.0
UT	0.0	0.0	19.0
CBZ	0.5	1.0	14.0
VPA	2.2	1.1	22.2
DPH	0.0	1.0	10.0

-----

The mean percentage error scores across the three conditions in the category-decision task for the five groups are presented in table 8.3q. The pattern of means revealed very few errors in the first two conditions, with more errors in the third condition. Many subjects had zero errors across all conditions, and with such small numbers of errors the data were not analysed statistically. The pattern of means was consistent, with for all five groups obtaining similar error scores.

The pattern of means for the attention-switching task revealed that the CTL group and the UT group had faster response time means than the three drug groups. Hence, in condition two the mean response times for the CTL, UT, CBZ, VPA and DPH groups were 1579.1, 1534.8, 1647.6, 1874.0, and 1634.1 ms. Also, the standard deviations were smaller for the CTL and UT group compared to the other three groups.

Surveying the mean scores across the conditions for all five groups, the mean scores consistently increased across the conditions, with the final condition producing mean response times more than double those in condition one.

The mean percentage errors for each condition for each of the five groups are summarised in table 8.3r. The mean error percentages were very low in condition one and gradually increased across conditions. Again many subjects had no errors in any of the conditions and the errors

scores were of a similar size across all subject groups. Thus, no further analysis was carried out on the data.

-----

Table 8.3r Mean percentage error scores for attention-switching task for five groups

Group	Mean percentage error score (%)		
	Condition 1	Condition 2	Condition 3
CTL	2.2	11.6	12.1
UT	3.1	7.3	15.9
CBZ	3.0	6.0	11.2
VPA	3.9	5.6	14.0
DPH	4.4	10.0	17.0

-----

The response time data for both tasks were analysed using two-way ANOVA, with a between-subjects factor of groups and a within-subjects factor of condition. Table 8.3p presents the results of this analysis and reveals that there were no significant main effects of groups. There were main effects of condition for the category-decision task ( $F_{2,106} = 43.26, P < 0.001$ ) and for the attention switching task ( $F_{2,110} = 362.64, P < 0.001$ ). There were no group by condition interactions. Hence, increasing task complexity did not have a greater detrimental effect on any one group performance.

#### Post hoc analyses

The Newman Keuls test was used to investigate the effect of condition for these two tasks. On the category-decision task, all the conditions were significantly

different from each other ( $P < 0.01$ ) with the conditions becoming increasingly difficult, i.e condition one (that of colour) was the easiest, followed by condition two (that of animate/inanimate), with condition three (colour or animate/inanimate) being the most difficult.

In the attention-switching task, condition three (requiring the switching of attention from perception to memory) was significantly more difficult than conditions one (reading task) and two (memory task) at the  $P < 0.01$  level. Hence, these results were as expected in the design of the tests.

#### 8.4 Summary

Although not totally consistent, the following pattern of means and standard deviations emerged. In general, the CTL group obtained means in the direction of better performance and also had smaller standard deviations compared to the other four groups. Of the three drug groups, the VPA group performed less well compared to the CBZ and DPH groups which performed in a similar fashion. Interestingly, the means of the UT group for some of the tasks, were in the direction of poorer performance when compared to the CBZ and DPH groups but better than the VPA group.

The ANOVAs revealed a number of trends and significant findings. On the memory tasks, i.e the trigram and spatial tasks, the CTL group performed significantly better than

VPA group at the 0.05 level. There were trends i.e.  $P < 0.1$ , for the main effects of group on the visual memory task and the motor task. There were no significant group differences in the distraction tasks or the response time tasks.

Hence, this set of results predominantly supported the null-hypotheses i.e. no significant differences were shown between the drug groups themselves and in comparison with the untreated epilepsy group, and in most of the analyses the epilepsy groups were not significantly different when compared with the control group.

The analyses of the effects of condition supported the view that the tests varied in difficulty as expected by the design of the test battery. One interesting finding was the change in performance of subjects in the distractor conditions in the memory tasks. The subjects had been asked to maintain a constant performance on the distractor tasks. However, it transpired that the subjects showed reduced performance on the visual (drawing shapes) secondary task when the primary memory task was of a visual nature and also showed reduced performance on the motor (tapping) distractor task when the primary task was a spatial memory task. This pattern of reduced performance supported the theoretical view that there is more interference between motor and spatial tasks and also more interference between two visual tasks, as discussed in chapter six.

The hypothesis in relation to task difficulty i.e. that as the tasks became more difficult, there would be an increasing number of significant differences between the five groups, was not supported.

Figure 8c: Graph of the spread of individuals' mean scores on S.R.T. for five groups in study two

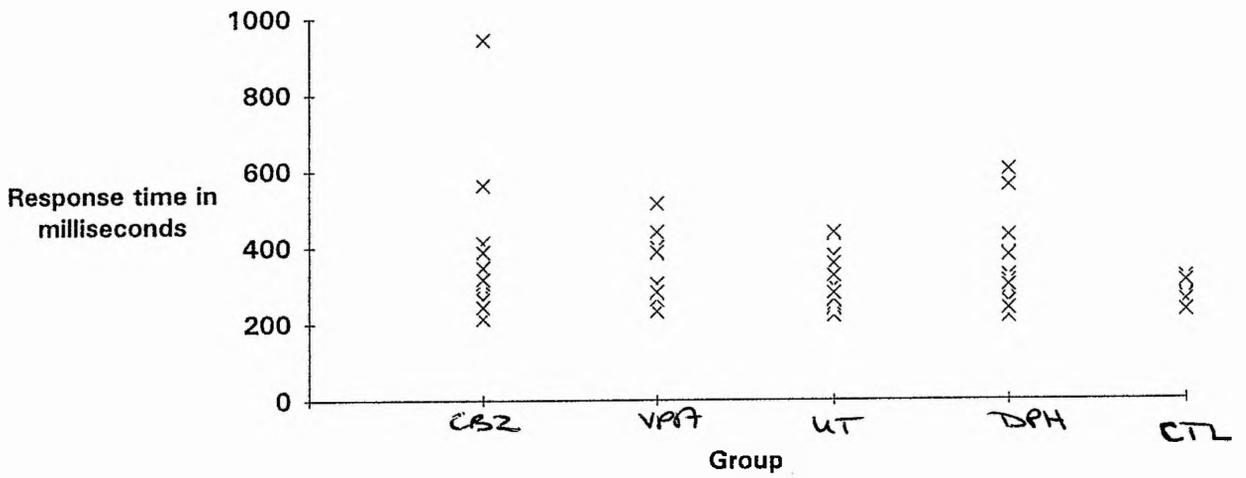
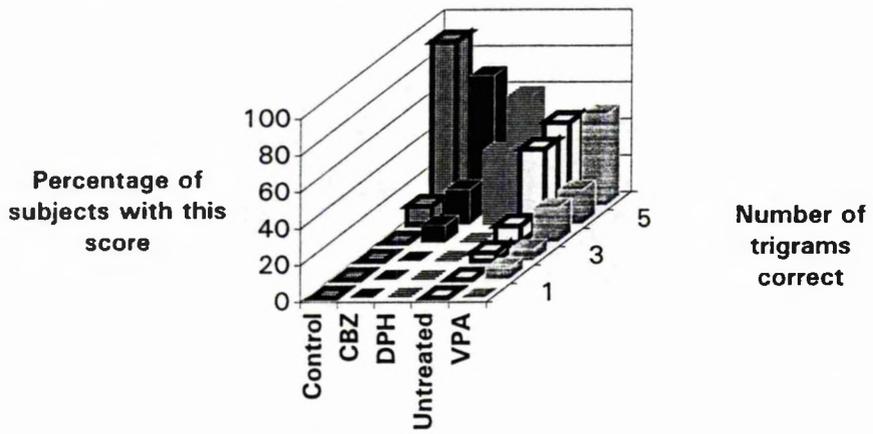


Figure 8d: Graph of the spread of individuals' scores in condition five of the trigram task for the five groups in study two



### 8.5 Further analysis of the data

The between-group comparisons revealed few significant differences between the five groups. However, the patterns of means across the whole test battery were consistent. The CTL group obtained higher means than the CBZ group, followed by the UT and DPH groups, with the VPA group obtaining the lowest means. It was also noticeable that the standard deviations tended to become larger in the opposite direction, so the groups with lower performance mean scores tended to have the larger standard deviations. On the reaction time task, in condition one, the means and standard deviations (shown in brackets) for the five groups i.e. the CTL, UT, DPH, VPA and CBZ groups were 261.9ms (30.6), 301.9ms (61.1), 331.6ms (81.5), 335.4ms (101.4) and 340.8ms (157.1), respectively. To further illustrate this point, figures 8c and 8d show graphically the range of scores obtained on the reaction time task and the trigram task for the five groups.

On many of the tests, the null-hypothesis was supported, i.e. there were no significant differences between the groups. However, as ANOVA compares the variance within the groups to the variance across the groups, the large standard deviations would have reduced the possibility of obtaining significant between-group differences.

-----  
 Table 8.5a    Ranked mean z-scores for subjects  
                   across test battery  
 -----

Subj	Drug	Z-score	Rank	Subj	Drug	Z-score	Rank
403	CBZ	1.38	1	407	VPA	-0.37	43
469	UT	1.31	2	461	CBZ	-0.37	43
491	CTL	1.21	3	474	DPH	-0.39	45
409	UT	1.08	4	483	UT	-0.41	46
419	UT	0.99	5	464	VPA	-0.42	47
438	UT	0.81	6	493	UT	-0.42	47
478	CTL	0.79	7	495	DPH	-0.50	49
425	VPA	0.76	8	453	CBZ	-0.55	50
458	UT	0.69	9	446	DPH	-0.67	51
484	DPH	0.62	10	439	CBZ	-0.74	52
475	DPH	0.50	11	466	CTL	-0.76	53
488	UT	0.50	11	444	UT	-0.78	54
400	CBZ	0.39	13	452	VPA	-0.79	55
401	CBZ	0.37	14	455	CBZ	-0.81	56
461	CBZ	0.37	14	450	UT	-0.88	57
428	CBZ	0.36	16	473	CTL	-0.91	58
423	CTL	0.34	17	462	DPH	-0.92	59
471	UT	0.33	18	430	CBZ	-0.95	60
436	CTL	0.31	19	476	CTL	-0.99	61
426	DPH	0.28	20	498	UT	-1.00	62
416	DPH	0.27	21	496	UT	-1.07	63
410	CBZ	0.27	21	445	VPA	-1.10	64
411	VPA	0.26	23	467	VPA	-1.11	65
402	UT	0.22	24	433	CBZ	-1.20	66
404	CBZ	0.20	25	470	VPA	-1.23	67
481	CTL	0.18	26	427	VPA	-1.35	68
448	CBZ	0.10	27	463	UT	-1.52	69
429	UT	0.09	28	417	CBZ	-1.55	70
418	UT	0.05	29	496	CBZ	-1.55	70
518	CBZ	0.03	30	456	CBZ	-1.74	72
413	CBZ	0.01	31	468	DPH	-1.74	72
486	CTL	-0.04	32	442	VPA	-1.80	74
499	UT	-0.16	33	449	CBZ	-1.81	75
461	UT	-0.17	34	431	UT	-1.83	76
432	VPA	-0.18	35	435	DPH	-2.01	77
479	VPA	-0.21	36	485	VPA	-2.02	78
421	DPH	-0.24	37	497	DPH	-2.14	79
447	VPA	-0.28	38	454	UT	-2.45	80
487	DPH	-0.31	39	492	VPA	-2.50	81
408	DPH	-0.33	40	459	VPA	-2.83	82
433	DPH	-0.33	40	472	UT	-3.09	83
477	DPH	-0.35	42	434	CBZ	-3.61	84

-----

Given the large standard deviations, are there subjects who could be identified as out-liers compared to the control subjects? If there are out-liers, are there clinical variables that may indicate reasons for the poor performance of those subjects?

To answer these questions, the z-scores of each subject on each test were computed using the standard deviation of the control group. The mean of the z-scores across the tests was then obtained for each subject. The mean z-scores were ranked with 1 being the highest mean z-score and rank 84 the lowest. Table 8.5a shows the mean z-scores for the 84 subjects across the test battery.

The range of mean z-scores was from 1.38 to -3.61. The lowest average z-score for a control subject was -0.99. This subject was ranked 61; hence, there were 23 epilepsy subjects with mean z-scores below this control subject z-score. Indeed, there were eight subjects who had a score more than double this z-score in the direction of poorer performance, i.e. larger than -1.98. These subjects were identified as out-liers. The eight subjects consisted of three subjects on VPA, two on DPH, one on CBZ and two untreated epilepsy subjects. Hence, this analysis did not indicate that ACDs may produce cognitive impairments, as there were out-liers in the UT group.

One possible explanation for the occurrence of the large number of out-liers may be the presence of factor(s) relating to the epilepsy and its treatment, that could

impair the performance of some subjects. For instance, could seizure frequency be related to subject performance? The clinical details pertaining to the eight individuals identified as out-liers will be described to provide a picture of the characteristics of the subjects obtaining very poor results.

One subject on CBZ : Subject No. 434

This subject was a 19 year old woman, for whom epilepsy had been diagnosed one and a half years previously. She suffered from generalised tonic-clonic seizures at a frequency of at least three seizures per month. She was taking 800 mg of CBZ daily and her serum level of medication at the time of testing was 10.9 mg/ml which is at the higher end of the recommended therapeutic range.

Three subjects on VPA : Subject No.s 442 459 and 492  
Subject 459

This 51 year old woman was diagnosed as suffering from epilepsy at the age of 37 (duration of the disease was, therefore, fourteen years). Her diagnosis was complex partial, secondarily generalised seizures and her seizure frequency was category three, i.e greater than three in the past six months, but less than three per month. This lady took 800 mg of VPA per day and her VPA serum concentration was 66 mg/ml, which is in the middle of the therapeutic range.

Subject 485

This 31 year old woman had suffered from complex partial seizures for three years. However, she had suffered no seizures in the previous six months. This subject was on a daily dose of 800 mg of VPA and had a serum level of 48 mg/ml at the time of testing. This level of anticonvulsant medication is at the low end of the therapeutic range.

Subject 492

This 23 year old man was diagnosed as suffering from epilepsy at the age of sixteen (disease duration was, therefore, seven years). He was diagnosed with complex partial, secondarily generalised seizures, and his seizure frequency was category five, i.e. none in the previous six months. He was on a dose of 500 mg of VPA per day and his VPA serum concentration was 101 mg/ml, which is high and falls just above the optimum therapeutic range.

These three brief subject profiles do not point to any one factor as a possible reason for their poor performance on the battery of tests as many other subjects performing in the normal range of the tests had similar case histories.

Two subjects on DPH : Subject No.s : 435 and 497Subject 435

This 23 year old woman had suffered from generalised tonic-clonic seizures for eleven years. Hence, the duration of the disease was nine years. She had a seizure frequency

of three, i.e. she had suffered more than three seizures in the past six months. She was on a daily dose of 425 mg DPH and had a serum level of 47.4 mg/ml at the time of testing. This level of DPH is more than double the maximum recommended therapeutic level.

Subject 497

This 57 year old man suffered from complex partial seizures, secondarily generalised. He suffered his first seizure at the age of seventeen and therefore, the duration of the disorder was 40 years. His seizure frequency category was three, i.e. he had suffered more than three seizures in the past six months. He was on a daily dose of 375 mg DPH and had a serum level at the time of testing of 13.5 mg/ml, which is in the middle of the therapeutic range.

Two subjects in the UT group : Subject No.s 454 and 472

Subject 454

This 23 year old woman had suffered complex partial seizures identified as originating from the temporal lobe (left or right temporal lobe not identified). She had suffered the seizures for four years and had a seizure frequency category of three, i.e she had had more than three seizures in the past six months.

Subject 472

This 27 year old man had suffered generalised tonic-clonic seizures for the previous eight years. He had a

seizure frequency of two, i.e. he had suffered more than three seizures in the previous month.

Looking at the performance and clinical details of subjects did not point to any one factor as the reason for some subjects' poor performance, although a very high serum concentrations of DPH may be indicated as a possible factor for one of the subjects. Further analyses were carried out to try to identify relevant factors, other than drug group, which may have affected subject performance. These analyses comprised of the following :

1. Pearson correlations to investigate the relationship between the performance of subjects on the battery of tests to factors associated with their epilepsy and medication.

2. A within-group analysis of those subjects who had changes in their anticonvulsant medication between testing sessions (N=16).

3. A small within-group analysis was carried out on eight subjects who completed the test battery on one occasion, and for whom a seizure had recently occurred near one testing session and there had been no recent seizure occurrence near another testing session.

-----  
Table 8.6a : Significant Pearson correlation coefficients  
for epilepsy subjects  
 -----

	Anx	Hos	Dpn	Age	S.ty	S.fre	Ons	Dur
Anx		.578**	.585**					
Hos	.578**		.548**					
Dpn	.585**	.548**						
Age							.550**	
S.ty						-.298*		
S.fre					-.298*			-.307*
Ons			.550**					-.541**
Dur						-.307*	-.541**	
Voc								
Pcom								
RT								
Mot								
TG								
S3								
SP								
SH								

-----  
 Key : \* =  $P < 0.01$ , \*\* =  $P < 0.001$ ,

(-) denotes negative correlation

Anx : Anxiety, Hos : Hostility, Dpn : Depression,

S.ty : Seizure type, S.fre : Seizure frequency,

Ons : Onset, Dur : Duration, Voc : Vocabulary,

Pcom : Picture Completion, RT : Reaction time,

Mot : Motor task, TG : verbal memory task,

S3 : Counting backwards, SP : Spatial memory task,

SH : Visual memory task.  
 -----

-----  
**Table 8.6b : Significant Pearson correlation coefficients  
 for epilepsy group (continued).**  
 -----

	Voc	Pcom	RT	Mot	TG	S3	SP	SH
Anx								
Hos								
Dpn								
Age								
Con								
Dose								
S.ty								
S.fre								
Ons								
Dur								
Voc		.409**			.402*	.593**	.339*	
Pcom	.409**				.401*		.324*	
RT								
Mot								
TG	.402*	.401*				.413*		
S3	.593**				.413*			
SP	.339*	.324*						
SH								

-----  
 Key : \* = P < 0.01, \*\* = P < 0.001

(-) denotes negative correlation.

Anx : Anxiety, Hos : Hostility, Dpn : Depression,  
 S.ty : Seizure type, S.fre : Seizure frequency,  
 Ons : Onset, Dur : Duration, Voc : Vocabulary,  
 Pcom : Picture Completion, RT : Reaction time,  
 Mot : Motor task, TG : verbal memory task,  
 S3 : Counting backwards, SP : Spatial memory task,  
 SH : Visual memory task.  
 Dose : Dose of ACDs, Con : Serum Concentration of ACDs.

-----

### 8.6 Relationships between epilepsy and cognitive performance variables

To investigate the strength of possible relationships between epilepsy and test performance variables, sixteen variables were identified, and the Pearson product moment correlation was used to measure the inter-relationships. The three drug groups were treated as one epilepsy group (N=52) in the first analysis. The sixteen variables identified were taken from the clinical and performance data as analysed in the ANOVAs. They consisted of levels of anxiety (Anx), hostility (Hos), depression (Dpn) (data from the MAACL), age of subjects (Age), type of seizure (S.ty), frequency of seizures (S.fre), age at onset of the disease (Ons), duration of the disease (Dur), Vocabulary score (Voc), Picture Completion score (Pcom), simple reaction times (RT), motor task scores (Mot), verbal (trigrams) (TG), spatial (SP), and visual memory task scores (SH). The correlation analysis produced a matrix of correlation coefficients which identified significant correlations at the  $P < 0.01$  and  $P < 0.001$  levels.

The significant correlations are shown in tables 8.6a and 8.6b. The mood variables all intercorrelated between themselves at the  $P < 0.001$  level, revealing that subjects who tended to identify many mood indicating words in one area of the MACCL, also identified them in the two other areas of the MAACL.

Several of the epilepsy variables also intercorrelated. Seizure type and seizure frequency type correlated negatively at the  $P < 0.01$  level. Hence, those subjects with generalised tonic-clonic seizures tended to have a lower frequency of seizures compared to those subjects with a diagnosis of complex partial secondarily generalised seizures. Seizure frequency also correlated negatively with duration of disease ( $P < 0.001$ ). Hence, those subjects with a smaller duration of the disease tended to have a higher frequency of seizures. Duration also correlated with age of onset ( $P < 0.001$ ) and onset correlated with age itself ( $P < 0.01$ ) as would be expected.

However, none of the epilepsy variables correlated with any of the test performance variables. Some tasks correlated significantly with each other including Vocabulary, Picture Completion, verbal memory task, spatial memory task and counting backwards. However, motor performance, reaction times and the visual memory task did not correlate with any other variables.

-----  
 Table 8.6c : Significant Pearson correlations for the three  
drug groups

Subject groups : 1:CBZ, 2:VPA and 3:DPH  
 -----

	Anx	Hos	Dpn	Age	Con	Dose	S.ty	S.fre	Ons	Dur
Anx 1.			.650*							
2.	.730*									
3.	.838**		.810**							
Hos 1.										
2.	.730*									
3.	.838**		.740*							
Dpn 1.	.650*									
2.										
3.	.810**		.740*							
Age 1.										
2.										
3.								.667*		
Con 1.						.879**				
2.						.922**				
3.						.753*				
Dose 1.						.879**				
2.						.922**				
3.						.753*				
S.ty 1.										
2.										
3.										
S.fr 1.									.554*	
2.										
3.									.554*	
Ons 1.										-.783**
2.										
3.			.667*							-.690**
Dur 1.									.783*	
2.										
3.										-.690*

-----  
 Key : \* = P < 0.01, \*\* = P < 0.001

(-) denotes negative correlation.

Anx : Anxiety, Hos : Hostility, Dpn : Depression,

S.ty : Seizure type, S.fre : Seizure frequency,

Ons : Onset, Dur : Duration,

Dose : Dose of ACDs, Con : Serum Concentration of ACDs.  
 -----

-----  
Table 8.6d : Significant Pearson Correlation Coefficients  
for the three drug groups (continued)  
 -----

Subject groups : 1:CBZ, 2:VPA and 3:DPH  
 -----

	Voc	Pcom	RT	Mot	TG	S3	SP	SH
Voc 1.						.556*		
2.						.777**		
3.								
Pcom1.								
2.								
3.								
RT 1.								
2.								
3.								
Mot 1.								
2.								
3.								
TG 1.								
2.								
3.								
S3 1.	.556*							
2.	.777**							
3.								
SP 1.								
2.								
3.								
SH 1.								
2.								
3.								

-----  
 Key : \* = P < 0.01, \*\* = P < 0.001

(-) denotes negative correlation.

Voc : Vocabulary, Pcom : Picture Completion,

RT : Reaction time, Mot : Motor task,

TG : verbal memory task, S3 : Counting backwards,

SP : Spatial memory task, SH : Visual memory task.  
 -----

The clinical group was divided into the three ACD groups and the correlation analyses were repeated on these smaller groups. Two extra variables of drug dose and serum concentration of anticonvulsant were added to the matrices. The large number of variables compared to the small number of subjects per group render these analyses less sensitive and fewer significant correlations were observed per drug group compared to the combined epilepsy group. The significant correlations are summarised in tables 8.6c and 8.6d. Again there were no significant correlations between the epilepsy variables and the performance variables. Hence, these comparisons are not included in the tables.

It is interesting to note that there were no correlations between the two drug measures and the epilepsy variables and the performance variables. The smaller number of significant correlation coefficients makes it difficult to identify any patterns of individual drug group correlations.

In summary, the correlation matrices do not indicate any one epilepsy or drug variable to be of significance in relation to test performance. However, it must be borne in mind that as this analysis had few data points relative to the number of correlations computed, one is less confident about the lack of findings.

---

Table 8.7a Changes in medication over sessions  
 Session (1, 2, 3 or 4) and concentration (mg/ml)

Subject	Concentration	High	Low	Difference	
CBZ 417	(1)	10.6	(2)	5.8	4.8
401	(2)	4.1	(3)	1.2	2.9
471	(2)	9.2	(1)	0	9.2
448	(2)	12.7	(1)	9.6	3.1
413	(2)	8.2	(1)	0	8.2
418	(4)	10.1	(1)	0	10.1
456	(3)	21.9	(2)	10.6	11.3
461	(3)	5.4	(1)	0	5.4
496	(2)	8.2	(1)	0	8.2
DPH 435	(1)	47.4	(3)	24.3	23.1
487	(2)	19.1	(1)	14.9	4.2
446	(3)	34.6	(1)	23.1	11.5
421	(2)	16.8	(1)	12.6	4.2
468	(1)	40.8	(3)	18.8	22.0
420	(3)	29.7	(1)	26.1	3.6
497	(2)	15.7	(1)	13.5	2.2

---

### 8.7 Changes in medication

Sixteen subjects changed dose and hence serum concentration of their anticonvulsant medication during the course of the study. Performance on the test battery could thus be compared across high and low concentrations of anticonvulsant medication. Table 8.7a shows the changes in blood serum concentrations of anticonvulsant medication in different testing sessions. For nine of the subjects the changes involved CBZ and for seven of the subjects the changes involved DPH.

The mean change in level of blood serum concentration for the CBZ subjects was 7.02 mg/ml with a standard deviation of 2.89, and for the DPH subjects the mean change was 10.1 mg/ml with a standard deviation of 8.34.

-----  
Table 8.7b Mean total Number of taps in motor task and mean response times in reaction time tasks across changes in medication

		Subject group : Means (S.D.)		
Test		All Subjects, N = 16	CBZ, N = 9	DPH, N = 7
		All	CBZ	DPH
Motor tasks (Combined)	L	227.7 (44.1)	232.7 (46.0)	222.6 (45.3)
	H	209.2 (42.4)	214.5 (35.8)	202.4 (51.5)
-----		All	CBZ	DPH
Reaction time tasks				
Condition 1	L	363.4 (107.6)	336.6 (89.1)	398.0 (126.1)
	H	361.4 (111.9)	320.6 (82.5)	413.4 (128.5)
Condition 2	L	379.1 (98.0)	373.7 (93.3)	386.0 (110.9)
	H	387.3 (94.8)	354.2 (81.9)	429.9 (98.8)
Condition 3	L	463.6 (138.0)	426.9 (148.1)	510.9 (117.2)
	H	506.9 (156.7)	456.7 (124.4)	571.7 (179.0)

-----  
 Key : L : Low and H : High ACD concentration  
 -----

-----  
Table 8.7c ANOVAs of motor task and reaction time task for drug changes across sessions  
 "F" ratio, degrees of freedom and significance level  
 -----

Motor tasks (Group Effect)	Combined	F = 2.96 (1/15)	P > 0.1
	CBZ	F < 1	
	DPH	F = 2.29 (1/6)	P > 0.1
-----			
Reaction time task :			
Combined :			
Effect of change		F = 2.24 (1,15)	P > 0.1
Effect of condition		F = 17.24 (2,30)	P < 0.001
Change by condition		F = 2.81 (2,30)	P = 0.076
CBZ :			
Effect of change		F < 1	
Effect of condition		F = 6.65 (2,16)	P < 0.01
Change by condition		F = 2.69 (2,16)	P = 0.098
DPH :			
Effect of change		F = 8.85 (1,6)	P < 0.05
Effect of condition		F = 12.08 (2,12)	P < 0.01
Change by condition		F < 1	

-----

### 8.71 Motor and Reaction time tasks

A within-group ANOVA was carried out on the motor test performance of the sixteen subjects combined into one group, and then two further ANOVAs were carried out on the drug groups (CBZ and DPH).

The mean tapping rate scores (summed across conditions) for the motor task in the high and low concentrations groups are shown in table 8.7b. The high concentration group had lower mean tapping rates, but the ANOVA revealed no significant effects of drug changes (shown in table 8.7c). There were also no significant interactions of drug change by condition, so these results have not been included in table 8.7b or 8.7c

Three within-group ANOVAs were carried out on the reaction time data (on the combined group and separately on the CBZ and the DPH groups). The pattern of means of the combined scores and the CBZ scores revealed no consistent pattern between high and low drug conditions. However, the DPH group did reveal slower response times in the high drug condition. Indeed, the ANOVAs showed no significant main effects of change of drug levels, either for the combined group or for the CBZ group alone, but the ANOVA on the DPH group did reveal a main effect of drug change with slower response times in the higher drug concentration condition ( $F_{1,6} = 8.85, P < 0.05$ ).

The effects of condition were highly significant as would be expected as the tasks increased in complexity (see

section 8.34). There were no significant drug change by condition interactions, although there were trends in the combined group ( $F_{2,30} = 2.81$   $P < 0.1$ ) and in the CBZ group ( $F_{2,16} = 2.69$ ,  $P < 0.1$ ).

-----  
Table 8.7d Mean scaled score for digit span and mean score correct for trigram task for low vs high medication comparisons.

Subject group : Means (S.D.)

Test	All Subjects N =16	CBZ N = 9	DPH N = 7
	All	CBZ	DPH
Digit Span	L 10.13 (2.36)	10.00 (2.34)	10.29 (2.56)
	H 10.31 (2.94)	9.33 (2.87)	11.57 (2.70)
	All	CBZ	DPH
Trigram task			
Condition 1	L 5.94 (0.25)	5.89 (0.33)	6.00 (0.00)
	H 5.86 (0.34)	5.80 (0.44)	6.00 (0.00)
Condition 2	L 5.13 (1.15)	5.22 (1.09)	5.00 (1.29)
	H 4.63 (1.67)	5.00 (1.58)	4.14 (1.77)
Condition 3	L 3.06 (2.08)	3.89 (2.09)	2.00 (1.63)
	H 2.69 (1.89)	3.56 (1.74)	1.57 (1.51)
Condition 4	L 5.38 (0.81)	5.22 (0.97)	5.57 (0.53)
	H 5.25 (1.00)	5.56 (1.01)	4.86 (0.90)
Condition 5	L 5.38 (0.62)	5.33 (0.71)	5.43 (0.53)
	H 5.19 (0.83)	5.44 (0.73)	4.86 (0.63)

-----  
 Key : L : Low and H : High ACD concentration  
 -----

-----  
Table 8.7e : ANOVAs of low vs high drug groups for digit span and trigram tasks

Subjects (High vs Low) : "F" ratio and  
 Combined level of  
 CBZ Significance  
 DPH

Digit Span		
Combined	F < 1	
CBZ	F = 2.29 (1/8)	P > 0.1
DPH	F = 2.21 (1/6)	P > 0.1
Trigram task : Combined		
Effect of Change	F = 3.10 (1/15)	P = 0.098
Effect of Condition	F = 32.64 (4/60)	P < 0.001
Change by condition	F < 1	
CBZ		
Effect of Change	F < 1	
Effect of Condition	F = 9.98 (4/32)	P < 0.001
Change by condition	F < 1	
DPH		
Effect of Change	F = 5.17 (1/6)	P = 0.063
Effect of Condition	F = 41.98 (4/24)	P < 0.001
Change by condition	F < 1	

-----

### 8.72 Verbal Memory Tasks

The analysis of the trigram tasks revealed some interesting findings and a detailed summary of the results for the memory tasks is presented, including the means and standard deviations for each condition and the "F" ratios and significance levels for the main effect and interactions (see tables 8.7d and 8.7e)

The trigram task revealed a pattern of consistently higher means across all conditions for the low concentration condition. The ANOVA for the combined drug groups showed a trend in the direction of increased medication showing poorer performance. The ANOVA for the DPH group also showed a similar trend ( $F(1,6) = 5.17, P = 0.063$ ). There were no significant findings or trends found in the CBZ group analysis.

There was a marked effect of task condition, which was not unexpected as the same result was obtained in section 8.35, and hence no further analysis was carried out on the condition effect. There were no medication change by condition interactions.

The digit span task did not reveal any pattern in the means, and therefore, not surprisingly, there were no significant findings in the ANOVA analysis.

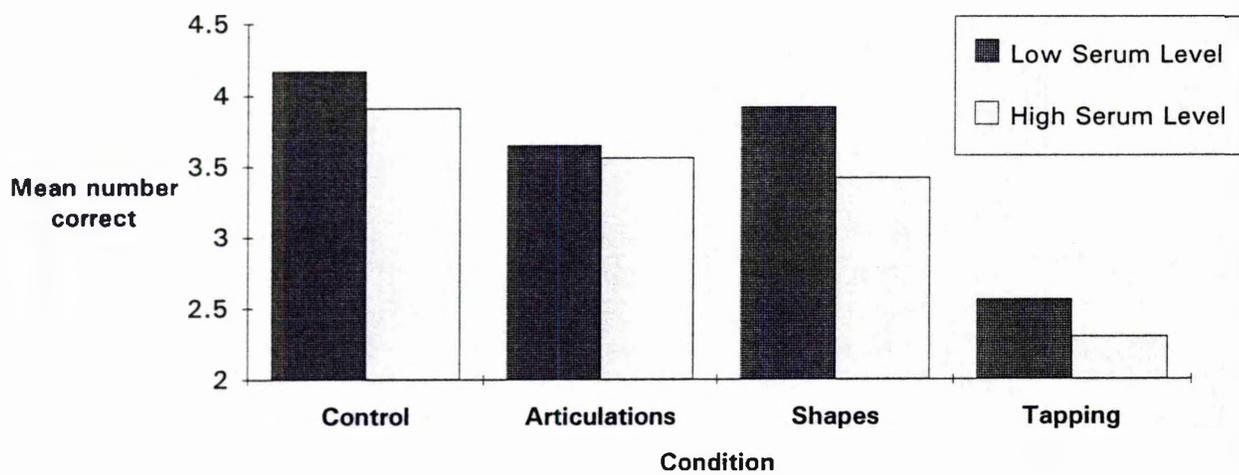
Table 8.7f Mean score correct for the visual and spatial tasks for low vs high medication comparisons

Test	Subject group ; Mean (S.D.)		
	Subjects N = 16	CBZ N = 9	DPH N = 7
	All	CBZ	DPH
Visual task			
Condition 1	L 4.94 (1.06)	5.44 (0.73)	4.29 (1.13)
	H 5.13 (0.96)	5.33 (0.87)	4.86 (1.07)
Condition 2	L 3.25 (1.18)	3.89 (1.05)	2.43 (0.79)
	H 2.88 (1.54)	3.89 (1.17)	1.57 (0.79)
Condition 3	L 4.80 (1.07)	5.33 (0.71)	4.14 (1.07)
	H 4.44 (1.53)	5.00 (0.70)	3.71 (1.25)
Condition 4	L 4.38 (1.36)	5.00 (0.87)	3.57 (1.51)
	H 4.36 (1.22)	4.67 (1.12)	4.00 (1.63)
	All	CBZ	DPH
Spatial task			
Condition 1	L 4.17 (0.75)	4.11 (0.88)	4.25 (0.60)
	H 3.91 (0.88)	3.97 (0.96)	3.82 (0.83)
Condition 2	L 3.65 (1.18)	3.75 (1.24)	3.54 (1.17)
	H 3.56 (0.95)	3.72 (0.99)	3.36 (0.92)
Condition 3	L 3.92 (0.91)	4.06 (1.03)	3.75 (0.78)
	H 3.42 (1.08)	3.72 (1.09)	3.03 (1.04)
Condition 4	L 2.56 (0.87)	2.83 (0.73)	2.21 (0.96)
	H 2.30 (0.92)	2.64 (0.78)	1.86 (0.94)

Key : L : Low and H : High ACD concentration



Figure 8e: Graph of scores in the spatial memory task for high and low levels of medication in study two



### 8.73 Visual memory Tasks

Tables 8.7f and 8.7g summarise means, standard deviations and the within-group ANOVAs for the visual and the spatial memory tasks for subjects changing medication.

The means for the visual memory tasks displayed no consistent pattern. There was no main effect of medication change. The effect of condition was highly significant, at the  $P < 0.001$  level, showing the same picture of increasing task difficulty as described in section 8.36. No further analysis was carried out on the condition effect. There was no medication change by condition effect for either the combined group or the CBZ group, but there was a change by condition effect for the DPH group ( $F(3,18) = 4.50$ ,  $P < 0.05$ ) (see table 8.7g)

#### Post hoc Analysis

The drug change by condition interaction ( $P < 0.05$ ) in the visual task in the DPH group was analysed by the Newman Keuls test. This test revealed that in the low drug concentration, condition four, i.e drawing shapes as a distractor, resulted in significantly worse impairment compared to the other three conditions ( $P < 0.01$ ). In the high drug condition, the same poor performance in condition four compared to the other three task conditions was present to an even stronger degree ( $P < 0.001$ ). Also, there were trends ( $P < 0.1$ ) for the performance in conditions two and three towards poorer performance compared to condition

one (no distractor). There is therefore some tentative evidence that as the task became more difficult, the performance of the high drug group became more impaired.

The spatial task revealed a consistent pattern of means across all conditions, with the low concentration group producing the higher means (see figure 8e). The three within-group ANOVAs revealed a significant effect of medication change for the combined drug group ( $F(1,15) = 7.11, P < 0.05$ ) in the direction of better performance in the low concentration drug group. The analysis of the CBZ group alone did not produce a significant effect of change, whereas the DPH group produced a trend in the same direction as the combined group ( $F(1,6) = 4.76, P < 0.1$ ).

This result suggests that higher levels of medication may impair subjects on working memory tasks.

Although, the effects of conditions were present, as in section 8.36, there were no medication change by condition interactions on the spatial tasks for any of the groups.

-----  
Table 8.7h Mean rate of distractor task performance on low vs high medication comparisons

Subject groups : Means (S.D.)

Test	All Subjects N = 16	CBZ N = 9	DPH N = 7
	All	CBZ	DPH
Distractor tasks (Combined scores)			
Articulations	L 2.52 (0.90)	2.62 (0.89)	2.40 (1.03)
	H 2.37 (0.59)	2.50 (1.70)	2.21 (0.59)
Counting backwards	L 0.48 (0.21)	0.50 (0.19)	0.45 (0.23)
	H 0.44 (0.19)	0.47 (0.20)	0.40 (0.18)
Shapes	L 0.16 (0.05)	0.19 (0.04)	0.13 (0.03)
	H 0.17 (0.05)	0.20 (0.04)	0.13 (0.03)
Tapping	L 2.10 (0.62)	2.06 (0.60)	2.15 (0.73)
	H 2.01 (0.71)	2.03 (0.78)	1.98 (0.64)

-----

Key : L : Low and H : High ACD concentration

-----

-----  
Table 8.7i Analysis of results of low vs high drug groups  
 "F" ratio, degrees of freedom and significance level

Distractor tasks (Effect of change)			
Articulations	Combined	F = 1.32 (1/15)	P > 0.1
	CBZ	F < 1	
	DPH	F < 1	
Counting Backwards	Combined	F = 2.76 (1/15)	P > 0.1
	CBZ	F = 1.15 (1/8)	P > 0.1
	DPH	F = 1.49 (1/6)	P > 0.1
Shapes	Combined	F = 1.15 (1/15)	P > 0.1
	CBZ	F < 1	
	DPH	F < 1	
Tapping	Combined	F < 1	
	CBZ	F < 1	
	DPH	F < 1	

-----

#### 8.74 Distractor tasks

Although, the subjects were asked to maintain a steady performance rate as indicated by the experimenter, the pattern of means did show that the means for the low concentration condition were generally higher than for the high concentration group. However, this pattern of means did not produce significant findings in the within groups ANOVAs (see tables 8.7h and 8.7i). There were also no significant medication change by distractor condition interactions (the details of these non-significant interactions have been omitted from the tables of results).

#### 8.75 Summary

In summary, most of the tests did not produce significant differences between the high and low drug concentration conditions. This might have been expected as there were low numbers of subjects in the group and relatively small changes in drug serum concentrations. However, two of the memory tasks produced interesting findings. The spatial memory task showed a significant difference between the high and low drug concentration conditions of  $P < 0.05$ , in the direction of better performance in the low serum level condition for the combined drug group. The trigram task showed a trend in the direction of better performance by the low serum concentration condition ( $P < 0.1$ ).

When the combined group analysis was broken down to the two drug groups (CBZ and DPH), if the change condition

effect was maintained, this was present more in the DPH group and less in the CBZ. Also in the reaction times tasks, the analysis of the DPH group revealed a significant slowing of response times in the high concentration of medication condition ( $P < 0.05$ ) which was not present, even as a trend in the CBZ group, and did not show up in the combined group analysis.

A point worthy of note is the lack of any consistent pattern of standard deviations, unlike the results obtained in the between-groups comparisons. Hence, the standard deviations did not increase with the higher levels of medication.

-----  
Table 8.8a Seizure occurrence in relation to testing session

Subject	Last seizure before testing session (SE)	
	Recent (Test session)	Distant (Test session)
438	2 days ago (SE 2)	None in past weeks (SE 1)
434	2 days ago (SE 2)	None in past weeks (SE 1)
467	2 days ago (SE 2)	Minor two weeks ago (SE 1)
455	1 day ago (SE 2)	None in past weeks (SE 2)
439	2 days ago (SE 1)	None in past weeks (SE 3)
410	Earlier in day (SE 1)	None in past weeks (SE 2)
448	2 days ago (SE 2)	Minor two weeks ago (SE 1)
411	2 days ago (SE 2)	Major two weeks ago (SE 1)

-----

### 8.8 : Changes in seizure frequency

Eight subjects had recent seizures, i.e close to the time of testing on one session and no recent seizures near other testing sessions. Therefore, the effect of recent seizures on performance on the test battery could be investigated. Table 8.8a shows seizure occurrence in relation to time of testing session for the eight subjects. None of the recent seizures occurred more than two days before the testing session, and all the distant seizures occurred more than two weeks before the relevant testing session.

The details of the type of seizure were provided solely by the subject, in their own words, and could not therefore, be reliably classified as a particular seizure type. This differed to the main body of clinical data in which the seizure type was that identified by the Consultant Neurologists as recorded in the medical notes of each subject. There was also no differentiation between major and minor seizures in this analysis, with all seizures being combined together to form the subject group.

The data from the subjects were analysed using within-subject ANOVAs with a main factor of recency of seizure. The means (combined across conditions of task) and standard deviations from these analyses are summarised in tables 8.8b. Once again the category-decision task and the attention-switching task had to be left out of the analysis because of the missing data.

-----  
Table 8.8b Mean combined scores across conditions of tests  
for two conditions : Recent vs distant seizure occurrence

Test	Seizure occurrence : means (S.D.)	
	Recent	Distant
-----		
Motor tasks : Mean No of taps (Combined score)	205.6 (29.5)	203.2 (38.3)
-----		
Reaction time tasks : Mean response time in msec (Combined score)	378.2 (114.7)	376.8 (102.5)
-----		
Digit span : mean scaled score	12.1 (2.03)	11.6 (1.89)
-----		
Trigram task : Mean No. correct (Combined score)	5.15 (0.47)	5.08 (0.52)
-----		
Visual task : Mean No. correct (Combined task)	4.56 (0.96)	4.50 (1.02)
-----		
Spatial task : Mean No. correct (Combined score)	3.74 (0.82)	3.87 (0.94)
-----		
Distractor tasks : Mean rate of performance per sec.		
Articulations	2.69 (0.87)	2.62 (0.63)
Counting backwards	0.40 (0.17)	0.40 (0.09)
Shapes	0.19 (0.25)	0.18 (0.37)
Tapping	2.34 (0.58)	2.24 (0.51)
-----		

The means and standard deviations revealed no observable pattern. The ANOVAs showed no significant differences or trends in the main effect of recency of seizure occurrence (see table 8.8c) and no interaction of recency of seizure occurrence with condition. The effects of conditions were present, as expected, but these results are not included in table 8.8c. Hence, due to the lack of significant findings, only the mean combined scores are presented in table 8.8b and only the "F" ratios for the main effect of recency of seizure occurrence are presented in table 8.8c.

<u>Table 8.8c ANOVA of effect of recency of seizure occurrence</u>		
Test	Seizure occurrence : Recent versus distant	"F" ratio and level of Significance
Motor tasks Effect of seizure	F < 1	
Reaction time Effect of seizure	F < 1	
Digit span	F < 1	
Trigram task Effect of seizure	F < 1	
Visual task Effect of seizure	F < 1	
Spatial task Effect of seizure	F < 1	
Distractor tasks : Effect of seizure		
Articulations	F < 1	
Counting backwards	F < 1	
Shapes	F = 1.06 (1,7)	P > 0.1
Tapping	F < 1	

-----  
Table 8.9a : Mean combined scores of tests across the  
three sessions

Test	Session : Mean (S.D)		
	Session 1	2	3
-----			
Motor tasks : Combined mean No. of taps			
Effect of session	200.0 (57.2)	198.6 (53.5)	192.3 (56.1)
-----			
Reaction time tasks : Mean combined response times in ms			
Effect of session	363.5 (93.7)	363.0 (91.5)	347.4 (83.8)
-----			
Digit span task : Mean scaled score			
Effect of session	10.7 (3.08)	10.8 (2.99)	11.3 (2.41)
-----			
Trigram task : Combined mean No. correct			
Effect of session	4.84 (0.78)	4.89 (0.92)	5.50 (0.99)
-----			
Visual task : Combined mean No. correct			
Effect of session	4.32 (1.45)	4.30 (1.32)	4.01 (1.36)
-----			
Spatial task : Combined mean No. correct			
Effect of session	3.23 (1.18)	4.51 (1.23)	3.53 (1.09)
-----			
Distractor tasks : Combined mean rate per sec.			
Effect of session			
Articulations	2.71 (0.96)	2.71 (0.92)	2.85 (1.05)
Counting backwards	0.46 (0.19)	0.51 (0.22)	0.51 (0.21)
Shapes	1.85 (0.23)	1.84 (0.30)	1.84 (0.32)
Tapping	2.37 (0.68)	2.17 (0.63)	2.11 (0.66)
-----			

### 8.9 : Analysis of practice effects

Data across three testing sessions were obtained from 30 subjects. However, five of these subjects had changes in medication during the testing period and two had changes in seizure frequency. Hence, the data of 23 subjects (4 CTL, 6 UT, 7 CBZ, 4 VPA and 2 DPH subjects) were used to analyse practice effects on the test battery. (The category-decision and attention-switching tasks were not included in the analysis because of missing data and the tests of intellectual ability were excluded because they were only carried out in session one).

The combined means and standard deviations the tests, across the three sessions are summarised in table 8.9a. No obvious pattern arose across the means or standard deviations. The within-subject ANOVAs with factors of session and condition showed only one effect of session and no session by condition interactions. The distractor task of counting backwards did produce a significant main effect of practice ( $F = 10.89, 2,38, P < 0.01$ ). The "F" ratios, degrees of freedom and level of significance for these analyses are presented in table 8.9b.



### Post hoc analysis

The significant result obtained in the counting distractor ( $P < 0.01$ ) was analysed using Newman Keuls test. This analysis revealed that performance on sessions two and three was significantly better than on session one ( $P < 0.01$ ), although performance in sessions two and three did not differ from each other. Hence, it appeared that there was a significant amount of learning of this task between sessions one and two.

### 8.a For clinical interest : Subjects with epilepsy versus CTL subjects, and ACD versus non-ACD subjects.

The design of this study was a five groups analysis. However, from a clinical view-point it is interesting to explore firstly, how the CTL subjects compared with the clinical group, irrespective of type of medication; and secondly, how subjects on anticonvulsant medication compared with subjects not on any medication. These areas were explored in the main five groups analysis, by using the Scheffé test, where appropriate. However, the Scheffé test is very conservative and did not provide fruitful comparisons. Hence, two sets of between-groups ANOVA were carried out :

1. Comparing subjects with epilepsy (N=74) with CTL (N=10) subjects.
2. Comparing ACD (three drug groups combined, N=52) with non-ACD (N=32, CTL=10 plus UT=22) groups.

The differences in the sizes of the groups does mean that any results obtained from these analyses are less robust and should only be read as possible indications of what might have occurred in the data set.

The CTL group means were in the direction of better performance compared to the subjects with epilepsy. However, very few of the between-groups ANOVAs produced significant findings between the groups. This was not a surprising finding, given the small number of subjects in the control group. A similar picture was obtained in the ACD versus non-ACD group, with the non-ACD group obtaining the better scores, but not producing significantly better performance than the ACD group. Given the length of this results section and the lack of interesting findings in these of analyses, the details of these two sets of ANOVAs are presented in appendix seven.

#### 8.b Summary and preliminary discussion

This study was very large and hence an extensive analysis of the results was carried out. This preliminary discussion will summarise the main findings but will not endeavour to relate these results either to the other studies contained in this thesis or the published literature. A more comprehensive discussion will be presented in the main discussion chapter (chapter eleven). This section will present an over-view.

The main points are as follows :

1. The design of the study was a comparison of five groups, four of whom had epilepsy, and three of whom were taking anticonvulsant medication. All subjects completed an extensive battery of tests on one or more occasions. The battery of tests included tests of mood, intellectual functioning, and verbal, visual and spatial working memory, perceptual and motor tasks, and tasks aimed to tap the central executive component of working memory, i.e. category-decision and an attention-switching task, requiring alternation between perception and memory. Most subjects were able to complete the battery of tests, although on a small number of occasions a subject would choose not to continue the tests. Also, an error in the computer program, resulted in the loss of approximately one third of the results in the category-decision and attention-switching tasks.

2. The performance of the subjects on the dual tasks supported the theoretical view of the differing verbal and visuo-spatial systems in working memory, with verbal distractors interfering to a greater degree on the verbal primary task, and visual and motor distractors impairing the visual and spatial tasks to a greater degree. Also, there was some evidence that subjects changed their performance on the distractor tasks to different degrees dependent on the primary task. In particular, the motor tapping rate decreased to a significant degree on the spatial memory task, whereas performance on the drawing

shapes distractor decreased significantly in the visual task. These two results support the view that there may be different spatial and visual systems in the working memory system.

3. Several clinical features of the epilepsy subjects were monitored to ensure a similar distribution of epilepsy variables across the groups. For the most part, the groups were well-matched on these variables, although the UT group was somewhat different to the three drug groups in that there were more subjects who were diagnosed with tonic-clonic seizures, subjects had a shorter duration of the disease and fewer subjects reported frequent seizure occurrence. The blood serum levels of the three drug groups were monitored. This revealed that there were more subjects with high levels (above the optimum range) of anticonvulsants in the DPH and VPA groups compared to the CBZ group.

4. The five groups set of ANOVAs revealed no differences between the groups on the measures of mood and intellectual ability.

5. The ANOVAs did reveal a small number of significant group effects on test performance, particularly in the trigrams and spatial memory tasks, in which the VPA group performed significantly worse than the CTL group. Although, there were many significant effects of condition in the tests, there were no group by condition interactions. Hence, the hypothesis that increasing task

complexity/difficulty would result in detrimental performance in some drug groups was not supported.

6. A small number of subjects (N=16) underwent changes in medication during the testing period. A set of within-group ANOVAs was carried out on the performance data for the two conditions of high and low serum concentrations of ACD. The sample was also divided into those subjects on CBZ (N=9) and those on DPH (N=7) and further ANOVAs were carried out on these two sets of data. Although the pattern of means was generally in the direction of poorer performance in the higher drug group, only one of these differences was significant i.e. the spatial memory task ( $P < 0.05$ ), with a trend in the trigram task ( $P < 0.1$ ).

The subjects with epilepsy (N=16) were sub-divided into two drug groups and the pattern of results tended to show that the DPH group was more likely to show significant impairments in the high drug condition. It was interesting to note that the reaction times in the DPH group were significantly slower in the DPH high drug concentration condition compared to the lower drug concentration condition, a finding that had not been shown in the larger group of subjects i.e. CBZ and DPH combined.

7. A small number (N=8) of subjects had seizures very close to the time of testing and on another testing occasion had had no seizures in the previous two weeks. Hence, within-groups analyses with the main factor of recent versus distant seizures were carried out on the data

set. No significant findings were obtained in these analyses. However, as all seizure types were combined into one analysis, it may be possible that effects of one type of seizure are masked in this combined analysis. Unfortunately, there were not the number of subjects available to carry out separate analyses with regard to the occurrence of particular seizure types.

8. The results from 23 subjects, for whom neither seizure frequency nor medication changed over the testing period and who had completed the test battery on three occasions, were analysed for practice effects on the test battery. The results from these testing sessions were analysed using within-groups ANOVAs, with a within-subjects factor of session. This set of analyses revealed only one significant effect of practice. This was the distractor task of counting backwards in threes, in which there was significant improvement in performance between session one and two.

## CHAPTER NINE

### STUDY THREE : A NEW DRUG : LAMOTROGINE

#### 9.1 Aim of study

The aim of this study was to investigate whether Lamotrogine, a new anticonvulsant drug, would have an effect on cognitive functioning. A survey of the literature at the time of commencing the study, revealed that no studies on the possible effects of Lamotrogine on cognitive functioning had been published. Hence, the work was exploratory. However, as much of the literature supported the view that subjects on ACDs showed cognitive impairments, for example the work of Thompson and Trimble (1981, 1982 and 1983), the hypothesis for this study was that subjects on commencing on Lamotrogine would show additional impairments of cognitive functioning.

#### 9.2 Introduction.

Clinical trials for Lamotrogine were set-up at the Dundee Royal Infirmary (DRI) by Drs. Davidson and Roberts, on behalf of the Wellcome Foundation. The study described in this chapter was an additional study involving some of the same subjects participating in the Dundee clinical trials.

The trials were of an add-on nature, whereby Lamotrogine was added to the anticonvulsant medication of patients with intractable epilepsy. All subjects were

already on polytherapy. Given the severity of the epilepsy and that the subjects were on polytherapy, it was expected that these subjects would show cognitive impairments (refer to work of Thompson and Trimble (1982) amongst others, as described in chapter three). In order to support the hypothesis that Lamotrogine has detrimental effects on cognitive performance, it is necessary to measure an increase in the degree of cognitive impairment after commencing on Lamotrogine.

The study was carried out over a period of approximately one year and involved a within-subjects design, in which the subjects were tested before and after starting on Lamotrogine. Eleven subjects were tested one month before commencing on Lamotrogine and approximately one month after starting on the drug. Ten of the subjects were re-tested after they had been taking Lamotrogine for a period of approximately three months. The eleventh subject was withdrawn from the study on clinical grounds. Control subjects also completed the battery to measure practice effects on the test battery across the three sessions.

### 9.3 Background and context of the study

A significant portion (approximately twenty per cent) of individuals suffering from epilepsy continue to have seizures whilst taking anticonvulsant medication. There is therefore, great need for the development of new and effective treatments. There is also the need for careful

clinical trials on all prospective ACDs to ensure that the drugs are safe and cause the minimum of side-effects.

A lack of understanding of the cellular and molecular basis of epilepsy has hindered the development of new ACDs. In the past decade, hypotheses concerning the basis of epileptic activity have been proposed. One of these hypotheses is that epileptic activity is due to a defect in the excitatory neuronal systems in the brain. This hypothesis has produced one avenue for the rational development of new ACDs, i.e. drugs that decrease this neuronal excitation. Lamotrogine, a potential new ACD, is thought to act by decreasing the release of glutamate (an excitatory neurotransmitter) and so reduce the amount of epileptic activity (Meldrum, 1991).

Lamotrogine is chemically unrelated to any of the other main anticonvulsants drugs. Nevertheless, in extensive preclinical evaluations, Lamotrogine has been shown to be an extremely potent anticonvulsant (see appendix eight for a description of chemical structure and pharmacokinetics) and studies on healthy volunteers and patients with epilepsy have also been promising (Millar, Sawyer, Roth, Peck, Leach, Wheatley, Parsons and Morgan, 1986).

Cohen, Ashby, Crowley and Peck (1985a, and 1985b), employing volunteer subjects, found negligible evidence of toxicity other than some subjects complaining of headaches. In subjects with epilepsy, a reduction in photosensitivity

(Binnie, Kastelleijn-Nolst Trenite, De Korte, 1985), and interictal spikes (Jawad, Oxley, Yuen and Richens, 1985) have been observed. Pilot studies carried out at the Chalfont Centre for Epilepsy and at other epilepsy centres have provided preliminary evidence for positive effects regarding seizure control, but these studies were carried out on only a small scale and, as such, provide limited evidence of efficacy.

A more recent study by Peck (1991) compared Lamotrogine with CBZ and DPH on a number of tasks with large perceptual and motor components. Healthy volunteers, taking Lamotrogine, were not impaired on these tasks, whereas impairments were seen on the CBZ and DPH conditions. However, the doses of Lamotrogine in the volunteer study were low compared with the doses of Lamotrogine prescribed to the clinical subjects in this study.

The clinical trials at the DRI investigated the effects of Lamotrogine on epilepsy variables i.e frequency and types of seizures. The monitoring of the epilepsy variables was detailed, as was the monitoring of possible side-effects and the effects on concomitant medication. This information was made available for use in this study on cognitive function.

## 9.4 Subjects

### 9.41 Criteria for Subject inclusion

The criteria for subject inclusion in this study were necessarily those set-out in the Wellcome study and were as follows :

1. Age of subject was between 12 and 70 years
2. Male and female (of non-childbearing potential).
3. Confident diagnosis of epilepsy, uncomplicated by suspected pseudo-seizures.
4. At least two seizures per month in the previous three months.
5. A seizure diary kept for the previous three months.
6. Seizures resistant to standard anticonvulsant medication.
7. Anticonvulsant medication stable for the preceding two months and unlikely to change during the course of the study.
8. Not taking more than three anticonvulsants and not participating in drug investigations in the previous six months.
9. Not suffering from any severe organic or psychiatric disease, severe mental subnormality, or progressive neurological disease.
10. No abnormal medical laboratory values of any clinical significance.

11. Not on regular drugs other than anticonvulsants or oral contraceptives.

12. Not had status epilepticus (a particular type of epileptic activity) in the past six months, or more than once in the past two years.

13. No past record of serious non-compliance, or failure to attend clinic, or documented adverse experiences.

14. Given informed consent to participate in the study.

The epilepsy parameters were monitored closely by the responsible clinician, and were categorised in this study as in studies one and two. Hence, the types of seizures were categorised into the three groups of (1) generalised tonic-clonic, (2) complex partial and (3) complex partial, secondarily generalised.

The seizure frequency categories had to be expanded due to the larger number of seizures suffered by subjects in this study. Hence, category one i.e. more than three seizures in one week was expanded into four categories :

1a : greater than three seizures per day.

1b : greater than two seizures per day.

1c : greater than one seizure per day.

1d : greater than three seizures per week.

The number of seizures was monitored for the period before the first testing session and for the periods between subsequent testing sessions as subjects were

requested to keep a seizure frequency diary for the duration of the study.

Other parameters monitored were those of the serum levels of the other prescribed anticonvulsants at each testing session, and any changes in health which might indicate possible side-effects of Lamotrogine.

-----  
 Table 9a : Epilepsy variables for Lamotroqine subjects  
 -----

Subj. No.	Seizure Type	Age at onset (yrs)	Duration (yrs)	EEG	CT
100	2 (I)	3	19	A	N
102	2 (I)	5	30	A	N
103	3 (I)	8	18	A	N
104	2 (S)	9	31	A	?
106	2 (I)	18	15	A	N
107	3 (I)	1	28	A	N
109	2 (I)	18	9	A	N
110	2 (S)	24	16	A	?
114	3 (I)	11	6	A	N
115	2 (?)	9	16	A	N

-----  
 Key : Seizure Type : 1 : Tonic-clonic      I : Idiopathic  
                           2 : Complex partial      S : Symptomatic  
                           3 : Complex partial, secondarily generalised  
                           A : Abnormal and N : Normal  
 -----

#### 9.42 Subject details

The number of subjects with epilepsy who agreed to participate in the study was sixteen, although five dropped out before the second testing session i.e. were not tested whilst on Lamotrogine. One subject (subject 101) stopped taking Lamotrogine soon after the second testing session, and also had frequent disruptive seizures during the testing session. This subject was removed from the study. Thus, the data from ten subjects were reported in the analysis. Their mean age was 29.4 years with a standard deviation of 7.17 years. All the subjects who were prescribed Lamotrogine took it as an adjunct to their regular ACD medication. The other ACDs taken by the subjects included CBZ, VPA, DPH, Phenobarbitone and Primidone.

Table 9a summarises the epilepsy data of the ten subjects. All the subjects were diagnosed as having complex partial seizures, with two subjects having complex partial seizures, secondarily generalised. Seven of the subjects had idiopathic seizures, two had symptomatic seizures and one was unclassified with regard to aetiology. The mean age of onset of the seizures was 10.6 years with a standard deviation of 6.94 years. The mean duration of the disease was 18.8 years with a standard deviation of 8.06 years. All subjects had an abnormal EEG, and of the eight subjects who had had a CT scan all were normal.

Six control subjects participated in the study. The control subjects were all relatives of the subjects with epilepsy. The mean age of the controls was 34.6 years and the standard deviation was 8.1 years.

#### 9.5 Procedure

The psychometric tests used in the study were a combination of tests already in use in either the first Dundee study (see chapter four) or the Glasgow study (see chapter seven). Significant constraints on choice of tests were the availability of just one BBC microcomputer, the necessity to select tests that could be used on subsequent re-testing occasions and the administration of a battery of tests that was not draining on subjects. The battery of tests comprised the following tasks:

1. WAIS Vocabulary and Picture Completion test.  
(Completed on session one only)
2. MACL (Mood Adjective Check-list)
3. Motor tapping task
4. Digit span
5. Trigram task
6. Benton Visual Retention task
7. Category-decision task (as designed for the Glasgow study)
8. Attention-switching task (as designed for the Glasgow study)

The rationale for all but one of the tests has already been explained in chapters four and seven. However, one unfamiliar test, the Mood Adjective Check List (MACL), was already being employed at the DRI by other researchers, and provided measures of depression, anxiety, hostility, vigour and fatigue for the subjects in this study. The version of the test administered was that of Lishman's (1972), an adaptation of McNair's and Lorr's (1964) MACL.

To mitigate the possible effects of fatigue on the test battery, the order of the tests was varied across the subjects. Wherever possible, the subjects also completed the tests at the same time of day to avoid daily fluctuations of drug concentrations affecting performance.

All subjects completed the tests on three occasions, approximately two months apart. The subjects with epilepsy completed the first test session before commencing on Lamotrogine, the second session after being on Lamotrogine for at least one month and the third session two months later.

-----  
 Table 9b : Drug variables across sessions for Lamotrogine  
 study

Subject Number	a) Lamotrogine dose (mg)		
	b) Serum level of anticonvulsants ( $\mu$ mol/l)		
	Session 1	Session 2	Session 3
100	a) zero L. b) CBZ : 45 PRM : 107 VPA : 515	100N, 50M L. CBZ : 42 PRM : 139 VPA : 467	100N, 50M L. CBZ : 27 PRM : 85 VPA : 712
102	a) zero L. b) CBZ : 35 VPA : 796	100N, 100M L. CBZ : 31 VPA : 611	100N, 100M L. CBZ : 33 VPA : 579
103	a) zero L. b) CBZ : 31 PRM : 77	200N, 200M L. CBZ : 35 PRM : 79	200N, 200M L. CBZ : 31 PRM : 70
104	a) zero L. b) DPH : 83 PB : 43	200N, 100M L. DPH : 82 PB : 33	200N, 100M L. DPH : 71 PB : 47
106	a) zero L. b) CBZ : 37	200N, 200M L. CBZ : 37	200N, 200N L. CBZ : 32
107	a) zero L. b) CBZ : 52 VPA : 435	100N, 100M L. CBZ : 43 VPA : 359	100M, 100N L. CBZ : 48 VPA : 553
109	a) zero L. b) CBZ : 28 PRD : 99	200N, 100M L. CBZ : 42 PRD : 90	200N, 200M L. CBZ : ?? PRD : ??
114	a) zero L. b) CBZ : 36	200N, 200M L. CBZ : 37	200N, 200M L. CBZ : ??
115	a) zero L. b) CBZ : 29 DPH : 48	400 daily CBZ : 25 DPH : 64	300 daily CBZ : ?? DPH : ??

-----  
 Key : PRM : Primidone; PB : Phenobarbitone  
 N : Nocte (i.e. in the evening)  
 M : Mane (i.e. in the morning)  
 -----

## 9.6 Results

The data from the ten clinical subjects and the six control subjects were analysed using ANOVA, with a main effect of groups, a within-subjects factor of session and for some tests, a within-subjects effect of condition. Thus, the effects of Lamotrogine, if present, would become apparent with significant group by session interactions.

Before presenting the results from these analyses, the clinical data will be described.

### 9.61 Clinical Data

The doses of Lamotrogine and the serum level concentrations of the other anticonvulsant medications taken by the epilepsy subjects are presented in table 9b. Subjects, in general, started on a twice daily regimen of Lamotrogine varying from 50 to 200 mg. Nine of the ten subjects remained on that dose for the second and third testing sessions. Subject 115, however was on a reduced dose by the third testing session.

With regard to the blood serum concentrations of the other anticonvulsant medications, no pattern of change was observed across the testing sessions. Unfortunately, the blood serum level concentrations of three of the subjects for test session three were unavailable.

Table 9c : Seizure frequency and reported  
side-effects in Lamotrogine study

Subject Number	a) Seizure frequency categories		b) Side-effects	
	Session 1	Session 2	Session 2	Session 3
100	a) 1b b) none	1b intermittent diplopia nausea	1b intermittent diplopia nausea	1c unsteady nausea
102	a) 2 b) none	3 headaches diplopia	3 headaches diplopia	5 headaches
103	a) 1b b) none	1b none	1b none	1c none
104	a) 2 b) none	2 unsteady gait	2 unsteady gait	2 none
106	a) 3 b) intermittent diplopia	3 intermittent diplopia	3 intermittent diplopia	3 intermittent diplopia
107	a) 2 b) mouth ulcers	3 rash	3 rash	3 none
109	a) 2 b) none	3 depression	3 depression	2 none
110	a) 2 b) constipation poor sleep	2 constipation rash	2 constipation rash	2 none
114	a) 1d b) none	2 headaches mild drowsiness	2 headaches mild drowsiness	4 none
115	a) 2 b) none	2 nausea	2 nausea	2 headaches drowsiness mild anoxia

The frequency of seizures was monitored at each testing session, and any changes in physical or mental health were recorded. Table 9c summarises this information presenting both the seizure frequency categories (category 1a being the most frequent seizure category and category 5 indicating fewest seizures), and reported changes in health.

Comparing the clinical data across the four sessions showed no change in seizure frequency for four subjects, a reported decrease in seizure frequency for five subjects, and subject 109 reported a decrease in frequency in session two, but returned to the same frequency in session three as was present in session one. Thus, where seizure frequency changes were observed, they were in the direction of improved seizure control.

The changes in health reported included headaches cited three times, nausea cited three times, diplopia, i.e. double vision, cited twice and unsteadiness cited twice. Several other health problems were cited by only one subject on one testing occasion. It was noticeable that some health problems were noted in testing session one, and could not, therefore, be associated with Lamotrogine.

-----  
 Table 9d : Mean scores on test battery across three  
 sessions

Test	Subject group : Means (S.D.s)					
	Lamotrogine			CTL		
Session :	1	2	3	1	2	3
-----						
Intellectual Ability (Combined score)	(Mean scaled scores)					
	7.1			8.8		
	(3.05)			(3.25)		
Vocabulary	7.2			9.2		
	(3.29)			(3.31)		
Picture completion	6.9			8.5		
	(2.42)			(3.21)		
-----						
Digit span	(Mean scaled scores)					
	8.5	9.2	9.5	10.8	10.8	12.3
	(2.01)	(2.35)	(2.07)	(2.79)	(2.86)	(2.88)
-----						
Trigram task	(Mean number correct)					
Condition 1	5.3	5.6	5.7	5.7	5.8	6.0
	(0.94)	(0.52)	(0.48)	(0.52)	(0.41)	(0.00)
Condition 2	5.0	4.3	3.5	5.3	5.2	5.7
	(1.05)	(1.64)	(1.35)	(0.82)	(1.67)	(0.52)
Condition 3	2.6	2.4	1.9	3.2	4.3	4.0
	(1.08)	(1.17)	(0.88)	(1.60)	(1.63)	(1.55)
-----						
Benton memory task	(Mean no. correct and mean no. errors)					
Score	5.4	5.4	5.0	7.8	8.7	7.8
	(1.78)	(2.59)	(1.83)	(2.14)	(1.21)	(1.84)
Errors	7.6	6.8	7.8	3.0	1.8	2.5
	(3.75)	(4.69)	(4.05)	(2.97)	(1.84)	(2.17)
-----						
Motor task	(Mean no. taps in 60 seconds)					
Condition 1	266	250	246	328	328	330
	(50.5)	(56.4)	(66.4)	(44.7)	(56.7)	(41.4)
Condition 2	133	129	131	176	181	185
	(36.0)	(37.1)	(33.0)	(31.5)	(24.7)	(20.2)
-----						
Category-decision	(Mean response time in milliseconds)					
Condition 1	768	796	726	493	511	525
	(279)	(362)	(287)	(66)	(83)	(125)
Condition 2	935	917	851	667	623	684
	(279)	(298)	(257)	(102)	(119)	(100)
Condition 3	1599	1623	1253	1015	921	920
	(287)	(257)	(339)	(125)	(100)	(335)
-----						
Attention switching	(Mean response time in milliseconds)					
Condition 1	2012	2086	2070	1559	1546	1753
	(598)	(595)	(671)	(439)	(260)	(266)
Condition 2	1976	2026	2106	1727	1686	1665
	(661)	(353)	(589)	(278)	(261)	(266)
-----						
Distraction tasks	(mean rate of performance per sec)					
Articulations	1.76	2.33	2.25	2.15	2.55	2.39
	(0.33)	(0.71)	(0.70)	(0.47)	(1.13)	(0.74)
Counting backwards	0.40	0.45	0.47	0.55	0.61	0.63
	(0.24)	(0.27)	(0.32)	(0.08)	(0.11)	(0.14)

-----

### 9.62 Quantitative Analysis

The quantitative analysis of the test performance data was carried out primarily by separate between-groups ANOVAS for each of the tests comparing the Lamotrogine group and the control (CTL) group. There was also a within-group factor of sessions, and on some tests a second within-group factor of condition.

The MACL data was not obtained from interval scales and the scores did not follow a normal distribution. Hence, a non-parametric test, the Mann Whitney test, was used to compare the groups in session one, and Freidman's test was used to compare performance across the sessions. There were no significant differences revealed by the across session analyses, but the subjects with epilepsy were significantly more depressed compared to the control group ( $P < 0.05$ ) in session one.

The means and standard deviations for the test battery results of the two groups are presented in table 9d. The "F" ratios, degrees of freedom and level of significance for these tasks are presented in table 9e.

Most of the tasks on the test battery were performed less well by the clinical group. Hence, the means were in the direction of poorer performance. For example, on the category-decision task, the mean response times in session one, for the group with epilepsy, across the three conditions, were 768, 935, and 1599 milliseconds, whereas the mean response times for the CTL group were 493, 667 and

1015 milliseconds, respectively. The standard deviations were generally larger for the Lamotrogine group, for example 279, 279, and 638 for the category-decision task, compared to 66, 102 and 459 respectively for the CTL group on the same task.

<u>Table 9e : Lamotrogine vs CTL : Results of ANOVA</u>		
Test	"F" ratios (Df) and levels of significance	
Intellectual Ability (Main effect of groups)	F = 1.55 (1/14)	P > 0.1
Vocabulary	F = 1.33 (1/14)	P > 0.1
Picture completion	F = 1.29 (1/14)	P > 0.1
Digit span (GP)	F = 3.87 (1/14)	P = 0.0693
(Effect of GP/SE)	F = 1.05 (2/28)	P > 0.1
Trigram task (GP Effect)	F = 9.56 (1,14)	P < 0.01
(Effect of GP/SE)	F = 6.26 (2,28)	P < 0.017
(Effect of GP/CC)	F = 3.47 (2,28)	P < 0.05
(Effect of GP/SE/CC)	F = 1.58 (4,56)	P > 0.1
Distraction tasks		
Articulations (GP effect)	F < 1	
(Effect of GP/SE)	F < 1	
Counting backwards (GP)	F = 1.85 (1/14)	P > 0.1
(Effect of GP/SE)	F < 1	
Benton Visual Retention task		
Scores (Effect of GP)	F = 10.36 (1/14)	P < 0.01
(Effect of GP/SE)	F < 1	
Errors (Effect of GP)	F = 8.26 (1/14)	P < 0.05
(Effect of GP/SE)	F < 1	
Motor task		
(Effect of GP)	F = 9.17 (1/14)	P < 0.01
(Effect of GP/SE)	F = 2.55 (2/28)	P = 0.0964
(Effect of GP/CC)	F = 1.92 (1/14)	P > 0.1
(Effect of GP/SE/CC)	F < 1	
Category decision task		
(Effect of GP)	F = 6.97 (1,14)	P < 0.05
(Effect of GP/SE)	F < 1	
(Effect of GP/CC)	F = 2.60 (2,28)	P = 0.0917
(Effect of GP/SE/CC)	F < 1	
Attention switching task		
(Effect of GP)	F = 1.54 (1,14)	P > 0.1
(Effect of GP/SE)	F < 1	
(Effect of GP/CC)	F < 1	
(Effect of GP/SE/CC)	F = 1.12 (2,28)	P > 0.1

Figure 9a: Graph of trigram data across sessions for the Lamotrogine and control group

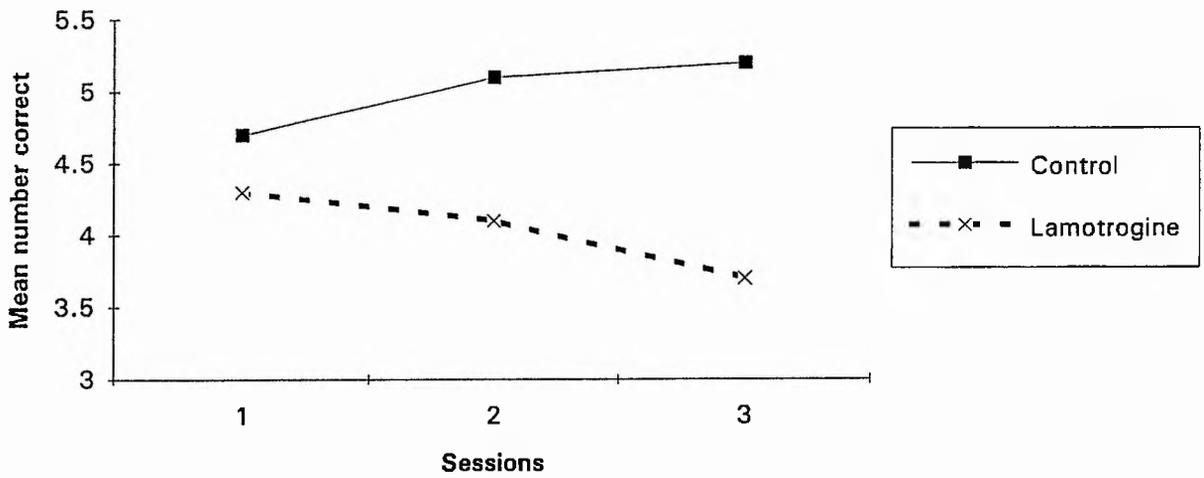
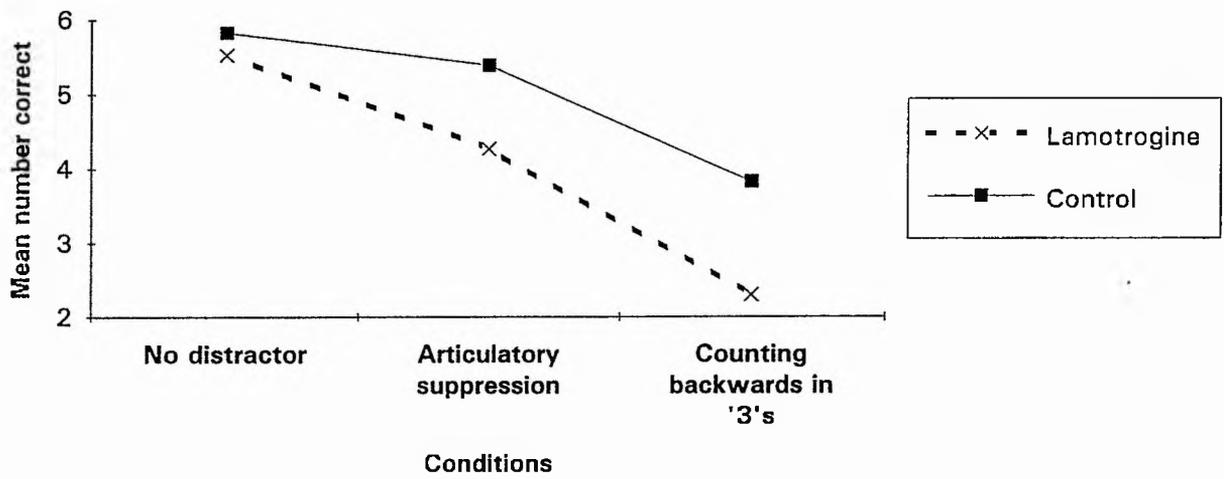


Figure 9b: Graph of trigram data across conditions for the Lamotrogine and control groups



The ANOVAs (as summarised in table 9e) revealed a number of significant differences across the test battery and in each case, the performance was poorer in the clinical group. The motor task, the trigram task and the Benton Visual Retention task all produced significant differences at the  $P < 0.01$  level, whilst the category-decision task produced a significant difference at the  $P < 0.05$  level. The two groups were not significantly different on the measures of intellectual ability.

The trigram task also produced a significant group by session interaction ( $F_{2,28} = 6.26, P < 0.05$ ), in which the clinical group means decreased over the three sessions and the control group means increased over the sessions (see figure 9a).

In relation to the group by condition interactions, there was a significant group by condition interaction in the trigram task ( $F_{2,28} = 3.47, P < 0.05$ ), (see figure 9b).

#### Post hoc analyses

A group by session effect ( $F_{(2,28)} = 6.26, P < 0.05$ ) and a group by condition effect ( $F_{2,28} = 3.47, P < 0.05$ ) were obtained on analysing the trigram data. Newman Keuls tests were used to analyse this set of results.

In relation to the Lamotrogine subjects, Newman Keuls test revealed a significant difference in performance between session one and session three ( $P < 0.05$ ) and between session two and session three ( $P < 0.05$ ), in the

direction of poorer performance in each succeeding session. The CTL group did not reveal any significant effect of sessions. Analysis of the effect of groups across sessions revealed that the groups were not significantly different in session one; there was a trend in the direction of poorer performance for the Lamotrogine group in session two, and the groups were significantly different in session three ( $P < 0.05$ ), in the direction of poorer performance by the Lamotrogine group.

In relation to the effect of condition on the trigram task, the Lamotrogine subjects displayed significantly poorer performance in condition two i.e with articulatory suppression distractor compared to condition one i.e with no distractor ( $P < 0.01$ ). Also, condition three i.e with counting backwards in threes, was significantly more difficult compared to both condition one and to condition two ( $P < 0.0001$ ). The CTL group did not reveal a significant difference between condition one and two, but revealed significantly worse performance in condition three compared to both condition one ( $P < 0.0001$ ) and condition two ( $P < 0.001$ ). Hence, introducing the secondary task of articulatory suppression, was sufficient for the performance of the clinical group to decline, unlike the CTL group which was able to maintain performance on the primary task.

(Note; Unfortunately, the data from condition three of the attention switching task was not included in the



### 9.7 Summary and discussion

Lamotrogine (a new anticonvulsant undergoing clinical trials) was given as an adjunct medication to ten subjects with epilepsy. The ten subjects completed the test battery on three occasions, once before commencing on Lamotrogine and twice after starting on Lamotrogine. Six control subjects also completed the test battery on three occasions. The following points summarise the main findings from the study:

1. The group with epilepsy was a sample of relatively young adults (mean age 29.4 years), whose epilepsy had an early onset (mean age at onset was 10.6 years) and hence a long duration of the disease (mean duration of 18.8 years). The control group was a slightly older group (mean age 34.6 years).

2. On most tasks, the subjects with epilepsy performed significantly worse than the control group. They were also significantly more depressed. However, the group with epilepsy did not perform significantly differently from the control group on tests of intellectual ability. Furthermore, the group with epilepsy had no history of other neurological disease and had normal CT scans. Hence, the differences in the performance of the control group and the epilepsy group supported the view that people with a long history of epilepsy, frequent seizures and

polypharmacy tend to have impaired cognitive functioning (see chapter two and three for a review of these areas).

3. The subjects with epilepsy were monitored for changes in seizure frequency across the sessions. On commencing Lamotrogine, half of the subjects had seizure frequencies that remained fairly constant, but for the other half the frequency of seizures decreased. Seizure frequency did not increase for any subjects, so any impairments in cognitive functioning in sessions two and three, could not be attributed to increased seizure frequency.

4. The health changes reported after subjects began taking Lamotrogine included headaches, nausea, unsteadiness and diplopia. However, it should be noted that most these health changes were noted by only one or two subjects and no health change was observed widely across the group.

5. In general, most subjects were able to complete the battery of tests, although one subject who had had repeated seizures in the testing sessions was withdrawn from the study and was not included in the analysis. Five subjects with epilepsy were unable to complete part three of the attention-switching task. Accordingly, this part of the task was excluded from the analysis for all subjects.

6. On the trigram task, the subjects with epilepsy performed worse across the three sessions, unlike the controls who maintained or even marginally improved performance across the sessions. There was also a

significant group by session interaction on the trigram task. This result provided a small amount of evidence that Lamotrogine may have an adverse effect on cognitive functioning.

7. The subjects with epilepsy appeared to have more difficulty than the CTL group on the trigram task as the task conditions became more complex. This group performed significantly worse on conditions two and three compared to condition one, whereas the control subjects performed significantly worse only in condition three compared to condition one. Thus, the relatively simple distractor task of "articulatory suppression" was enough to impair subjects on Lamotrogine on the primary trigram task, whereas the performance of the control subjects was only significantly affected by the more difficult distracting task of counting backwards in threes.

## CHAPTER TEN

### EXPLORATORY STUDIES USING RESPONSE-TIMED TASKS.

#### 10.1 Introduction

Towards the end of the data collection time for the Dundee study described in chapters four and five, it became apparent that the number of significant differences between the drug groups was smaller than might have been expected based on the results of Thompson and Trimble (1981, '82 and '83). At that time, I wondered whether one possible reason for this difference may have been that I had chosen predominantly memory tasks for this study. However, it was feasible that some of the Thompson and Trimble tasks had large perceptual and motor components, for example in the category-decision task, and that it was these aspects of the tasks that were sensitive to ACDs.

A small and exploratory pilot study was carried out in Dundee using a set of measures to investigate perceptual and motor components of tasks, with clinical and control subjects.

#### 10.2 Method

##### 10.21 Rationale

The rationale for the design of the tasks was to systematically vary aspects of the perceptual and motor functioning required by subjects, and to identify, if

present, possible impairments in specific areas of perceptual and/or motor functioning.

Simple reaction time tasks were used and were varied in both the size of the presented stimulus (affecting the amount of retinal stimulation) and also the dominance of the hand responding to the stimulus (varying sidedness of motor output).

Another task exploring motor output was employed. This task required the subject to respond using both hands on the response keys, either ipsilaterally or contralaterally to the stimulus presented on the screen.

Finally, perceptual discrimination tasks were employed. These tasks varied the difficulty of the discriminations of the two presented stimuli and required the subjects to respond using both hands.

#### 10.22 Subjects

The subjects invited to participate in this study were all the monotherapy and CTL subjects who had participated in the Dundee main study (see chapters four and five) and those subjects in the Lamotrogine study (see chapter nine). This invitation to participate provided eleven CTL subjects, seventeen subjects on monotherapy (nine on CBZ, five on DPH and three on VPA) and nine subjects on polytherapy (i.e a range of ACDs, plus Lamotrogine). The criteria for subject exclusion remained the criteria for

the original studies in which the subjects had participated.

The subjects provided information about seizure frequency since their last testing session. It was found that the majority of monotherapy subjects reported no recent seizures, and all the monotherapy subjects fell in to categories three, four and five in terms of seizure frequency.

The polytherapy group had more frequent seizures as described in chapter nine, but none on the actual day of testing.

The serum levels of ACDs were also measured after the testing and revealed that all subjects had significant amounts of their prescribed medications in their blood stream.

### 10.33 Procedure

Each subject completed the four tasks, in a specified order, on a BBC microcomputer. The stimuli appeared on the visual display unit and the responses were made on the attached response keys. All data were recorded in centiseconds by the microcomputer. Any data points of less than 12 centiseconds were treated as "anticipations" and were removed from the data sample before analysis. This procedure resulted in 0.35% of the data points being removed from the analysis.

Task (A) : Simple reaction time (SRT).

The subject was asked to press the response key with his/her index finger of his/her dominant hand, whenever a stimulus, (a white square), appeared on the middle of the screen. The subject was asked to respond as quickly as possible. Each stimulus was cued by a warning signal, (a "bleep" produced by the computer). The tone-stimulus interval was variable (0.5 - 2.0 secs).

The stimuli varied in size. Half the stimuli (the large stimuli), were 2cm by 2cm, and half (the small stimuli), were 1cm by 1cm. The small stimuli were the same size as the stimuli used in the reaction time experiments in the Glasgow study. Large and small stimuli were presented in random order.

There were 20 practice trials and 80 experimental trials.

Task (B) : Motor Task.

The stimuli, both large and small as in task (A), appeared on the screen shifted either to the left or to the right of centre; the eccentricity for the subject, as measured from the centre of the squares, was approximately 2.3 degrees.

The task was divided into four blocks of trials. In all trials, the subject placed his/her index fingers on two response keys placed 17.5cm apart. In two blocks of trials,

the subject was asked to press the response key on the same side (ipsilaterally) as the stimulus. In the remaining two blocks, the subject was asked to respond by pressing the key on the opposite side (contralaterally) to the stimulus. The subject completed the trials in a specified order for the four blocks, balancing the order of ipsilateral and contralateral conditions across the subject groups.

Again, each trial was accompanied by an auditory warning signal ("bleep") and the signal to stimulus time was variable (0.5 - 2.0 secs). There were 12 practice trials, followed by trials in which 40 large and 40 small stimuli were presented randomly.

Task (C) : Simple reaction time (SRT).

This task was essentially the same as task (A), except that the subject was asked to respond with their non-dominant hand.

Task (D) : Perceptual Discrimination task (PDT).

In this task, two stimuli appeared on the screen simultaneously, on the left and right of the screen; the eccentricity again being approximately 2.3 degrees. The stimuli differed in size. One pair of stimuli were a 2.5cm by 2.5cm square and a 1cm by 1cm square, and the other pair were squares of 1.75cm by 1.75cm and 1.5cm by 1.5cm i.e they were more difficult to tell apart. There were four blocks of trials and the mode of responding was the same as

in task (B). In two of the blocks, the subject was asked to press the key on the same side as the larger of the two stimuli, and in the other two blocks the subject responded on the same side as the smaller of the two stimuli. The blocks were completed in a specified order to balance the possible effects of order of completing tasks.

Thus, the task involved rapid discriminations between two stimuli. Obviously, a more difficult discrimination was required for stimuli that were more similar in size. Equal numbers of easy and more difficult discriminations were presented randomly throughout the blocks of trials.

Again, each trial had a warning signal and a variable signal-stimulus interval (0.5 - 2.0 secs). For each block there were 12 practice and 40 experimental trials.

-----  
Table 10a : Mean Response Times (in msec) and standard deviations for three groups (Pilot investigation)  
 -----

Task	CTL	MONOT	POLYT
<u>a) Reaction Time task</u>			
(Dominant hand)			
1. Large stimuli	286 (53)	295 (73)	433 (220)
2. Small stimuli	294 (60)	302 (75)	428 (119)
<u>c) Reaction Time task</u>			
(Non-Dominant hand)			
1. Large stimuli	296 (43)	328 (110)	394 (202)
2. Small stimuli	301 (46)	323 (69)	362 (110)
<u>b) Motor Task</u>			
Ipsi Large	346 (192)	391 (241)	410 (321)
Ipsi Small	346 (201)	384 (236)	431 (328)
Contra Large	441 (183)	494 (261)	664 (410)
Contra Small	458 (216)	494 (281)	587 (389)
<u>d) Perceptual Task</u>			
Easy Ipsi	357 (92)	388 (126)	476 (171)
Easy Contra	410 (103)	408 (131)	525 (198)
Hard Ipsi	390 (105)	467 (101)	528 (189)
Hard Contra	457 (117)	472 (131)	555 (210)

-----

### 10.3 Results

The means and standard deviations for the four tasks are presented in table 10a. In all tasks and in all conditions of the tasks the CTL had faster response times than the MONOT group, who in turn had faster response times than the POLYT group. The standard deviations in the CTL group were smaller than for the other groups, with the POLYT group having largest standard deviations.

The fastest response times were obtained in the simple reaction time responding with the dominant hand, followed by the simple reaction time task using the non-dominant hand. Not surprisingly, the perceptual discrimination task and the motor task had slower response times.

Each of the tasks was analysed using ANOVA with a between-groups factor of drug group and a within-groups factor(s) of condition of task. The "F" ratios, degrees of freedom and levels of significance of the analyses are presented in table 10b.

-----  
 Table 10.b : Analysis of the response time tasks across the  
three groups

Task "F" ratios, Dfs and levels of significance  
 -----

RT (dominant)

Effect of group	F = 5.22 (2, 34)	P < 0.05
Effect of size	F < 1	
Effect of GP by size	F < 1	

RT (non-dominant)

Effect of group	F = 2.94 (2, 33)	P = 0.0670
Effect of size	F < 1	
Effect of GP by size	F < 1	

Motor Task

(Ipsi/Contralateral)

Effect of Group	F = 2.22 (2, 34)	P > 0.1
Effect of Ipsi/Contra	F = 42.27 (1, 34)	P < 0.001
Effect of GP by IC	F = 2.45 (2, 34)	P > 0.1
Effect of GP by size	F < 1	
Effect of GP by IC by size	F = 1.24 (2, 34)	P > 0.1

Perceptual Task

Effect of Group	F = 1.79 (2, 34)	P > 0.1
Effect of easy/hard (EH)	F = 56.85 (1, 34)	P < 0.001
Effect of Ipsi/Contra	F = 11.65 (1,34)	P < 0.01
Effect of GP by IC	F < 1	
Effect of GP by EH	F = 1.37 (2, 34)	P > 0.1
Effect of GP by IC by EH	F < 1	

-----

There was a main effect of group in the simple reaction time task responding using the dominant hand ( $F_{2,34} = 5.22, P < 0.05$ ) and a trend on the simple reaction time task with the non-dominant hand ( $F_{2,34} = 2.94, P = 0.067$ ). However, there was no effect of condition, i.e. large versus small stimuli, on either of these two tasks.

The main effect of groups on the simple reaction time task was further analysed using Newman Keuls test, and it was found that both the CTL group and the MONOT group performed significantly better than the POLYT group at the  $P < 0.05$  level.

There was no effect of groups on the motor task. There was a marked effect of condition ( $F_{1,34} = 42.27, P < 0.001$ ) such that subjects found responding on the opposite side to the stimulus much more difficult than responding on the same side. However, there was no group by condition interaction.

There was no effect of groups on the perceptual discrimination task. There were two effects of conditions. The easy versus hard condition ( $F_{1,34} = 56.85, P < 0.001$ ), showed that the subjects performed significantly worse on the more difficult discrimination. Also, there was an effect of condition for the side of response ( $F_{1,34} = 11.65, P < 0.01$ ), with subjects responding significantly slower, if responding to the side of the smaller stimulus. However, there were no group by condition interactions.

The analyses were repeated after removing the outlier scores i.e scores three standard deviations away from the subject's mean score. These analyses produced a similar pattern of scores, in which the trend in the reaction time task with the non-dominant hand became a significant result ( $P < 0.05$ ).

#### 10.4 Summary and Discussion

The finding that the POLYT group performed significantly worse on the simple reaction time tasks is not surprising given the impaired performance of this group as described in chapter nine. The lack of significant differences between the MONOT group and the CTL group would indicate that if perceptual and/or motor abilities are the important aspect in differentiating between MONOT and CTL subjects, the differences are not large enough to be picked up on a small scale study such as the one described.

It is possible that by combining the three drug groups into one MONOT group, impairments due to one specific ACD have not been identified. It is also possible that the design of the tasks employed were not of a type suitable to detect the effects of ACDs. For instance, the tasks did not require a large amount of visual scanning by the subjects as would be required in a visual scanning task. Nevertheless, this pilot study would not encourage one to develop further simple perceptuo-motor tests to use in investigations of ACDs.

## CHAPTER ELEVEN

### SUMMARY AND DISCUSSION

#### 11.1 Introduction

The first part of this chapter, section 11.2, summarises the main findings of the studies described in the thesis. Section 11.3 discusses various aspects of the studies including the design, the clinical factors, the rationale of the test batteries and methods of data analysis. This part of the discussion also endeavours to discuss the findings and points of interest contained in the experimental work in relation to the literature reviews presented in chapters two, three and six. The third part, section 11.4, describes future avenues of investigation, that may help to unravel some of the complexities of work in this area. The final section (11.5) consists of a short summary and concluding comments on the thesis and the studies therein.

#### 11.2 Summary of main findings in the studies

##### 11.21 Dundee study One (chapters four and five)

This first study was a between-groups study comparing four anticonvulsant drug (ACD) groups i.e polytherapy (POLYT), carbamazepine (CBZ), sodium valproate (VPA) and phenytoin (DPH) and one control (CTL) group, with a total of 63 participating subjects. The main emphasis of the study was to compare the performance of the monotherapy

drug groups on a range of cognitive tasks, with a particular focus on memory tasks.

The hypotheses were only supported to the extent that the POLYT group was often impaired compared to the CTL group and less frequently compared to the CBZ group. The POLYT group performed significantly worse than the CTL group on the Rivermead Behavioural memory test ( $P < 0.05$ ) and significantly worse than the CTL and the CBZ group on the category-decision task ( $P < 0.05$ ). The POLYT group also performed significantly worse compared to the CTL, the CBZ and the DPH group on the tests of intellectual ability ( $P < 0.05$ ).

The subjects on monotherapy did not differ significantly from the CTL group, although the pattern of means supported the view of the CTL and CBZ groups performing better than the DPH and VPA groups. The hypothesis that the DPH group would perform significantly worse than both the VPA and CBZ groups was not supported.

Although there were few significant differences between the groups, the pattern of mean scores across the test battery was very consistent, with the CTL group and the CBZ group obtaining means in the direction of better performance, followed by the VPA and the DPH groups, with the POLYT group obtaining the worst mean scores. Larger subject groups may have yielded more significant findings, but another possible reason for the very consistent pattern in the means but few significant differences between the

groups was the large standard deviations in the drug groups. Further analysis revealed that these large standard deviations were due, in part, to out-liers in the clinical groups. Hence, a sizeable minority of subjects with epilepsy were impaired on the test battery.

The battery of tests used in this first study was chosen from the literature on ACDs up to 1987 (in particular, the studies by Thompson and Trimble 1981, '82 and '83) These studies had identified memory tests as likely to be sensitive to ACDs. The Rivermead Behavioural memory test (RMBT) was chosen as a measure of memory that also endeavoured to have a greater degree of ecological validity. This test did reveal a significant difference between the POLYT group and the CTL group, unlike the memory questionnaire which was also included to measure everyday memory functioning.

#### 11.22 Glasgow study (chapters seven and eight)

This large study involved over one hundred subjects and over two hundred testing sessions. The main design of the study was a between-groups design with four clinical groups and one CTL group. The repeated testing of subjects on the battery of tests allowed for two small within-subject comparisons; on the effects of changes in medication and the effects of recently occurring seizures.

With regard to the hypotheses for this study, the following points should be made; there was only a small

amount of support for the hypothesis that the groups with epilepsy would be impaired, compared to the CTL group, and where this arose it was the VPA group that performed worse than the CTL group i.e. on the trigrams task and the spatial memory task ( $P < 0.05$ ). The between-group ANOVAs revealed no significant differences between the three drug groups.

There was no evidence that the subjects with epilepsy on ACD medication performed less well than the subjects with epilepsy not on medication. There were no significant differences between the DPH group and the other drug groups, so refuting the hypothesis that the DPH would show more impairments. It was also hypothesized that where task demands increased, more impairments would be found in the ACD groups. As there were no significant condition by group interactions, this hypothesis was not supported.

The study did show a consistent pattern of means across the test battery. The CTL group consistently had means in the direction of better performance, followed by the CBZ, UT and DPH group, and finally the VPA group. One possible explanation for the paradox of a consistent pattern in the means, but very few significant differences between the groups, was the large variance of scores within the groups with epilepsy compared with the CTL group. This difference in the spread of scores appeared to be due, in part, to a number of subjects with epilepsy performing very poorly. This point was supported by an analysis using mean

z-scores that revealed large numbers of out-liers in the clinical groups compared to the CTL group, as was seen in the Dundee study. The reasons for the very poor performance of some of the clinical subjects was not obvious and a correlation analysis revealed that no epilepsy or drug factor correlated to performance on any of the tests.

A small portion of the subjects with epilepsy (N=16) had a change in medication between the testing sessions. ANOVAs carried out on the battery of tests revealed a significant impairment for the subjects with higher, rather than lower drug serum levels, on the spatial task ( $P < 0.05$ ). A trend in the same direction was shown on the trigram task ( $P < 0.1$ ). The group was divided into two smaller groups (CBZ=9 and DPH=7) and this revealed that the DPH group was more likely to show impairments with increases in drug serum concentrations, and indeed the DPH group also had significantly slower reaction times with higher drug concentrations ( $P < 0.05$ ); this was a result not present in the combined group (N=16) analysis.

The within-group analysis of the subjects who had seizures near the time of testing during one session and less frequent seizures at another time of testing revealed no significant findings across the test battery.

The analysis of practice effects on the test battery revealed only one significant practice effect, which was on the counting backwards in threes distractor task on the trigram task. There was a significant improvement in

counting backwards in threes between session one and two ( $P < 0.01$ ).

The battery of tests employed in this study was developed using the framework of working memory (Baddeley and Hitch, 1974) and attentional resource theory (Norman and Bobrow, 1975). The range of tests and distractor conditions aimed to provide a balance of tests across perceptual and motor abilities, and verbal, spatial and visual working memory tasks. The tests were designed to gradually increase in difficulty so enabling the testing of the hypothesis that increasing the demands of tasks would have a detrimental effect on some drug groups. The analysis of the conditions of the tests supported the validity of the design. The tests did increase in difficulty as predicted and also tapped into different parts of the working memory system. Thus, different types of distractor condition had differential effects on performance on the primary tasks. Furthermore, different primary tasks also had differential effects on the performance of the distractor tasks.

#### 11.23 Lamotrogine study (chapter nine)

The main emphasis of this study was a within-subject study in which ten subjects with epilepsy were given Lamotrogine as an adjunct medication to their normal ACD regime. The study was exploratory in nature, as Lamotrogine

is a relatively new ACD, and as such the effects, if any, on cognitive functioning were unknown.

There was also a small control group (N=6) included to ensure that there were no significant practice effects across the test battery. The inclusion of the CTL group revealed that the subjects with epilepsy were very much impaired on the test battery, as they performed very much worse than the CTL group, regardless of whether they were taking Lamotrogine. This result is interesting because the groups of clinical subjects in studies one (Dundee) and two (Glasgow) were, in general, not significantly different in performance, compared to the control groups. However, the severity of the epilepsy disorder was much more severe in the clinical group in this third study, both in terms of frequency of seizures and duration of the disorder, may account for the results obtained.

Analysing the results across the three testing sessions revealed that there was a significant deterioration in the performance of the subjects with epilepsy when they started taking Lamotrogine, on the trigram task ( $P < 0.01$ ), and this was most apparent with the most difficult condition of the task. There was also a trend in the same direction showing poorer performance across the sessions on the motor task.

In terms of seizure frequency, half of the clinical subjects reported no changes on starting Lamotrogine, but the other half did report a reduced seizure frequency after

starting Lamotrogine. A number of health changes were reported but with no one health change being noted widely across the group.

#### 11.24 Further investigations using response-timed tasks (chapter ten)

The small number of significant differences between the groups in the Dundee study led to speculation that choosing a battery of tasks which was heavily weighted towards memory tasks led to important aspects of the functioning of the clinical subjects being missed. It seemed possible that many of the tests reported by Thompson and Trimble had large perceptual and motor components, for example visual scanning tasks, and that it was these visual and motor components that were sensitive to ACDs. Researchers such as Dodrill (1977) had specifically identified DPH as impairing subjects on tasks with a large motor component, and Gillham, Williams, Weidman, Butler, Larkin and Brodie (1988) reported significant correlations between poor performance on psychomotor tests and concentration levels of CBZ.

A pilot study was carried out using perceptual and motor tasks on subjects who had previously participated in either the Dundee study or the Lamotrogine study. The three groups (CTL, MONOT, and POLYT) completed the battery of tests. The results revealed that the POLYT group was indeed slower on the simple reaction time tasks compared to the

MONOT and CTL group. However, the tasks did not reveal significant differences between the CTL and the MONOT groups. It would have been preferable to have been able to investigate the individual ACDs in three separate groups, but the number of volunteers for this study did not allow for such comparisons. Hence, it is possible that if a particular drug did affect perceptual and/or motor abilities, this would have been masked in the monotherapy group.

### 11.3 Further discussion of studies

A number of interesting aspects from the research are not apparent from the description of the group comparisons. In this section, I shall endeavour to high-light some of these aspects and also to relate some of the points raised to the literature presented in chapter two, three and six.

#### 11.31 Design of studies

The original design for both Dundee study one (chapters four and five) and Glasgow study (chapters seven and eight) were between-group designs with matched subjects, all on monotherapy, i.e on one of the three main-line ACDs. This design was chosen because of the lack of availability of subjects changing medication, such that the option of within-subject comparisons was not available.

The control groups were included to provide a base-line of normal performance on the tests batteries, as it had been expected that the groups with epilepsy would

perform at a lower level. Hence, a smaller number of control subjects were identified, enough only to provide an indicator of normal subject performance. On many occasions this poorer performance by groups with epilepsy did not in fact occur. The groups with epilepsy performed at the same or similar levels as the control groups. Hence, it would have been advantageous to have had larger control groups, in order to make more sensitive comparisons with the clinical groups and to explore whether some of the trends in the results would indeed have become significant differences between the control and drug groups. However, as the identification of control subjects was mainly done via clinical subjects asking relatives or friends to participate in the studies, it would not have been easy to find a large number of control subjects, post the time of the initial testing.

In Dundee, the through-put of subjects was slow and it was found that a number of subjects, whose medical notes indicated that they were on a monotherapeutic regime, turned out to be on polytherapy. It therefore seemed sensible to test several other subjects on polytherapy to form a polytherapy group. As it transpired, this was a worthwhile avenue to take, as it revealed that subjects with epilepsy on polytherapy did perform significantly less well on the Rivermead Behavioural Memory task and the category-decision task, compared to the CTL group.

An interesting group in the Glasgow study were the untreated clinical group. If the subject groups were well-matched and the ACD medication did affect cognitive functioning, then it would be reasonable to expect an UT group to perform significantly better than some or all of the ACD groups. This was not the case. This could be interpreted as strong evidence that the ACDs do not affect cognitive performance in a marked way. However, one issue that would need to be addressed is why those subjects were not taking ACD medication. Although there appeared to be no hard and fast criteria at the epilepsy clinic in Glasgow, it did appear that for some of those subjects in the UT group, there were question marks over their diagnosis, and suspicions by the doctors involved that rather complex personality and other factors affected the reported frequency of seizures and symptoms of the disease. It may be possible that such vague personality factors, such as motivation and energy levels, may have partially affected the performance of some subjects in this group.

The design of the Glasgow study included repeated testing of subjects. This allowed for subjects under-going changes in medication to be tested before and after the changes were made. The reasons for the changes in medication were clinical, and the numbers of subjects that fell in to this group were small (N=16); but it still seemed worthwhile to carry out a within-groups analysis on this group of subjects. This analysis produced evidence

that increased levels of DPH produced some reduction in cognitive functioning, both on tests of working memory and reaction time tasks.

The Lamotrogine study was also a within-subject design and there was close monitoring of epilepsy and drug variables, making this study more robust because there was more information available on the clinical subjects. The ANOVA showed that there was some indication that taking Lamotrogine impaired cognitive functioning.

#### 11.32 Clinical Aspects of the studies

A number of clinical factors were monitored in the Dundee and Glasgow studies, including type of seizures, frequency of seizures, and onset and duration of the disease. The monotherapy groups tended to be well matched and correlation analyses of test performances and these epilepsy variables supported the view that these factors did not have a large bearing on the performance of the subjects.

However, the polytherapy group, in the Dundee study, reported more frequent seizures and a longer duration of the disease than the other three drug groups. and the untreated group in the Glasgow study had a shorter duration of the disease than the three drug groups. Thus the matching of subjects in both studies was quite good, but not as close as would be desirable.

The analyses of the mean z-scores did reveal a number of subjects with epilepsy who performed very poorly, even though many subjects in the same drug groups performed in the normal range. It is possible, therefore, that there were epilepsy and other variables, which were not monitored, that could have had a bearing on the performance of individual subjects.

Dodrill (1986) reported that large number of seizures, i.e over one hundred, and prolonged exposure to seizure activity as in status epilepticus for example, would lead to deterioration of mental functioning. Although seizure frequency at and around the time of testing was monitored, the overall number of seizures was not recorded. Indeed, it would be difficult to obtain accurate information outside of a residential setting.

Delaney et al (1980) reported that subjects suffering temporal lobe seizures are more likely to show impaired memory functioning and that the laterality of the seizures would affect the type of effects seen. The medical notes on the subjects included in the Dundee and the Glasgow study did not provide enough information to be certain of details of the subjects' epilepsy. Hence, seizure types were categorised in three broad groups i.e tonic-clonic, complex partial and complex partial, secondarily generalised. As the laterality was for most subjects unknown, the possible effects of laterality of seizures of the temporal were not investigated.

The presence and amount of interseizure activity and possible absence seizures were not measured in either the Dundee or the Glasgow studies. Given the number of clinical subjects performing poorly, it would have been desirable to measure the amount of interseizure activity and to screen out absence seizures. Interseizure activity could have resulted in transitory cognitive impairment, "TCI", as described by Aarts et al (1984).

The amount of information, with regard to the aetiology of the seizure disorders and the possibilities of brain damage, was very small. The majority of subjects in the Glasgow study had had a CT scan and any subject with an abnormal CT scan was excluded from the study. However, in the Dundee study the majority of subjects had not had a CT scan. With the new brain imaging techniques, such as PET and MRI scanning, it may be possible to identify smaller areas and different types of brain damage that may not have been identified in the past. Although, the possibility of brain damage can not be ruled out in the subject samples included in the studies, as Dodrill (1992) has pointed out, there are individuals for whom small lesions of the brain have been identified using the newer imaging techniques; yet these individuals show few if any detectable cognitive impairments.

The dose and serum concentrations of the ACD medication were monitored in all the studies. A large number of the results from the blood sample analyses at the

Dundee Royal Infirmary did not reappear in the subjects' medical notes. Hence, there were fifteen missing serum concentration levels from the Dundee study. The results that were obtained revealed that the monotherapy and polytherapy groups' mean serum levels fell within the therapeutic range for the ACDS, but that there were a few subjects who fell out-side of this range.

In the Glasgow study, the serum level results were more consistently available, and hence, there were few missing results. The mean serum level for the CBZ and the VPA groups were within the therapeutic range, but there were three subjects in the CBZ group and seven in the VPA group who had levels of medication above this therapeutic range. The DPH group mean serum level was above the therapeutic range and ten subjects were above the top of this range. The importance of this difference is hard to assess. There were very few significant differences between CTL and ACD groups, in terms of performance on the test batteries. However, one of the subjects with the highest levels of DPH did perform very poorly on the battery of tests.

The studies carried out by Thompson and Trimble (1981, 1982 and 1983) and by Brodie et al (1986) measured the serum concentrations of the ACDs involved in their studies and revealed mean serum concentrations falling within the therapeutic range, although the range of serum levels reported would indicate that they also had subjects for

whom their drug serum concentrations were markedly outside the therapeutic range. Thompson and Trimble (1983) did try to take account of the possible effect that subjects with very high blood serum concentrations might have on test results. The data they obtained from 28 subjects having a reduction in their serum levels were re-analysed after removing fourteen subjects whose high concentrations were above the therapeutic range. This second analysis resulted in only four measures out of twenty being significantly different, compared to seven significant measures when all 28 subjects were included in the analyses.

### 11.33 Test design

The subjects in the Dundee and Glasgow studies completed different test batteries. The subjects in the Lamotrogine study completed some of the tests from the Dundee study and some from the Glasgow study. The reasons for the tests being different in each of the studies were dependent both on the theoretical questions being asked of each study and also on practical constraints, such as the available apparatus.

The Dundee study included a range of tests aimed at exploring the nature of tests that may be sensitive to ACD medication. The tests were chosen after consideration of the literature described in chapter two and three. This literature (for example Thompson and Trimble, 1981 and Andrewes et al, 1986) had claimed that memory tests would

reveal differences in cognitive functioning of subjects on specific ACDs. Interpretations such as these led to the inclusion of a number of memory tests in study one. Some of the memory tests were of a more visuo-spatial nature, as these types of memory test had rarely been used in relation to ACDs. Also, the Rivermead Behavioural memory test (RMBT) (Wilson et al, 1985) and a memory questionnaire (taken from the work of Sunderland et al, 1983) were included to measure memory impairments in a way that might indicate the nature of any identified impairments in everyday life. The results obtained showed no significant differences between the groups on the visual and spatial tests. There were also no differences on the memory questionnaire. The RMBT, on the other hand, did reveal a significant impairment for the POLYT group compared to the CTL group. There may be some value in employing this easy to use memory test to identify subjects with epilepsy having problems with their memory, particularly as this test may indicate in what type of everyday functioning the memory lapses occur.

As well as including this range of memory tests, a category-decision task (pen and paper version of the task designed by Thompson and Trimble, 1981) was included as this type of task was identified as being particularly sensitive to ACD effects. This version of the test did prove sensitive enough to distinguish between the POLYT group and the CTL group, but did not distinguish between the three individual drug groups.

Tests of intellectual ability were also included in the battery, with the hope that if there were differences between the groups on the memory and category-decision tasks, that these would not be apparent on the tests of intellectual abilities. Unfortunately, where group differences were found in relation to the POLYT group, significant differences were found in the category-decision task, the RMBT and the tests of intellectual ability. One could interpret this finding in one of two ways. Either the subjects in the POLYT group had lower intellectual abilities, regardless of the fact that they were suffering from epilepsy and this lower intellectual ability could account for their poor performance; or epilepsy and/or taking multiple ACDs results in lower performance on tests of intellectual ability. One piece of information that may help to decide between these two alternatives was that this finding of significantly worse performance on the tests of intellectual ability was not found in the Lamotrogine study, where the polytherapy subjects performed less well than the CTL group on many of the tests but were not impaired on the tests of intellectual ability. The CTL group in this study were made up exclusively from family members of the clinical subjects and it would therefore have been surprising to find large difference in intellectual abilities between the two groups. This finding would tend to support the view that the POLYT group in the Dundee study may have had lower premorbid levels compared

to the other groups and this may have affected their performance on the other tests.

The battery of tests used in the Glasgow study did have tests in common with other researchers in this area. For example, there was a simple motor task consisting of repeatedly tapping as quickly as possible for 60 seconds; a task that had been employed in the Brodie et al (1986) study. There was also a motor task involving tapping alternately on two switches, as described in the Thompson and Trimble (1981) battery of tests. The category-decision task employed by Thompson and Trimble was also used in this battery of tests.

However, the main rationale for the tests used in this study was to develop a battery of tests based on the theoretical frameworks of working memory and resource theory, as described in chapter six. Thus, the battery of tests included verbal, visual and spatial working memory tasks as well as tasks endeavouring to measure the central executive. The tasks were designed to increase in complexity, so as to test the hypothesis that more demanding tasks are more likely to be sensitive to the effects of ACDs. One positive aspect of the battery selected was that there were very significant effects of condition such that all the tasks did increase in task difficulty. Another positive factor was that the three specific working memory tasks did differentiate between the verbal and visuo-spatial systems of the working memory.

Furthermore, the significant slowing of tapping rate in the spatial memory task provided evidence that the visual and spatial tasks were, to some degree, different parts of the working memory system. Where differences were identified between or within the subject groups, these working memory tasks, particularly the trigrams and spatial task, were as sensitive as the other tasks included in the battery such as motor and reaction time tasks.

With regards to the other tests included in the Glasgow test battery, unfortunately, a "bug" in the computer programme in the attention-switching and the category-decision tasks meant that approximately one third of the data for these two tasks were lost, and as such the numbers of subjects available for analysis was very small and revealed no interesting findings. These two tasks were again employed in the Lamotrogine study, but it was found that part three of the attention-switching task was so difficult for some of the polytherapy subjects that this condition of the test had to be removed from the test battery. The category-decision task was used in the Lamotrogine study and, although it revealed impairments in the polytherapy group compared to the CTL group, it was not sensitive to the effects of taking Lamotrogine in addition to the original medication, unlike the trigrams and motor task. The category-decision task, therefore, did not prove to be a sensitive measure in the Lamotrogine study, whereas Thompson and Trimble had found it to be a very sensitive

measure in their ACD studies. In summary, the tests included in the test batteries, in an attempt to measure "central executive" functioning were not successful, either in their ease of use or in the results obtained.

Tests of intellectual ability and measures of mood of subjects at the time of testing were also included in the Glasgow battery. Unlike the Dundee study there were no significant differences between the groups on the tests of intellectual ability. It was noticeable, however, that the pattern of means revealed that the VPA group obtained the lowest means on the intellectual ability measures as it did on many other of the measures. There were no significant differences between the groups on the mood scores.

Although the test battery used in the Glasgow study was comprehensive, it was also quite draining for some of the subjects (comments to this effect were made by some subjects at the time of testing). Care must therefore be taken to design batteries of tests that are not too taxing for subjects. This point was taken on board for the Lamotrogine study and this battery of tests was shorter and therefore less taxing. A further constraint on the choice of tests in the Lamotrogine study, was that there was access to only one computer which meant, for example, that the combination of reaction time and motor tasks could not be included in this battery. Thus, only the motor tasks were included in this test battery.

### 11.34 Method of data analysis

The data was generally analysed by analysis of variance, but some of the data analysed in this way did not show a normal distribution. In particular, there were ceiling effects on a number of the tasks and, a number of out-liers in the epilepsy groups. The decision to continue using ANOVA was based on the facts that most of the data did show approximate normal distributions; this type of analysis was used on similar tasks by most researchers in the field; and ANOVA allows for more detailed analysis, i.e. more than just the effects of groups.

In relation to the data analysis, an interesting finding in the Glasgow study was that subjects changed their performance on distractor tasks, dependant on the nature of the primary task. Hence, the ANOVAs of the distractor tasks across the three primary tasks were necessary and provided more evidence that the three primary tasks were tapping into different parts of the working memory system.

The battery of tests employed in the Glasgow study was also analysed for practice effects. This analysis revealed that there was a learning effect on the distractor task of counting backwards in threes. It may, in hind-sight, have been worthwhile to ask the subjects to start counting backwards from a different number each time they completed the test battery which may have reduced the learning effect.

Additional analyses involving the identification of out-liers using mean z-scores, showed a number of clinical subjects performing very poorly on the tests. Do the results of other researchers in this area show similar patterns of results? The data from two of the studies were examined to investigate the nature of the spread of the individual scores on tests. The first study treated in this way was the Thompson and Trimble (1981) study comparing placebo and DPH taken by volunteer subjects (as described in chapter three). Of the sixteen means measured across the battery of tests, the DPH condition had higher standard deviations in twelve of the comparisons, two comparisons produced the same standard deviations for both drug conditions and the placebo group had the higher standard deviations on only two of the measures. On some of the measures, the standard deviations for the DPH condition were extremely large, for example in the Stroop task the standard deviation for the DPH condition was almost three times the size for the placebo condition, and in the category-decision task the standard deviation was double the size in the DPH condition compared to the placebo condition. It is somewhat surprising that with such large variation across the subject samples, significant differences were found between the two conditions, but there was a within-subject design and the actual data used in the ANOVAs were the difference scores between the original base-line scores and the two drug condition

scores. These two aspects of the design meant that significant differences were more likely to be found.

Brodie et al (1986) compared a control group with an untreated group of subjects with epilepsy and a group of subjects with epilepsy on medication. The results of this study were presented in terms of means and range of scores obtained. It was found that on the nine measures used, the range of scores for the treated group with epilepsy were larger than for the control group. Not all the ranges were very far apart but tasks such as the tapping task revealed a range of scores double that of the control group. This task produced a highly significant difference between the two groups ( $P < 0.001$ ). A similar picture arose on other tasks in the Brodie battery of tests including the choice reaction time measures.

The significant differences found by Brodie et al (1986) using the tapping task are very much at odds with the results obtained with the Glasgow study described in this thesis. One of the factors that may account for this difference in results was the fact that the Brodie et al study carried out non-parametric analyses (Mann-Whitney U) on their data. The variance within the groups does not affect this analysis to any large degree, unlike ANOVA in which the variance within the groups is intrinsic to the analysis. However, the using of Mann-Whitney U test would be considered a less powerful analysis than using ANOVA and does not allow for the analysis of two or more independent

variables simultaneously, as is required in much of the data presented in this thesis.

#### 10.4 Future avenues of investigation

One of the main difficulties in the studies described in this thesis is the problem of disentangling the possible effects of epilepsy and drug variables on cognitive functioning. As described on a number of occasions earlier, there were no clear-cut differences between the drug groups, but there were a number of individuals performing very poorly (out-liers) on some of the tests. To investigate the poor performance of some subjects, two approaches were taken. Scrutinizing individual clinical details of these subjects did not point to any one factor that could account for their poor showing and correlating epilepsy, drug and performance variables did not yield fruitful results that could indicate relevant factor(s) either.

However, although many factors in relation to the subjects' epilepsy were monitored through the course of the studies, one factor, the amount of abnormal brain activity, of epileptiform nature or otherwise, at the time of testing was unknown, and it would seem plausible that such abnormal activity could account for some the poor showing of some subjects. Hence, one way forward in these types of studies would be to monitor brain activity at the time of testing. In this way, the association between epileptiform activity

and cognitive performance can be investigated. Also, if ACDs effect brain activity, the changes in brain activity and the affect of these changes on cognitive performance may also be a worthwhile area to explore.

Another way forward from the type of studies described in this thesis, is to take a more clinical path. It may be possible to include tasks such as the Rivermead Behavioural Memory Test as part of a routine screening of subjects, in out-patient settings. This would allow clinicians to identify those subjects experiencing difficulties, both for the purpose of more intensive investigation of their difficulties and also to offer appropriate support, if necessary.

#### 11.5 Summary

The thesis consists of four studies, of which the Glasgow study is by the far the most substantial. The general conclusion was that the hypotheses developed from the literature presented in chapters two, three and six were not supported. The monotherapy groups did not differ from each other, and were frequently not significantly different from the CTL groups, with only a small number of significant differences between the VPA and the CTL group in the Glasgow study. The polytherapy groups in both the first Dundee study and the Lamotrogine study did perform significantly differently from the CTL groups, but a number of factors relating both to epilepsy variables as well as

medication could account for these differences. The two small-within group drug change comparisons i.e in the Glasgow study and the Lamotrogine study, did provide a small amount of evidence that larger levels of medication, both in terms of increasing levels of DPH and also commencing Lamotrogine, impaired cognitive functioning.

The small number of significant differences between the ACDs is in contrast to much work done in this area, particularly in comparison to the work of Thompson and Trimble (1981, '82 and '83). This could have been because of the between-group design, but recent studies, for example Meador et al (1990), in which within-group designs have been used, have also found very few significant differences between the drug groups. Re-analyses by Dodrill and Troupin (1991) have also shown that differences may disappear when DPH subjects above the therapeutic range are removed from the subject sample. Other reasons, such as different types of statistical analysis as in the Brodie et al 1986 study, may also account for why the studies in this thesis found so few significant differences. It appears that the effects of ACDs on cognitive functioning are subtle enough to only be apparent in very specific circumstances.

An interesting observation across the studies were the large standard deviations across the clinical subject groups. There were a number of out-liers in the clinical groups. The reasons for the poor performance of the out-

liers may be because of some clinical factor not identified, but may also be possible that some, but not all subjects, suffer from cognitive impairment associated with ACD medication, just as some but not all patients suffer different physical side-effects, i.e there are individual differences in response to the medication. It is interesting to note that large ranges of scores and large standard deviations were obtained in other published work, but to date I have not read any discussion on the reasons for these large ranges of scores.

Some of the clinical aspects of the studies described in this thesis were disappointing, for example, the identification of large numbers of suitable subjects was not as successful as was hoped for at the out-set. If one is to monitor and partial out the multitude of possible clinical variables that potentially may effect subject performance, one needs very large subject samples and good clinical information about the subjects identified. Also, the monitoring of on-going epileptiform activity was not possible, and such monitoring would be a step forward in these types of studies.

Ways of further improving the types of study described in this thesis include the rather obvious design change of increasing the amount of within-subject experiments. Adherence to a large number of clinical variables when selecting subjects would also be of benefit. In relation to the Glasgow test battery, one may wish to remove demanding

tests, for example, the attention-switching task as this task was draining for some subjects.

I believe that the test batteries developed for the studies had many positive aspects to them. The Dundee study battery employed tests such as the RMBT which are designed to have more "ecological validity" and therefore may be more useful from a clinical perspective. The Glasgow battery of tests contained a balance of tests across perceptual, motor, working memory and control processes, and was developed from an established theoretical literature. The tasks also manipulated task complexity, allowing for the testing of the hypothesis that ACD effects on cognitive performance are more likely to occur with more difficult tasks (an hypothesis not supported in this study).

The general vein running through the thesis is that the cognitive effects of the main-line ACDs seem to be slight, and that adverse outcomes may only become apparent under specific circumstances, for example, at high serum levels or when starting a new drug. However, it would also seem important to take into account individual differences in possible reactions to medication and the consequent effects on cognitive functioning.

REFERENCES

- Aarts, J.H.P., Binnie, C.D., Smit, A.M. and Wilkins, A.J. (1984). Selective cognitive impairment during focal and generalised epileptiform EEG activity. *Brain*, 107, 293-308.
- Allport, D.A. (1980). Attention and performance. In *Cognitive Psychology: new directions*. Editor: G. Claxton, Routledge and Kegan Paul, London.
- Andrewes, D.G., Bullen, L., Tomlinson, L., Elwes, R.D.C. and Reynolds, E.H. (1986) A comparative study of the cognitive effects of phenytoin and carbamazepine in new referrals with epilepsy. *Epilepsia*, 27, 128-134.
- Andrewes, D.G., Puce, A. and Bladin, P.F. (1990) Post-ictal recognition memory predicts laterality of temporal lobe seizure focus: comparison with post-operative data. *Neuropsychologia*, 28 (9), 957-967.
- Andrewes, D.G., Tomlinson, L., Elwes, R.D. and Reynolds, E.H. (1984) The influence of carbamazepine and phenytoin on memory and other aspects of cognitive function in new referrals with epilepsy. *Acta Neurologica Scandinavia*, 69, 23-30.
- Atkinson, R.C. and Shiffrin, R.M. (1968) Human memory: A proposed system and its control processes. In: *The psychology of learning and motivation: advances in research and theory Volume 2*. Editor: K.W. Spence, 89-195. Academic Press, New York.
- Atkinson, R.C. and Shiffrin, R.M. (1971) The control of short-term memory. *Scientific American* 225, 82-90.
- Babcock, H. (1930) An experiment in the measurement of mental deterioration. *Archives of Psychology*, 117, 105.
- Baddeley, A.D. (1978) The trouble with levels: a reexamination of Craik and Lockhart's framework for memory research. *Psychological Review*, 85, 139-152.
- Baddeley, A.D. (1986) *Working memory*. Clarendon Press, Oxford .
- Baddeley, A.D. and Hitch, G. (1974) Working memory. *The Psychology of Learning and Motivation*, 8, 47-87.
- Baddeley, A.D., Lewis, V.J. and Vallar, G. (1984) Exploring the articulatory loop. *Quarterly Journal of Experimental Psychology*, 36, 233-252.

- Baddeley A.D. and Lieberman, K. (1980) Spatial working memory. In: Attention and performance VIII. Editor: R. Nickerson, p521-539. Erlbaum, Hillsdale, New Jersey.
- Baddeley, A.D., Thomson, N., and Buchanan, M. (1975) Word length and the structure of short-term memory. *Journal of Verbal Learning and Verbal Behaviour*, 14, 575-589.
- Bennet-Levy, J. (1984) Determinants of performance on the Rey-Osterrieth complex figure test: an analysis, and a new technique for single-case assessment. *British Journal of Clinical Psychology*, 23, 109-119.
- Bennett, T. L. (1992) Cognitive effects of epilepsy and anticonvulsant medications. In: *The Neuropsychology of Epilepsy*, Editor: T.L. Bennett, p73-96. Plenum Press, New York and London.
- Benton, A.L., Glithorn, A., Fogel, M.L. and Kerr, M. (1963) A perceptual maze task sensitive to brain damage. *Journal of Neurosurgery and Psychiatry*, 26, 540-544.
- Binnie, C.D., Aarts, J.H.P., Houtkooper, M.A., Laxminarayan, R., Martins de Silva, A. and Meinardi, H. (1984) Temporal characteristics of seizures and epileptiform discharges. *Electroencephalography and Clinical Neurophysiology*, 58, 498-505.
- Binnie, C.D., Kasteleijn-Nolst Trenite, D.G.A. and De Korte, R. (1986) Photosensitivity as a model for acute antiepileptic drug studies. *Electroencephalography and Clinical Neurophysiology*, 63, 35-41.
- Booker, H.E. (1972). Primidone toxicity. In: *Antiepileptic Drugs*. Editors: D.M. Woodbury, J.K. Penry and R.P. Schmidt. Raven Press, New York, p 377.
- Boxer, C., Herzberg, J. and Scott, D. (1976) Has sodium valproate hypnotic effects? *Epilepsia*, 17, 367-370.
- Broadbent, D.E. and Gregory, M. (1965) Some confirmatory results on age differences in memory for simultaneous stimulation. *British Journal of Psychology*, 56, 77-80.
- Brodie, M.J., McPhail, E.M., Macphee, G.J.A., Larkin, J.G. and Gray J.M.B. (1987) Psychomotor impairment and anticonvulsant therapy in adult epileptic patients. *European Journal of Clinical Pharmacology*, 31, 655-660.

- Browne, T.R., Penry, J.K., Porter, R.J. and Dreifuss, F.E. (1974) Responsiveness before, during and after spike-wave paroxysms. *Neurology*, 24, 659-665.
- Callagan, N., Kenny, R.A., O'Neil, B., Crowley, M. and Goggin, T. (1985) A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry* 48, 639.
- Cohen, A.F., Ashby, L., Crowley, D. and Peck, A.W. (1985) CNS effects in normal volunteers of phenytoin, diazepam and lamotrigine (BW430C), a new anticonvulsant. *British Journal of Clinical Pharmacology*, 20, 286.
- Cohen, A.F., Ashby, L., Crowley, D., Land, G., Peck, A.W. and Miller, A.A. (1985) Lamotrigine (BW430C), a potential anticonvulsant. Effects on the central nervous system in comparison with phenytoin and diazepam. *British Journal of Clinical Pharmacology*, 20, 619-629.
- Commission on classification and terminology of the International League Against Epilepsy (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*, 22, 489-501.
- Commission on classification and terminology of the International League Against Epilepsy (1989) Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*, 30, 389-399.
- Craik, F.I.M. and Lockhart, R.S. (1972) Levels of processing: a framework for memory research. *Journal of Verbal Learning and Verbal Behaviour*, 11, 671-684.
- Davidson, D.L. (1983) Anticonvulsant drugs. *British Medical Journal*, 286, 2043-2045.
- Delaney, R.C., Rosen, A.J., Mattson, R.H. and Novelly, R.A. (1980) Memory function in focal epilepsy: a comparison of non-surgical, unilateral temporal lobe and frontal lobe samples. *Cortex*, 16, 103-117.
- Dikmen, S. and Mathews, C.G. (1977) Effect of major motor seizure frequency upon cognitive-intellectual functions in adults. *Epilepsia*, 18, 21-29.

- Dodrill, C.B. (1986) Correlates of generalized tonic-clonic seizures with intellectual, neuropsychological, emotional and social function in patients with epilepsy. *Epilepsia*, 27, 399-411.
- Dodrill, C.B. (1992) Interictal cognitive aspects of epilepsy. *Epilepsia*, 33 (suppliment 6), S07-S10.
- Dodrill, C.B. and Troupin, A. S. (1977) Psychotropic effects of carbamazepine in epilepsy: a double-blind comparison with phenytoin. *Neurology*, 27, 1023-1028.
- Dodrill, C.B. and Troupin, A.S. (1975) Effects of repeated administrations of a comprehensive neurological battery on epileptic subjects. *Journal of Mental Disorders*, 161 : 185-190.
- Dodrill, C.B. and Troupin, A.S. (1991) Neuropsychological effects of carbamazepine and phenytoin: A reanalysis. *Neurology*, 41, 141-143.
- Eadie, M.J., Tyrer, J.H. (1989) Anticonvulsant therapy, pharmacological basis and practice. 3rd Edition. p3-46 Churchill, Livingston.
- Elithorn, A., Jones, D., Kerr, M. and Lee, D (1964) The effects of the variation of two physical parameters on empirical difficulty in a perceptual maze task. *British Journal of Psychology*, 55, 31-37.
- Escueta, A. and Walsh, K. (1983) The selection process for surgery of intractable complex partial seizures: surface EEG and depth electrography. In: *Epilepsy*. Editors: A. Ward junior, J.K. Penry and D. Purpura. p 295-325. Raven Press, New York.
- Eysenck, M.W. (1984) *Handbook of cognitive psychology*. Erlbaum Associates, Hillsdale, New Jersey.
- Feldman, R. (1983) Complex partial seizures (psychomotor or temporal lobe seizures) In: *Epilepsy: Diagnosis and Management*. p39-50. Little, Browne and Company.
- Fenwick, P. (1981) Precipitation and inhibition of seizures. In: *Epilepsy and Psychiatry*. Editors: E. Reynolds, and M. Trimble. Churchill Livingston, London.
- Fenwick, P. (1992) The relationship between mind, brain and

- seizures. *Epilepsia*, 33 (suppliment 6), 51-56.
- Fowler, P.C., Richards, H.C., Berent, S. and Boll, T.J. (1987) Epilepsy, neuropsychological deficits and EEG lateralisation. *Archives of Clinical Neuropsychology*, 2, 81-92.
- Gallagher, B.B. (1982) Clinical pharmacology and rational prescribing. *Epilepsia*, 23, 519-528.
- Gastaut, H. and Broughton, R. (1972) Epileptic seizures: clinical and electrographic features, diagnosis and treatment. Charles Thomas, Springfield Illinois.
- Gastaut, H., Gastaut, J.L., Concalves e Silva, G.E. and Fernadez Sanchez, G.R. (1975) Relative frequency of different types of epilepsy: a study employing the classification of the International League Against Epilepsy. *Epilepsia* 16, 447-461.
- Gay, P.E. (1984) Effects of antiepileptic drugs and seizure type on operant responding in mentally retarded persons. *Epilepsia*, 25, vol 3, 337-386.
- Gram, L., Bentsen, K., Parnas, J and Flachs, H. (1982) Controlled trials in epilepsy: a review. *Epilepsia*, 23, 291-319.
- Gram, L., Wulff, K., Sommerbeck, K.W., Rasmussen, K.R., Flachs, H., Lohren, V. and Wurtzjurgensen, A. (1977) Valproate sodium: a controlled clinical trial including monitoring of drug levels. *Epilepsia*, 18, 141-148.
- Hallworth, M.J. and Brodie, M.J. (1987a) Therapeutic monitoring of carbamazepine. *Hospital Update*, 57-63.
- Hallworth, M.J. and Brodie, M.J. (1987b) Therapeutic monitoring of Phenytoin. *Hospital Update* 830-840.
- Harding, G.F.A., Alford, C.A. and Powell, T.E. (1985) The effect of Na valproate on sleep, reaction times, and visual evoked potentials in normal subjects. *Epilepsia*, 26, 597-601.
- Harris, J.E. and Morris, P.E. (1984) Everyday memory, actions and absentmindedness. Academic Press, United Kingdom.
- Haward, L. (1970) Effects of sodium diphenylhydantoin and primidone upon concentration: A comparative study. In: *Drugs and Cerebral Function*. Editors: W. Lynn Smith. Charles C. Thomas, Springfield, Illinois, p103-120.

- Hermannn, B.P., Wyler, A.R. and Rickey, E.T. (1988)  
Wisconsin card sorting test performance in patients  
with complex partial seizures of temporal-lobe origin.  
Journal of Clinical and Experimental Neuropsychology,  
10, 467-476.
- Hindmarsh, I. (1980) Psychomotor function and psychoactive  
drugs. British Journal of Clinical Pharmacology, 10,  
189-209.
- Idestrom, C.M., Schalling, D., Carlquist, V. and Sjoquist,  
F. (1972). Behavioural and psychophysiological  
studies: acute effects of diphenylhydantoin in  
relation to plasma levels. Psychological Medicine, 2,  
111-120.
- Jawad, S., Oxley, J.R., Yuen, W.C. and Richens, A. (1985)  
Reduction of interictal electroencephalographic spikes  
by lamotrogine in epileptic patients. British Journal  
of Clinical Pharmacology, 20, 287.
- Kahneman, D. (1973) Attention and Effort. Englewood  
Cliffs, New Jersey: Prentice-Hall.
- Kiloh, L.G., McComas, A.J. and Osselton, J.W. (1972)  
Clinical Electroencephalography. 3rd edition.  
Butterworth, London.
- Kirk, R.E. (1982) Experimental Designs; Procedures for the  
Behavioural Sciences, p988 Brooks/Cole, Belmont,  
California, .
- Laidlaw, J. and Richens, A. (1993) Textbook of epilepsy.  
4th edition. Churchill Livingstone, London .
- Lansdell, H. and Mirsky, A.F. (1964) Attention in focal and  
centrencephalic epilepsy. Experimental Neurology, 9,  
463-469.
- Lee, D.J. (1984) The Behavioural effects of antiepileptic  
drugs in animals and man : Studies involving the use  
of DPH, CBZ and VPA administered alone and in selected  
combinations. PhD : Hull.
- Lesser, R.L., Pippenger, C.E., Luders, H. and Dinner, D.S.  
(1984) High-dose monotherapy in treatment of  
intractable seizures. Neurology, 34, 707-711.
- Levy, J. (1974b) Psychological implications of bilateral  
asymmetry. In: Hemisphere function in the human brain.  
Editors: S.J. Dimond and J.G. Beaumont, chapter 6.  
Elek Science, London.

- Helmstaedter, C., Pohl, C., Hufnagel, A. and Elger C.E. (1991) Visual deficits in nonresected patients with right temporal lobe epilepsy. *Cortex*, 27 (4), 547-555.
- Hermannn, B.P., Wyler, A.R. and Rickey, E.T. (1988) Wisconsin card sorting test performance in patients with complex partial seizures of temporal-lobe origin. *Journal of Clinical and Experimental Neuropsychology*, 10, 467-476.
- Hindmarsh, I. (1980) Psychomotor function and psychoactive drugs. *British Journal of Clinical Pharmacology*, 10, 189-209.
- Idestrom, C.M., Schalling, D., Carlquist, V. and Sjoquist, F. (1972). Behavioural and psychophysiological studies: acute effects of diphenylhydantoin in relation to plasma levels. *Psychological Medicine*, 2, 111-120.
- Jawad, S., Oxley, J.R., Yuen, W.C. and Richens, A. (1985) Reduction of interictal electroencephalographic spikes by lamotrogine in epileptic patients. *British Journal of Clinical Pharmacology*, 20, 287.
- Kahneman, D. (1973) Attention and Effort. Englewood Cliffs, New Jersey: Prentice-Hall.
- Kiloh, L.G., McComas, A.J. and Osselton, J.W. (1972) Clinical Electroencephalography. 3rd edition. Butterworth, London.
- Kirk, R.E. (1982) Experimental Designs; Procedures for the Behavioural Sciences, p988 Brooks/Cole, Belmont, California, .
- Laidlaw, J. and Richens, A. (1993) Textbook of epilepsy. 4th edition. Churchill Livingstone, London .
- Lansdell, H. and Mirsky, A.F. (1964) Attention in focal and centrencephalic epilepsy. *Experimental Neurology*, 9, 463-469.
- Lee, D.J. (1984) The Behavioural effects of antiepileptic drugs in animals and man : Studies involving the use of DPH, CBZ and VPA administered alone and in selected combinations. PhD : Hull.
- Lesser, R.L., Pippenger, C.E., Luders, H. and Dinner, D.S. (1984) High-dose monotherapy in treatment of intractable seizures. *Neurology*, 34, 707-711.
- Levy, J. (1974b) Psychological implications of bilateral asymmetry. In: Hemisphere function in the human brain. Editors: S.J. Dimond and J.G. Beaumont, chapter 6. Elek Science, London.

- Lishman, W.A. (1972) Selective factors in memory: Part 2 : Affective disorder. *Psychological Medicine*, 2, 248-253.
- Logie, R.H. (1986) Visuo-spatial processing in working memory. *The Quarterly Journal of Experimental Psychology*, 38a, 229-247.
- Macphee, G.J.A., Goldie, C., Roulston, D., Polter, L., Agnew, E., Laidlaw, J. and Brodie, M.J. (1986) Effects of carbamazepine on psychomotor performance in naive subjects. *European Journal of Clinical Pharmacology*, 30, 37-42.
- Macphee, G.J.A., Mcphail, E.M., Butler, E. and Brodie, M.J. (1986) Controlled evaluation of a supplementary dose of carbamazepine on psychomotor function in epileptic patients. *European Journal of Clinical Pharmacology*, 31, 195-199.
- Mattson, R.H., Cramer, J.A. and Collins, J.F. (1985) Comparison of carbamazepine, phenobarbital, phenytoin and primidone in partial and secondarily generalised tonic-clonic seizures. *New England Journal of Medicine*, 313, 145-151.
- Mayeux, R., Brandt, J., Rosen, J. and Benson, F. (1980) Interictal memory and language impairment in temporal lobe epilepsy. *Neurology*, 30, 120-125.
- McNair, D.M. and Larr, M. (1964) An analysis of mood in neurotics. *Journal of Abnormal and Social Psychology*, 69, 620-627.
- Meador, K.J., Loring, D.W., Huh, K., Gaulogher, B.D. and King, D.W. (1990) Comparative cognitive effects of anticonvulsants. *Neurology*, 40, 391-394.
- Meinardi, H. (1972). Carbamazepine. In: *Antiepileptic Drugs*. Editors: D.M. Woodbury, J.K. Penry, and R.P. Schmidt. Raven Press, New York.
- Meldrum, B.S. (1988) Initiation and neuroanatomical spread of seizure activity. In: *Recent advances in epilepsy*, volume 4. Editors: T.A. Pedley and B.S. Meldrum, p1-19, Churchill Livingstone, Edinburgh.
- Meldrum, B.S. (1991) Excitatory Amino Acid Transmitters in Epilepsy. *Epilepsia*, 32, supplement 2, 51-53.

- Miller, A.A., Sawyer, D.A., Roth, B., Peck, A.W., Leach, M.J., Wheatley, P.L., Parsons, D.N. and Morgan, R.J.I. (1986) Lamotrigine. In Current problems in epilepsy, volume 4: new anticonvulsant drugs. Editors: B.S. Meldrum and R.J. Porter. John Libbey, London.
- Mirsky, A.F. and Van Buren, J.M. (1965) On the nature of the "absence" of centrencephalic epilepsy: a study of some behavioural, electroencephalographic and autonomic factors. *Electroencephalography and Clinical Neurophysiology*, 18, 334-348.
- Moray, N. (1967) Where is attention limited? A survey and a model. *Acta Psychologica*, 27, 84-92.
- Morris, R.G. (1984) Dementia and the functioning of the articulatory loop system. *Cognitive Neuropsychology*, 1, 143-157.
- Morris, R.G. (1986) Short-term forgetting in senile dementia of the Alzheimer's type. *Cognitive Neuropsychology*, 3, 77-98.
- Navon, D. (1984) Resources- a theoretical soup-stone. *Psychological Review*, 91, 216-234.
- Navon, D. and Gopher, D. (1979) On the economy of the human processing system. *Psychological Review*, 86, 254-255.
- Norman, D.A. and Bobrow, D.G. (1975) On data-limited and resource-limited processes. *Cognitive Psychology*, 7, 44-64.
- Norman, D.A. and Shallice, T. (1980) Attention to action. Willed and automatic control of behavior. University of California San Diego CHIP Report 99.
- O'Leary, D.S., Lovell, M.R., Sadcellares, C., Berent, S., Gierdani, B., Seidenberg, M. and Boll, T.J. (1983) Effects of age of onset of partial and generalized seizures on neuropsychological performance in children. *Neurology, Neurosurgery, and Psychiatry*, 171, 624-629.
- Parsons, D.N. and Miles, D.W. (1984) Metabolic studies with BW430C. *Epilepsia*, 25, 655.
- Peck, A.W. (1991) Clinical Pharmacology of Lamotrogine, *Epilepsia*, 32, supplement 2, 509-512.
- Peterson, L.R. and Peterson, M.J. (1959) Short-term retention of individual verbal items. *Journal of Experimental Psychology*, 58, 193-198.

- Pfefferbaum, A., Wertegrat, B.G., Roth, W.T. and Kofell, B.S. (1984) Clinical Applications of the P3 component of event-related potentials in Dementia, Depression and Schizophrenia. *Electroencephalography and Clinical Neurophysiology*, 59, 104-124.
- Phillips, W.A. and Christie, D.T.M. (1977a) Components of visual memory. *Quarterly Journal of Experimental Psychology*, 29, 117-133.
- Phillips, W.A. and Christie, D.T.M. (1977b) Interference with visualization. *Quarterly Journal of Experimental Psychology*, 29, 637-650.
- Pond, D.A. and Burden, G.S. (1963) Review of the social and medical services for the epileptic patient in England and Wales. *Epilepsia*, 4, 77-89.
- Puente, R.M. (1976) The use of carbamazepine in the treatment of behavioural disorders in children. In: *Epileptic seizures-behaviour-pain*. Editor: W. Birkmayer, p243-252. Hans Hubers Publishers, Berne.
- Quinn, J.G. and Ralston, G.E. (1986) Movement and attention in visual working memory. *Quarterly Journal of Experimental Psychology*, 8(1), 689-703.
- Reitan, R.M. and Wolfson, D. (1985) *The Halstead-Reitan Neurological Test Battery: theory and clinical interpretation*. Neuropsychology Press, Tuscon, Arizona.
- Reynolds, E.H. (1983) Mental effects of antiepileptic medication: a review. *Epilepsia*, 24, 585-595.
- Rimmer, E.M. and Richens, A. (1988) Clinical pharmacology and medical treatment. In: *A textbook of epilepsy*, third edition. Editors: J. Laidlaw, J. Richens, and J. Oxley, p421-483, Churchill Livingstone, London, Melbourne and New York.
- Rodin, E.A., Katz, M. and Lennox, K. (1976) Differences between patients with temporal lobe seizures and those with other forms of epileptic attacks. *Epilepsia*, 17, 313-320.
- Schain, R.J., Ward, J.W. and Guthrie, D. (1977) Carbamazepine as an anti-convulsant in children. *Neurology*, 27, 476-480.
- Schmidt, D. (1982a) Two antiepileptic drugs for intractable epilepsy with complex-partial seizures. *Journal of Neurology, Neurosurgery and Psychiatry* 45, 1119-1124

- Seidenberg, M., Beck, N., Geisser, M, (1986) Academic achievement of children with epilepsy. *Epilepsia*, 27, 753-759.
- Siegal, S. (1959) *Nonparametric statistics for the behavioural sciences*. International student edition, McGraw-Hill Company, New York.
- Shallice, T. and Warrington, E. K. (1970) Independent functioning of verbal memory stores: A neuropsychological study. *Quarterly Journal of Experimental Psychology*, 22, 261-273.
- Shorvon, S.D. and Reynolds, E.H. (1979) Reduction in polypharmacy for epilepsy. *British Medical Journal*.
- Smith, D.B. (1991) Cognitive effects of antiepileptic drugs. In: *Advances in Neurology*, volume 55, Editors: D. Smith, D. Treiman and M. Trimble, p197-212. Raven Press, New York.
- Smith, D.B., Craft, B.R., Collins, J., Maltson, R.H. and Cramer, J.A. (1986) Behavioural characteristics of epilepsy patients compared with normal controls. *Epilepsia*, 27, 760-768.
- Smith, W. and Lowrey, J. (1972) The effects of diphenylhydantoin on cognitive functions in man. In: *Drugs and Cerebral Function*. Editor: W. Lynn Smith. Charles C. Thomas, Springfield, Illinois.
- Sommerbeck, K.W., Theilgaard, A., Rasmussen, K.E., Lohren, V., Gram, L. and Wulff, K. (1977) Valproate sodium: Evaluation of so-called psychotropic effect. A controlled study. *Epilepsia*, 18, 159-166.
- Sonnen, A.E.H., Zelvelder, W.H. and Bruens, J.H. (1975) A double-blind study of the influence of dipropylacetate on behaviour. In: *Controlled Trials of Antiepileptic Drugs*. Editor: M. Dam. *Acta Neurologica Scandinavia* supplement 60, p43-47. Munksgaard, Copenhagen.
- Stephens, J.H., Shaffer, J.W. and Brown, C.C. (1974) A controlled comparison of the effects of diphenylhydantoin and placebo on mood and psychomotor functioning in normal volunteers. *Journal of Clinical Pharmacology*, 14, 543-551.
- Stores, G. (1973) Studies of attention and seizure disorders. *Developmental Medicine and Child Neurology*, 15, 376-382.

- Stores, G. (1981) Behavioural effects of antiepileptic drugs. In Febrile seizures. Editors: K.B. Nelson and J.H. Ellenberg. Raven press, New York.
- Sunderland, A., Harris, J.E. and Baddeley, A.D. (1983) Do laboratory tests predict everyday memory? A neuropsychological study. *Journal of Verbal Learning and Verbal Behaviour*, 22, 341-357.
- Sweetland, R.C. and Keyser, D.J. (1983) Tests, a comprehensive reference for assessments in psychology, education and business. Test Corporation, Kansas city.
- Thompson, P.J. (1981) The effects of anticonvulsant drugs on the cognitive functioning of normal volunteers and patients with epilepsy. Unpublished PhD thesis: University of London.
- Thompson, P.J. and Trimble, M.R. (1983a) Anticonvulsant drugs, cognitive function, and behaviour. *Epilepsia*, 24, 555-563.
- Thompson, P.J. (1991) Memory Function in Patients with Epilepsy. In: *Advances in Neurology*, volume 55, Editors: D. Smith, D. Treiman and M. Trimble, p269-384. Raven Press, New York.
- Thompson, P.J. and Trimble, M.R. (1982) Sodium valproate and cognitive functioning in normal volunteers. *British Journal of Clinical Pharmacology*, 12, 19-24.
- Thompson, P.J. and Trimble, M.R. (1983b) Anticonvulsant serum levels: relationship to impairments of cognitive functioning. *Journal of Neurology, Neurosurgery and Psychiatry*, 46, 227-233.
- Thompson, P.J., Huppert, F. and Trimble, M.R. (1981) Phenytoin and cognitive functions: effects on normal volunteers and implications for epilepsy. *British Journal of Clinical Psychology*, 20, 155-162.
- Tizard, B. and Margerison, J.H. (1963 a) The relationship between generalised paroxysmal EEG discharges and various test situations in two epileptic patients. *Journal of Neurology, Neurosurgery and Psychiatry*, 26, 308-313.
- Troupin, A.S. (1977) Carbamazepine: a double-blind comparison with phenytoin. *Neurology*, 27, 511-519.
- Turnbull, D.M., Horrel, D., Rawlins, M.D. and Chadwick, D.W. (1985) Which drug for this adult epileptic patient: phenytoin or valproate? *British Medical Journal*, 209, 815.

- Walsh, K. (1987) Neuropsychology: a clinical approach, second edition. Churchill Livingstone, Edinburgh, London, Melbourne and New York.
- Watchel, P.L. (1967) Conceptions of broad and narrow attention. Psychological Bulletin, 68, 417-419.
- Weber, R.J., Burt, D.B. and Noll, N.C. (1986) Attention switching between perception and memory. Memory and Cognition, 14, number 3, 238-245.
- Wechsler, D. (1981) Wais-R manual. Psychological Corporation, New York.
- Wickens, C.D. (1980) The structure of attentional resources. In: Attention and Performance, Editors: R. Nickerson and R. Pew. Erlbaum Associates, Hillsdale, New Jersey.
- Wickens, C.D. (1984) Engineering Psychology and human performance. Charles E. Merrill Publishing Company.
- Wilkins, A.J. (1986) On the manner in which sensory and cognitive processes contribute to epileptogenesis and are disrupted by it. Acta Scandinavia, 74 (Supplement 109), 91-95.
- Wilkins, A.J., Zifkin, B., Andermann, F. and McGovern, E. (1981a) Seizures induced by thinking. American Neurology, 11, 608-612.
- Wilkus, R.J., Dodrill, C.B. and Troupin, A.S. (1978). Carbamazepine and the EEG of epileptics : A double-blind study in comparison to phenytoin. Epilepsia, 19, 283-291.
- Wilson, B.A., Cockburn, J. and Badderley, A.D. (1985) The Rivermead Behavioural Memory Test Manual. Thames Valley Test Company.

## APPENDICES

### Appendix One

#### Details of main-line anticonvulsant medication

(Information from Brodie and Hallworth, 1987)

#### Carbamazepine (CBZ)

Carbamazepine (CBZ) was synthesized by Schindler and Geigy in 1953 as part of a programme investigating analogues of Chlopromazine. The first study with patients with epilepsy was not carried out until 1963. Since then, CBZ has slowly gained acceptance and is now considered a first-line broad-spectrum anticonvulsant.

Absorption of CBZ is slow and probably incomplete. The drug is metabolized in the liver, partly to CBZ 10, 11 epoxide (CBZ-E) which also has anticonvulsant activity. The half-life of CBZ may be as long as 48 hours after a single dose, but is greatly reduced after prolonged administration (typically 7-14 hours). This is due to auto-induction of metabolism, the extent of which varies markedly in individuals.

#### Phenytoin (DPH)

Phenytoin (DPH) was synthesized by Blitz in 1908, but its anticonvulsant properties were not discovered until 1936. It was quickly shown to be as effective as phenobarbitone and much less sedative. Despite an

impressive toxicity profile, it remains one of the most widely used ACDs in clinical practice.

Absorption of DPH is slow, sometimes variable and occasionally incomplete. The elimination and half-life of DPH in an adult is in the order to 9-22 hours following a single dose, but is considerably longer at higher concentrations when saturation metabolism takes place. Hence, it may take several weeks for steady-state to be reached in some patients and unexpected toxicity may occur up to a month after altering treatment.

#### Sodium Valproate (VPA)

The anticonvulsant activity of valproic acid was reecognised in 1963 by Meunier and Grenoble, the sodium salt was marketed as an ACD in 1967, and in control studies the drug appears to be as effective as CBZ and DPH.

VPA has a complex pharmacokinetic profile which severely limits the usefulness of serum level measurements and target range. The drug has a relatively short half-life (8-15 hours) especially in children (4-16 hours) and the drug is primarily cleared by hepatic metabolism.

Appendix Two

List of objects used in category-decision tasks in Study 1 (pen and paper task) and in Study 2 (computerised task).

- |                 |               |
|-----------------|---------------|
| 1. Boy          | 23. Flag      |
| 2. Arrow        | 24. Girl      |
| 3. Saw          | 25. Comb      |
| 4. Spotted dog  | 26. Octopus   |
| 5. Ambulance    | 27. Spoon     |
| 6. Flower       | 28. Hand      |
| 7. Cup          | 29. Man       |
| 8. Chair        | 30. Tree      |
| 9. Sauce-pan    | 31. Kettle    |
| 10. Basket      | 32. Bird      |
| 11. Lizard      | 33. King      |
| 12. Shoes       | 34. Tap       |
| 13. Can of soup | 35. Bat       |
| 14. Paint brush | 36. Paddle    |
| 15. Elephant    | 37. Mouse     |
| 16. Alligator   | 38. Butterfly |
| 17. Stool       | 39. Snake     |
| 18. Fish        | 40. Knife     |
| 19. Horse       | 41. Cat       |
| 20. Umbrella    | 42. Train     |
| 21. Key         | 43. Watch     |
| 22. Coach       |               |

Appendix ThreeClinical details of subjects in Dundee study one

The following tables summarise the epilepsy variables monitored in Dundee study one for each of the drug groups as described in chapter five.

---

Table 2a Study One: Five group comparisons  
CBZ group : Individual subject details

Subject No.	Type of seizures	Frequency of seizure	Age at onset	Duration (yrs)
07	3 TL/L	5	54	2
08	3 TL/R	5	12	10
12	1	5	33	0.5
14	1 I	4	11	6
15	3	5	36	2
18	1	5	45	2
19	?	?	?	?
20	3	4	5	50
21	3	4	14	4
22	3 TL	4	4	40
23	1	5	36	16
25	3 TL	3	18	17
47	1	5	5	41
50	2	2	24	16

---

Key : TL : Temporal Lobe  
: L : Left-side and R : Right-side  
: I : Idiopathic

---

---

Table 2b Study One : Five group comparisons  
VPA group : Individual subject details

Subject No.	Type of seizures	Frequency of seizure	Age at onset	Duration (yrs)
09	3	4	16	9
10	1	5	10	13
11	2 TL	4	47	1
13	2	2	?	?
17	3	5	46	1
29	1	5	10	6
30	1	5	15	17
39	1	5	28	12
42	2	3	14	4
48	3	5	47	5
53	1	2	12	11
54	1	5	9	11
67	3	5	16	3

---

Appendix Three contd.


---

Table 2c Study One : Five group comparisons  
DPH : Individual subject details

Subject No.	Type of seizures	Frequency of seizure	Age at onset	Duration (yrs)
06	3 TL/L I	3	42	9
26	2	3	4	47
31	1	4	28	11
37	1	5	20	0.5
38	1	?	47	3
44	1	5	41	7
52	1	5	7	20
58	1 I	5	5	14
60	1	5	23	9
61	1	5	18	17
62	1	5	29	10
64	1	5	17	17
65	?	5	37	4

---



---

Table 2d Study One : Five group comparisons  
POLYT group : Individual subject details

Subject No.	Type of seizures	Frequency of seizure	Age at onset	Duration (yrs)
24	3 TL	3	1	24
32	1	5	?	?
33	1	3	22	3
34	3	2	23	2
36	2	2	9	29
41	1	3	20	4
43	1 I	4	13	9
45	3 R	3	10	7
55	1	2	5	48
59	1	2	31	3
63	3	5	0.5	19
66	2	1	?	?
68	?	?	?	?

---

Appendix Four

The following tables summarise the individual drug details of the three monotherapy drug groups in Dundee study one as described in chapter five.

---

Table 3a Study one : Five groups comparisons  
 CBZ group : Dose and serum concentration details

Subject No.	Dose (mg per day)	Concentration ( $\mu$ mol/l)
07	400	27
08	1000	?
12	300	22
14	200	42
15	400	35
18	800	27
19	?	31
20	400	31
21	400	5
22	400	22
23	800	?
25	600	32
47	200	14
50	600	25

---



---

Table 3b Study one : Five groups comparisons  
 VPA group : Dose and serum concentration details

Subject No.	Dose (mg per day)	Concentration ( $\mu$ mol/l)
09	800	294
10	1200	286
11	800	?
13	400	281
17	400	226
29	1200	?
30	800	?
39	1500	?
42	700	?
48	?	399
53	1500	?
54	1000	182
67	1000	327

---

Appendix Four contd.

---

Table 3c Study one : Five groups comparisons  
DPH group : Dose and serum concentration details

Subject No.	Dose (mg per day)	Concentration ( $\mu$ mol/l)
06	300	?
26	425	113
31	400	50
37	?	15
38	200	62
44	300	?
52	250	?
58	300	68
60	400	?
61	100	?
62	200	27
64	?	5
65	?	?

---

Appendix Five

The following tables summarise the individual epilepsy details of subjects in Glasgow study one as described in chapter seven.

-----  
 Table 4a Glasgow study : Five group comparisons  
 UT group : Individual subject details  
 -----

Subject No.	Type of seizures	Frequency of seiz.	Age at onset	Duration (yrs)	EEG	CT
438	1	3	21	0.8	A	N
493	1 (L)	5	35	0.5	A	N
463	3 (I)	5	17	1	A	N
419	2 (TL)	3	22	0.5	A	?
409	1 (L)	3	18	1	A	?
418	1	3	16	2	A	N
469	2	3	20	1	A	?
488	1	3	18	0.5	A	?
402	3	2	15	1	A	?
458	P	5	13	5	A	N
450	1 (I)	4	16	5	A	N
429	1	5	13	15	A	N
431	3	3	1	17	A	N
472	1 (I)	2	19	8	A	N
454	2 (TL)	3	19	4	A	N
444	1	1	24	0.5	A	N
461	2	2	11	21	A	N
499	2	5	10	7	A	?
498	1	3	16	1	A	?
496	1	3	29	0.5	A	N
413	3 (L)	1	12	12	A	?
417	3	3	21	6	A	N

-----

Appendix Five contd

-----  
 Table 4b Glasgow study : Five group comparisons  
 CBZ group : Individual subject details  
 -----

Subject No.	Type of seizures	Frequency of seiz.	Age at onset	Duration (yrs)	EEG	CT
417	3	2	18	9	A	N
453	1 (I)	3	25	0.8	A	N
428	1 (I)	5	29	8	A	N
471	3	3	21	6	A	N
434	1	2	17	1.5	A	N
455	1	5	21	5	A	N
439	1	3	20	9	A	?
401	1	3	15	2	A	?
400	3	3	0	28	A	N
410	3	2	19	3	A	?
403	3 (R)	1	15	6	A	?
448	2	2	2	22	A	?
489	1	3	29	1	A	N
430	2	3	13	9	A	N
404	3 (LTL)	5	30	2	A	N
449	1 (I)	4	20	2	A	N
413	3 (L)	1	12	12	A	?
418	1	3	16	2	A	N
433	2 (R)	5	18	8	a	N
456	3	1	7	14	A	N
461	2	2	11	21	A	?

-----

Appendix Five contd

-----  
 Table 4c Glasgow study : Five group comparisons  
 VPA group : Individual subject details  
 -----

Subject No.	Type of seizures	Frequency of seiz.	Age at onset	Duration (yrs)	EEG	CT
442	1 (I)	4	15	5	A	?
459	3	3	37	14	A	?
492	3	3	16	7	A	N
479	3 (I)	5	28	3	A	N
485	3 (L)	5	33	1.5	A	N
445	3	2	35	1	A	N
411	2	1	14	4	A	?
425	1 (I)	5	12	10	A	N
432	1 (I)	5	13	11	A	?
427	1	5	16	2	A	N
407	1 (I)	5	11	5	A	?
464	3	2	8	15	A	?
470	1	2	2	39	A	?
452	1	5	14	4	A	N
467	2 (I)	2	3	41	A	?
447	3	3	12	5	A	N

-----

Appendix Five contd

-----  
 Table 4d Glasgow study : Five group comparisons  
 DPH group : Individual subject details  
 -----

Subject No.	Type of seizures	Frequency of seiz.	Age at onset	Duration (yrs)	EEG	CT
462	1	3	7	22	A	N
435	1 (I)	3	12	11	A	N
487	1	5	38	3	A	N
484	2	2	1	30	A	N
446	3	4	40	4	?	N
421	1 (L)	5	17	10	A	N
495	3	5	40	3	A	N
426	1 (I)	5	4	13	A	N
468	3	1	22	24	A	N
443	1	4	36	4	A	N
416	3	2	6	23	A	N
408	3 (R)	3	56	1	A	N
475	1 (TL)	3	27	3	?	?
497	3	3	17	40	A	?
474	3 (TL/L)	2	28	2	A	N

-----

Appendix Six

The following tables summarise the individual drug details of the subjects with epilepsy participating in Glasgow study one as described in chapter eight.

-----  
 Table 5a Glasgow study : Five group comparisons  
 CBZ group : Individual medication details  
 Subject No. Dose (mg per day) Concentration (mg/ml)  
 -----

417	1000	10.6
453	400	11.5
428	400	6.9
471	400	9.2
434	800	10.9
455	800	9.6
439	1200	9.3
401	600	3.1
400	1000	12.4
410	1000	9.9
403	800	11.1
448	1200	9.6
430	600	12.7
404	800	7.3
449	800	9.0
413	1200	8.2
418	200	10.1
433	400	3.9
456	600	15.3
461	200	5.4
496	400	8.2

-----

Appendix Six Contd


---

Table 5b Glasgow study : Five group comparisons  
VPA group : Individual medication details

Subject No.	Dose (mg per day)	Concentration (mg/ml)
442	400	40
459	800	66
492	500	101
479	400	43
485	800	48
445	1600	62
411	1000	127
425	1600	74
432	1000	74
427	400	83
407	2000	147
464	1500	147
470	400	65
452	1500	114
467	1200	124
447	1500	145

---

Appendix Six contd


---

Table 5c Glasgow study : Five group comparisons  
DPH group : Individual medication details

Subject No.	Dose (mg per day)	Concentration (mg/ml)
462	400	33.4
435	425	47.4
487	350	14.9
484	350	19.6
446	600	23.1
421	400	12.6
495	400	3.3
426	300	26.2
468	425	40.8
443	325	18.6
416	250	29.3
408	450	37.5
475	250	47.5
497	375	13.5
474	475	39.4

---

### Appendix Seven

For clinical interest : Subjects with epilepsy vs CTL subjects, and ACD vs non-ACD subjects.

The design of Glasgow study one was a five groups analysis. However, from a clinical view-point it would be interesting to explore firstly, how the control subjects compared to the group with epilepsy, irrespective of type of medication, and secondly, how subjects on medication compared to subjects not on any medication. These areas were investigated in the main five groups analysis, by the use of Scheffé test, where appropriate. However, the Scheffé test is very conservative and did not provide a picture of the data of these comparisons. Hence, two sets of between groups ANOVA were carried out :

1. Comparing subjects with epilepsy (N=74) with CTL (N=10) subjects.
2. Comparing ACD (three drug groups combined, N=52) with non-ACD (N=32, CTL=10 plus UT=22) groups.

The differences in sizes of the groups meant that any results obtained from these analyses are was robust and should only be read as possible indicators of what might be occurring in the data set.

-----  
Table 8.9a : Mean scores for the tests of intellectual ability, the motor task, SRT, category-decision task and the attention-switching task for epilepsy vs control comparisons  
 -----

Test	Subject Groups : Means (S.D)	
	Epilepsy	Control
-----		
Intellectual Ability : Mean scaled score (Combined score)	8.46 (2.14)	9.15 (1.17)
-----		
Motor tasks : Mean No. of taps in 60s		
Condition one a) 1 key	294.5 (57.4)	320.6 (37.6)
b) 2 key	150.0 (34.6)	161.7 (25.3)
Condition two a) 1 key	259.8 (62.9)	288.9 (66.5)
b) 2 key	138.6 (35.1)	153.3 (36.1)
-----		
Reaction time tasks : Mean response time in ms		
Condition one	326.2 (107.0)	261.9 (30.6)
Condition two	368.1 (130.0)	292.2 (44.1)
Condition three	461.2 (196.8)	369.3 (52.0)
-----		
Category-decision task : Mean response time (N=48 and N =10)		
Condition one	602.6 (205.9)	552.9 (175.5)
Condition two	802.7 (287.5)	657.8 (114.3)
Condition three	1094.9 (495.9)	904.3 (337.7)
-----		
Attention-switching task : mean response time (N=50 and N=10)		
Condition one	1527.1 (361.4)	1514.0 (324.8)
Condition two	1662.8 (382.9)	1579.1 (227.9)
Condition three	5142.6 (1331.9)	4895.6 (932.2)
-----		

### Epilepsy subjects vs CTL subjects

The epilepsy and CTL groups were compared across all tests in the battery using a between groups ANOVA, with within-groups factor of condition where relevant.

The means and standard deviations for the combined intellectual ability score, the motor tasks, the reaction time tasks, the category-decision task, and the attention-switching task are presented in table 8.9a.

In summary, the means of the CTL group were in the direction of better performance (i.e shorter response times) compared to the clinical group. In the category-decision task, for example, the means for the control group were 552.9 ms, 657.8 ms, and 904.3 ms, whereas the clinical group means were 602.6, 802.7 and 1094.9 ms respectively. The standard deviations, were generally smaller in the control group, for example 175.5, 114.3, 337.7 versus 205.9, 287.5, and 495.9 in the category-decision task.

(Note: The number of errors in both the category-decision and the attention-switching task were very low in the first two conditions and slightly higher in the third condition).

-----  
Table 8.9b : ANOVA of intellectual ability, motor tasks, SRT, category-decision and attention-switching tasks for Epilepsy vs Control comparisons

Test                      Two groups        :        "F" ratio (Df) and  
                                  Epilepsy versus CTL        significance level

-----  
 Intellectual Ability        F = 1.03 (DF = 1/82)        P > 0.1  
 (Effect of Group)

-----  
 Motor tasks

Effect of Group                F = 2.14 (DF = 1/82)        P > 0.1  
 Effect of Condition        F = 30.68 (DF = 1/82)        P < 0.001  
 Effect of Keys                F = 386.34 (Df = 1/82)        P < 0.001

Interactions

Group by Condition        F < 1  
 Group by keys                F = 1.02 (DF = 1/82)        P > 0.1  
 Group by condition  
 by keys                        F < 1

-----  
 Reaction time tasks

Effect of Group                F = 3.63 (1,82)                P > 0.1  
 Effect of Condition        F = 16.33 (2,164)                P < 0.001  
 Interaction                    F < 1  
 (Group by Condition)

-----  
 Category-decision task

Effect of Group                F = 1.74 (DF = 1/55)        P > 0.1  
 Effect of Condition        F = 29.39 (DF = 2/110)        P < 0.001  
 Interaction                    < 1  
 (Group by Condition)

-----  
 Attention-switching task

Effect of Group                F < 1  
 Effect of Condition        F = 366.89 (DF = 2,116)        P < 0.001  
 Interaction                    F < 1  
 (Group by Condition)

-----

The ANOVA analyses across the tests of intellectual ability, the motor task, the simple reaction time tasks, the category-decision task and the attention-switching task are summarised in table 8.9b. The comparisons revealed no significant differences between the group with epilepsy and control group. There were no significant group by condition interactions, revealing no effects of task complexity on group performance.

-----  
Table 8.9c Mean scores correct in memory tasks and mean performance rate of the distractors for the group with epilepsy vs control group

Test	Subject Groups : Means (S.D)	
	Epilepsy	Control
Digit span	10.65 (2.94)	12.00 (2.24)
Trigram task (Combined score)	4.91 (0.85)	5.46 (0.40)
Visual task (Combined task)	4.29 (0.99)	4.78 (0.95)
Spatial task (Combined score)	3.33 (0.73)	3.78 (0.69)
Distractor tasks : rate of performance per second.		
Articulations	2.44 (0.91)	2.41 (0.79)
Counting backwards	0.43 (0.18)	0.53 (0.21)
Shapes	0.17 (0.07)	0.19 (0.06)
Tapping	1.97 (0.58)	1.98 (0.37)

-----

The mean scores and standard deviations for the memory tasks were summarised in table 8.9c. The control group means were in the direction of better performance on the memory tasks. For example, the combined score means on the three memory tasks for the control groups were 5.46, 4.78 and 3.78, whereas for the group with epilepsy, the combined score means were 4.91, 4.29 and 3.33 respectively. However, the standard deviations (S.D.s) were smaller in the control group, for example in the same three memory tasks the S.D.s for the control group were 0.40, 0.95 and 0.69, whereas for the group with epilepsy, the S.D.s were 0.85, 0.99 and 0.73 respectively.

-----  
Table 8.9d : ANOVA of the memory tests and distractor  
tasks for the group with epilepsy vs control group  
comparisons  
 -----

Test	"F" ratio (DF) and significance level	
Digit Span	F = 1.92 (1,82)	P > 0.1
Trigram task (Group)	F = 4.16 (1,82)	P < 0.05
Effect of Condition	F = 45.15 (4,328)	P < 0.001
Interaction (Group by condition)	F < 1	
Visual task (Group)	F = 2.02 (1,81)	P > 0.1
Effect of Condition	F = 33.58 (3,243)	P < 0.001
Interaction (Group by Condition)	F < 1	
Spatial task (Group)	F = 2.77 (1,80)	P = 0.089
Effect of condition	F = 32.47 (3,240)	P < 0.001
Interaction (Group by Condition)	F < 1	
Distractor tasks		
Articulations		
Effect of Group	F < 1	
Effect of test	F < 1	
Interaction (group by test)	F = 2.60 (2,164)	P = 0.077
Counting backwards	F = 1.73 (1,82)	P > 0.1
Shapes		
Effect of	F < 1	
Effect of test	F = 4.38 (2,162)	P < 0.05
Interaction (Group by test)	F < 1	
Tapping		
Effect of Group	F < 1	
Effect of Test	F = 1.79 (2,162)	P > 0.1
Interaction (group by test)	F < 1	

-----

The data from the memory tasks were analysed using ANOVA (see table 8.9d for the "F" ratios, degrees of freedom and levels of significance for all the tests). The memory tasks did produce some interesting findings in the direction of poorer performance of the group with epilepsy, with the trigram task data being significant at the 0.05 level ( $F(1,82) = 4.16, P < 0.045$ ) and the spatial memory task revealing a trend ( $F(1,82) = 2.77, P < 0.09$ ).

There were no significant group by test condition interaction on the memory tests, revealing no detrimental effect to task complexity on the clinical group.

The performance on the distractor tasks produced no differences between the two groups, although there was a trend in the group by condition interaction for the articulations ( $F(2,164) = 2.60, P < 0.078$ )

The effects of conditions were as expected from the previous analyses and as such have not been discussed in the five groups analyses.

-----  
Table 8.9e Mean scores for the intellectual ability, the motor tests, SRT, category-decision and attention-switching tasks for the ACD vs non-ACD comparisons

Test	Subjects : (Means and S.D.)	
	ACD	Non-ACD
-----		
Intellectual Ability : Mean scaled score (Combined score)	8.30 (1.92)	8.69 (2.05)
-----		
Motor tasks : Mean No. of taps per 60s		
Condition one a) 1 key	300.4 (57.84)	293.1 (53.55)
b) 2 keys	154.9 (33.00)	145.6 (34.58)
Condition two a) 1 key	270.4 (62.67)	251.8 (65.56)
b) 2 keys	144.3 (33.10)	133.9 (38.69)
-----		
Reaction time tasks : Mean response time in ms.		
Condition one	336.4 (120.4)	289.4 (56.2)
Condition two	377.6 (148.7)	329.0 (64.3)
Condition three	482.2 (226.2)	398.0 (75.2)
-----		
Category-decision task : Mean response times		
	N=37 (ACD)	N=21 (Non-ACD)
Condition one	615.6 (208.9)	553.7 (181.3)
Condition two	826.9 (294.4)	687.1 (172.1)
Condition three	1135.3 (478.9)	924.8 (337.7)
-----		
Attention-switching task : Mean response times		
	N=38 (ACD)	N=22 (Non-ACD)
Condition one	1558.4 (384.6)	1443.0 (284.5)
Condition two	1694.8 (391.2)	1557.0 (308.4)
Condition three	5151.1 (1532.6)	5001.9 (1210.1)
-----		

Anticonvulsant Drug versus non-ACD group

The total subject sample was divided into two groups, those taking anticonvulsant medication (N=54) and those on no medication (N=30). The performance of the two groups on each of the tests was analysed using ANOVA, with within subject factor of condition where relevant. Again, because this analysis was less robust due the differences in sizes of the two groups and was not the original design of the study, any results must be viewed as tentative.

Tables 8.9e summarises the means and the standard deviations of the two groups for the intellectual ability, motor, reaction time, category decision and attention switching tasks. The picture from this set of means reveals no mixed set of mean scores. The ACD group had a higher mean scores in the tapping motor task, whereas the non-ACD group had faster response times in the reaction times tasks, category decision and attention switching tasks.

-----  
Table 8.9f ANOVA for the tests of intellectual ability, motor, SRT, category-decision and attention-switching for the ACD vs Non-ACD comparisons.  
 -----

Test	Groups : ACD vs : Non-ACD	"F" ratio (Df) and Significance level
------	------------------------------	--

-----

Intellectual ability

Effect of Group	F < 1	
-----------------	-------	--

-----

Motor tasks

Effect of Group	F = 1.48 (1,82)	P > 0.1
-----------------	-----------------	---------

Effect of Condition	F = 82.96 (1,82)	P < 0.001
---------------------	------------------	-----------

Effect of Keys	F = 788.82 (1,82)	P < 0.001
----------------	-------------------	-----------

Interaction

Group by Condition	F = 1.49 (1,82)	P > 0.1
--------------------	-----------------	---------

Group by Keys	F <	
---------------	-----	--

Group by Condition by keys	F = 1.70 (1,82)	P > 0.1
----------------------------	-----------------	---------

-----

Reaction time tasks

Effect of Group	F = 4.98 (1,82)	P < 0.05
-----------------	-----------------	----------

Effect of Condition	F = 40.55 (2,164)	P < 0.001
---------------------	-------------------	-----------

Interaction (Group by Condition)	F = 1.07 (2,164)	P > 0.1
----------------------------------	------------------	---------

-----

Category-decision task

Effect of Group	F = 3.21 (1,55)	P = 0.078
-----------------	-----------------	-----------

Effect of Condition	F = 51.70 (2,110)	P < 0.001
---------------------	-------------------	-----------

Interaction (Group by Condition)	F = 1.41 (2,110)	P > 0.1
----------------------------------	------------------	---------

-----

Attention-switching task

Effect of Group	F < 1	
-----------------	-------	--

Effect of Condition	F = 366.88 (2,116)	P < 0.001
---------------------	--------------------	-----------

Interaction (Group by condition)	F < 1	
----------------------------------	-------	--

-----

Table 8.9f presents the "F" ratios, degrees of freedom and significance levels for the motor, reaction time, category decision and attention switching tasks. The groups were significantly different in the simple reaction time task ( $F_{2,82} = 4.98, P < 0.05$ ) in the direction of better performance of the Non-ACD group. Also, a trend was observed in the category decision task ( $F_{(1,55)} = 3.21, P = 0.0798$ , in the direction of better performance of the Non-ACD group. There were no other group differences. The expected condition effects were observed, but there were no group by condition interactions, revealing no specific effect of test condition on group performance.

-----  
Table 8.9g Mean score correct for the memory tasks for the  
ACD ands non-ACD group data

Test	Subject group : Drug vs Non Drug	
	Drug	Mean (S.D.) Non-Drug
Group		
-----	-----	-----
Digit span	10.98 (2.78)	10.53 (2.95)
-----	-----	-----
Trigram task (Combined score)	4.93 (0.88)	5.04 (0.68)
-----	-----	-----
Visual task (Combined score)	4.18 (1.12)	4.59 (0.92)
-----	-----	-----
Spatial task (Combined score)	3.39 (0.79)	3.53 (0.65)
-----	-----	-----
Distractor tasks		
Articulations	2.50 (0.94)	2.34 (0.63)
Counting backwards	0.42 (0.19)	0.47 (0.19)
Shapes	0.17 (0.06)	0.18 (0.06)
Tapping	2.04 (0.56)	1.89 (0.55)
-----	-----	-----

Table 8.9g summarises the means for the primary memory tasks and the secondary distractor tasks. In the memory tasks, the Non-ACD group means are in the direction of better performance. Hence, in the Non-ACD group the combined score means for the three primary memory tests were 5.04, 4.59 and 3.53, whereas for the drug group the means were 4.93, 4.18 and 3.39 respectively. The standard deviations, on the other hand, were smaller for the non-drug group in these three same tasks.

The means and standard deviations for the distractor tasks showed no obvious pattern, with similar means being obtained by both groups.

-----  
 Table 7.9h ANOVA of the memory task comparisons of the ACD  
 and non-ACD groups

Test	"F" ratio (Df) and significance level		
Digit Span	F < 1		
-----			
Trigram task			
Effect of Group	F < 1		
Effect of Condition	F = 119.60	(2,328)	P < 0.001
Interaction (Group by condition)	F < 1		
-----			
Visual task			
Effect of Group	F = 2.81	(1,80)	P = 0.097
Effect of Condition	F = 72.23	(3,243)	P < 0.001
Interaction (Group by Condition)	F = 1.11	(3,243)	P > 0.1
-----			
Spatial task			
Effect of Group	F < 1		
Effect of condition	F = 75.04	(3,240)	P < 0.001
Interaction (Group by Condition)	F < 1		
-----			
Distractor tasks			
Articulations			
Effect of Group	F < 1		
Effect of Test	F < 1		
Interaction (group by test)	F = 3.71	(2,164)	P < 0.05
Counting backwards	F = 1.64	(1/82)	P > 0.1
Shapes			
Effect of Group	F < 1		
Effect of Test	F = 9.73	(1,164)	P < 0.001
Interaction (Group by Test)	F = 1.08	(2,164)	P > 0.1
Tapping			
Effect of Group	F = 1.92	(1,81)	P > 0.1
Effect of Test	F = 4.86	(1,162)	P < 0.01
Interaction (Group by Test)	F < 1		

-----

Table 8.9h summarises the "F" ratios, degrees of freedom and levels of significance for the primary memory tasks and the distractor task analyses. There were few significant different differences between the groups, with only a trend in the visual memory being of interest ( $F(1,80) = 2.81, P = 0.097$ ) in the direction of better performance of the non-ACD group.

The effect of condition was again very apparent, but there was also only one interaction of group by condition, in the articulation distractor task ( $F = 3.71, Df 2,164,$  and  $P < 0.027$ )

In summary, although there were few differences between these two groups, those differences found showed poorer performance in the ACD group compared to the non-ACD group

Appendix EightDetails of Lamotrogine

Lamotrogine acts by inhibiting the release of excitatory amino acids, particularly glutamate. It does not alter the half-life of other ACDs, nor does it stimulate or inhibit other drug metabolizing enzymes.

The half-life in healthy volunteers has been shown to be in the region of 24 hours and animal studies have shown that Lamotrogine is well absorbed being mainly eliminated in the urine.

# Test Battery: Dundee Study One

## 1. 2 Sub-tests from WAIS-R

- a) Vocabulary test  
A list of vocabulary consisting of 35 words of increasing difficulty.
- b) Picture completion test  
20 individually presented incomplete pictures.

Mean scores are converted to age-scaled scores, based on a mean population score of 10 and a standard deviation of 3.

## 2. Category Decision Task

A pen and paper rapid response timed task, consisting of three conditions, each with 20 trials repeated twice.

Condition one: control condition.

Condition two: pressing Yes/No to say whether or not an object is presented on a dark background.

Condition three: pressing to show if the object presented is animate.

The trial time to complete the second set of each condition (20 trials) was recorded in seconds.

## 3. Perceptual Maze Task

The test material was composed of dot patterns super-imposed on a diagonal lattice background. The subject was required to join as many dots as specified in the allotted time. The number of patterns complete was recorded.

## 4. Revised Benton Visual Retention Test

The subject was presented with each of 10 simple drawings for 10 seconds, then was asked to wait 15 seconds, and they then attempted to draw the shapes from memory. The maximum score was 10.

## 5. Rivermead Behavioural Memory Test (RBMT)

The RBMT (an easy to use battery of memory tests) is designed to detect the impairment of everyday memory functioning. The raw score provided a profile score, and the profile score was converted into a screening score (maximum score 12).

## 6. Rey Figure

A measure of visuo-spatial abilities. The subject was required to a) copy a complex geometrical figure, b) to recall it from immediate memory and c) to recall the figure from delayed memory. Hence, there were 3 parts to the test with a maximum possible score of 36 in each part.

## 7. Memory Questionnaire

The subject was asked to rate the frequency of their memory lapses on 15 possible everyday examples of situations where one might expect them to show memory loss.  
Maximum score  $15 \times 3 = 45$ .

# Test Battery: Glasgow Study

## 1. 2 Sub-tests from WAIS-R

- a) Vocabulary test  
A list of vocabulary consisting of 35 words of increasing difficulty.
- b) Picture completion test  
20 individually presented incomplete pictures.

Mean scores are converted to age-scaled scores, based on a population mean of ten and a standard deviation of three.

## 2. Finger tapping tasks

- a) Tapping one switch with one finger continuously, as fast as possible for 60 s.
- b) Tapping two switches (placed 17.5 cm apart) alternately as quickly as possible, with the same finger for 60 s.

The total number of taps in 60 s was recorded.

## 3. Simple reaction time

Pressing the space bar on a BBC computer as quickly as possible, as soon as an orange cursor appeared in the middle of the screen.

The mean response time in milliseconds over 20 trials was recorded.

Note: The simple reaction time tasks were then combined with tapping tasks a) and b) making two dual-tasks.

## 4. Digit span task

The procedure and list of digits are those employed in WAIS-R and involve completing forward and backward digit span tasks.

The raw scores obtained were converted to age-scaled scores which have a mean population score of ten, and a standard deviation of three.

## 5. Trigram task

A working memory task requiring the subject to remember three consonants over a 10 s period. The task becomes more difficult when the subject is required to complete a secondary task in the 10 s period, before recalling the consonants.

Varying the secondary tasks resulted in five conditions of the task. The maximum score per condition was six, for six correctly recalled consonants.

**6. Visual task**

A working memory task requiring the subject to remember line-drawn simple shapes over a 10 s period. The task becomes more difficult when the subject is required to complete secondary tasks in the 10 s period, before recalling the shape. Varying the secondary tasks employed resulted in 4 conditions of the task.

The maximum score per condition was six, resulting from six correct shapes being recalled.

**7. Spatial task**

The subject was required to recall the position of three squares positioned randomly on a ten-by-ten square grid after a 10 s period.

The task becomes more difficult when the subject is required to complete secondary tasks. There were 4 secondary tasks, hence 4 conditions, each with a maximum score of 6.

**8. Category-decision task**

Objects, that could be categorised as animate/inanimate and were coloured red or green, were presented on the computer screen. The task consisted of three conditions:

- i) Pressing the YES switch if the object was coloured green and NO if coloured red.
- ii) Pressing YES if it was animate, and NO if it was inanimate.
- iii) Pressing the appropriate switch to whichever question was asked ie. animate/inanimate or red/green.

The mean response time in milliseconds per condition (20 trials per condition) was recorded.

**9. Attention-switching task**

The task consisted of three conditions:

- a) Recalling a set of 3 consonants as quickly as possible after a 5 s period.
- b) Reading aloud a set of 3 consonants as soon as they appeared on the screen.
- c) Alternating as quickly as possible between consonants to be recalled and consonants to be read from the screen.

The mean response time in milliseconds over the 10 trials per condition was recorded.

**10. Multiple affect adjective check-list (MAACL)**

Subjects were given a questionnaire assessing their levels of anxiety, depression and hostility at the time of testing. It consisted of the following items:

21 anxiety items  
40 depression items  
28 hostility items

Studies for a non-clinical population give the following results:

	Mean	Standard deviation
Anxiety	5.8	3.3
Depression	10.0	5.3
Hostility	6.3	3.3